PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

The medicine is dispensed with a doctor's prescription only

Name of the preparation, its form and strength

ARTHROTEC® 50 mg
ARTHROTEC® 75 mg
Tablets

Diclofenac Sodium 50 mg, 75 mg
Misoprostol 200 mcg

List of inactive and allergenic ingredients in the preparation in section 6.

Read this package insert carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed to treat you. Do not pass it on to others; it may harm them even if it seems to you that their medical condition is similar to yours. This medicine is intended for adults above 18 years of age.

1. WHAT SHOULD I KNOW ABOUT THE MEDICINE?

- The medicine contains lactose and may cause allergy in people sensitive to lactose.

For information on side effects, please see section 4.

WHAT IS THE MEDICINE INTENDED FOR?

- The medicine is intended for patients who need prolonged anti-inflammatory treatment in circumstances where there is a high risk of bleeding and stomach ulcer, i.e.: patients who have previously had a peptic ulcer or gastric bleeding, patients with cardiovascular diseases (heart/blood vessels), patients above 65 years of age and patients who smoke.

Therapeutic group:

The medicine is a combination of two active ingredients:

Diclofenac - belongs to the group of non-steroidal anti-inflammatory drugs (NSAIDs).

Misoprostol - a prostaglandin analog. Prostaglandins help protect the lining of the stomach and duodenum.

2. BEFORE USING THE MEDICINE

☒ Do not use the medicine if:

x you are sensitive (allergic) to the active ingredients or to any of the other ingredients contained in the medicine.

x you are sensitive to aspirin, salicylates, other non-steroidal anti-inflammatory preparations, or to other medicines that contain prostaglandin analogs.

x you are pregnant or breastfeeding, or are planning to become pregnant or to breastfeed.

If you have been exposed to the medicine in the course of pregnancy, consult with one of the teratology counselling centers to assess the risk of harm to the fetus.

x Do not use the medicine in case of gastrointestinal bleeding, active or suspected peptic ulcer, and also if there is other active bleeding (e.g.: cerebrovascular bleeding).

x Do not use the medicine in patients with severe kidney or liver failure.

x you have established heart disease and/or cerebrovascular disease e.g. if you have had a heart attack, stroke, transient ischemic attack or blockage of blood vessels to the heart or brain or an operation to clear or bypass blockages.

x you have or have had problems with your blood circulation (peripheral vascular disease).

x Do not use for treatment of pain due to cardiac bypass surgery.

x Do not use the medicine together with other NSAIDs including COX-2 enzyme inhibitors.

If you smoke and/or suffer from: diabetes, high blood pressure, angina, blood clots, high cholesterol or high triglyceride level, make sure your doctor knows before you are given this medicine.

Do not use the medicine without consulting a doctor before starting treatment:

- if you are suffering or have suffered in the past from impaired function of the liver (e.g.: hepatic porphyria) or kidneys.
- if you are suffering or have suffered in the past from impaired function of the digestive system (e.g.: peptic ulcer).
- if you bleed or bruise easily.
- if you suffer from an inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis).
- if you have or have ever had impaired function of the respiratory system, asthma or allergy.
- if you have an infection, as the medicine may mask a fever or other symptoms of infection.
- if you are dehydrated.
- if you suffer or have suffered in the past from connective tissue disease, lupus erythematosus.
- if you suffer or have suffered in the past from epilepsy.
- If you are over the age of 65, your doctor may want to conduct periodic tests.

Special warnings regarding use of the medicine

! If you are sensitive to any food or medicine, tell your doctor before taking the medicine.

! The medicine contains lactose and may cause allergy in people sensitive to lactose.

! Women who could become pregnant during the period of treatment with the medicine must use contraception.

! Blood tests should be carried out to rule out pregnancy about one month before starting treatment in women who could become pregnant during the period of treatment with the medicine.

! Treatment with the medicine will begin two or three days from the start of the next menstrual period.

! If you have become pregnant during treatment with the medicine, stop the treatment and refer to the doctor immediately. One of the active ingredients of the medicine, misoprostol, may cause a miscarriage.

! Do not use this medicine frequently or for a prolonged period without consulting the doctor.

! During the period of treatment with this medicine the following tests should be carried out: blood, urine, liver and kidney function, blood pressure. There may be an elevation in liver enzymes that requires discontinuation of treatment after consultation with the doctor. As with other NSAIDs, Arthrotec® may cause a rise in blood pressure.

! Patients under treatment with Arthrotec® who have coagulation disorders or are taking anticoagulants must be under medical follow-up.

! If you are due to undergo surgery (including dental surgery), tell the doctor that you are taking this medicine.

! If you are about to undergo laboratory tests, tell the doctor, since treatment with the medicine can affect the results.

! Medicines from the non-steroidal anti-inflammatory drugs (NSAIDs) group, such as Arthrotec®, may cause bleeding or an ulcer in the digestive system. In such instances, stop treatment and refer to a doctor.

! Arthrotec® may be associated with a slightly increased risk of heart attack (myocardial infarction) or stroke. The risk increases with high dosages and long duration of treatment.

Side effects can be minimised by using the lowest effective dosage for the shortest duration required.

! If you are taking or have recently taken other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist.

It is especially important to inform the doctor or pharmacist if you are taking:

- Aspirin or other NSAIDs.
- Medicines used to treat rheumatoid arthritis or osteoarthritis such as cyclo-oxygenase-2 (COX-2) inhibitors.
- Cyclosporine or tacrolimus (immunosuppressants, for example, for treatment after transplants) – since the combination increases the risk of renal toxicity.
- Lithium - since the combination increases the level of lithium in the blood.
- Digoxin (for treatment of irregular heart rate and/or heart failure) – since the combination increases the level of digoxin in the blood, and you must therefore be under medical follow-up.
- Anticoagulants (e.g.: warfarin) – you must be under medical follow-up.
- Medicines used to treat anxiety and depression, such as selective serotonin re-uptake inhibitors (SSRIs).
- Medicines for treatment of diabetes.
- Methotrexate (used to treat rheumatoid arthritis, cancer and psoriasis) – since the combination may increase the level of methotrexate in the blood.
- Corticosteroids – since the combination raises the risk of stomach ulcer or gastrointestinal bleeding.
- Cardiac medication and blood pressure lowering drugs [e.g.: diuretics, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)] – since Arthrotec® may affect the efficacy of these medicines.
- Magnesium-containing antacids – since the combination may cause worsening of diarrhea.
- Voriconazole (antifungal), sulfinpyrazone (for treatment of gout) – since the combination raises the level of diclofenac in the blood.
- Quinolone antibiotics – since the combination may increase the risk of convulsions.
- Ketoconazole (antifungal) - since the combination may decrease the level of ketoconazole in the blood.
- if you have taken the medicine mifepristone (used to terminate pregnancy) within the last 12 days. Arthrotec® should not be taken within 8-12 days of taking mifepristone.

! Use of the medicine and food

Take the medicine with or after a meal. Swallow the tablet whole with a small amount of water (do not chew the tablet).

! Use of the medicine and alcohol

Do not drink wine or alcoholic beverages during the period of treatment with the medicine.

! Pregnancy and breastfeeding

Do not use the medicine if you are pregnant or breastfeeding or planning to become pregnant or breastfeed.

- Women who could become pregnant must use contraception during the period of treatment with the medicine.
- Women who could become pregnant while under treatment with this medicine should undergo a blood test to rule out pregnancy about a month before starting treatment.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use according to the doctor's instructions!

The dosage and treatment regimen will be determined by the doctor only.

The doctor should determine the lowest effective dose for you for the shortest duration necessary.

Complete the full course of treatment recommended by the doctor.

Even if there is an improvement in your health, do not discontinue treatment with the medicine without consulting the doctor.

Do not exceed the recommended dose!

The tablet must not be crushed/halved/chewed, as it contains an inner core with an enteric coating.

If you took an overdose or if a child accidentally swallowed the medicine, proceed immediately to a hospital emergency room and bring the package of the medicine with you.

If you forget to take this medicine at the required time, take a dose as soon as you remember, unless it is time for the next dose. Never take a double dose!

Adhere to the treatment recommended by the doctor.

Do not take medicines in the dark! Check the label and the dose each time you take your medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult the doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of the medicine may cause side effects in some users. Do not be alarmed when reading the list of side effects, you may not experience any of them.

Discontinue use and refer to the doctor immediately in case of:

Severe stomach pain or any sign of bleeding or rupture in the digestive system, such as: black or bloody stools, vomiting blood – very rare.

A serious skin reaction such as: rash, blistering or skin inflammations that cause peeling of the skin (e.g.: Stevens-Johnson syndrome) – very rare.

Symptoms of severe hypersensitivity (rash, shortness of breath or difficulty breathing, swelling of the face and around the eyes) – rare.

Symptoms of liver damage: nausea, exhaustion, lethargy, itching, jaundice (yellowing of the skin and whites of the eyes), upper abdominal tenderness, flu-like symptoms – rare.

Symptoms of a cardiac event: chest pain, shortness of breath, weakness, speech disturbances – frequency unknown.

Symptoms of meningitis, e.g.: strong headaches, stiff neck, hoarseness, severe and persistent nausea and vomiting, spinal pain - frequency unknown.

Stroke – frequency unknown.

Side effects that require special attention:

Inflammation of the mouth, inflammation of the esophagus, inflammation of the stomach, inflammation of the duodenum, inflammation of the pancreas, digestive disturbances, purpura (appearance of red or purple spots on the skin – infrequent), changes in blood test results (elevated liver enzymes, low hematocrit), thrombocytopenia, inflammation of the kidneys, decreased urination, hearing disturbances.

In women – chest pain, abnormal contractions of the womb (frequency – unknown), bleeding in the womb (frequency – unknown), menstrual pain or irregularity (infrequent), abnormal or unexpected vaginal bleeding – infrequent (including post-menopausal bleeding), vaginitis.

Frequently occurring side effects:

Nausea, vomiting, abdominal pain, constipation, diarrhea, indigestion, burping, flatulence, dizziness, headache, itching, rash, sensitivity to sunlight – take protective measures, stomach or intestinal ulcers, sleep disturbances, changes in blood tests relating to liver function.

Diarrhea, sometimes severe, is the most common side effect. The risk for this effect can be reduced by taking the medicine with food. If you take antacids, avoid preparations that contain magnesium, to keep the diarrhea from getting worse.

- Patients above 65 years of age may experience more gastrointestinal effects when treated with a high dosage.

Infrequently occurring side effects:

Swelling of the mouth, reduction in the number of blood platelets (increased chance of bruising and bleeding), urticaria.

Rarely and very rarely occurring side effects:

Inflammation of the liver (may be manifested by yellowing of the skin, headache, fever, chills, general weakness) – rare.

Severe liver function impairment, including liver failure – very rare.

Side effects of unknown frequency:

Heart failure, palpitations, damage to the esophagus, worsening of inflammatory bowel diseases (Crohn's disease and ulcerative colitis), kidney and liver function impairment, epileptic seizures, allergic reaction (including asthma, breathing difficulties, itching, hair loss, inflamed blood vessels - which may cause fever, aches and appearance of purple blotches), symptoms of meningitis, e.g.: strong headaches, fever or loss of consciousness.

Edema (may cause swollen ankles and legs), bloody vomit, psychotic reactions (mental disorder that features loss of contact with reality), swelling of the tongue, mouth ulcers, dry mouth, depression, anxiety, mood swings, irritability, memory problems, confusion, feeling shaky, nightmares, drowsiness, tiredness, vision disturbances, blurred vision, ringing in the ears, changes in sense of taste, loss of appetite, rupture in the womb, non-separation of the placenta, clotting in the amniotic fluid, miscarriage, death of the unborn baby, premature birth and birth defects, low blood pressure, high blood pressure, reduction in the number of white blood cells, anemia.

- If any of the side effects worsens, or if you experience any side effect not listed in the leaflet, consult the doctor.

5. HOW SHOULD THE MEDICINE BE STORED?

Avoid poisoning! This medicine, and any other medicine, must be stored in a safe place out of the reach of children and/or infants, to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by a doctor.

Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.

Store the medicine at a temperature not exceeding 25°C, in a dry place.

6. FURTHER INFORMATION

In addition to the active ingredients, the medicine also contains:

Arthrotec® 50:
Lactose monohydrate, Microcrystalline cellulose, Corn starch, Povidone, Magnesium stearate, Methacrylic acid copolymer type C, Sodium hydroxide, Crospovidone, Hydroxypropyl methyl cellulose, Colloidal silicone dioxide, Hydrogenated castor oil, Talc, Triethyl citrate.

Arthrotec® 75:
Lactose, Microcrystalline cellulose, Maize starch, Polyvidone K30, Magnesium stearate, Methylhydroxypropylcellulose, Crospovidone, Colloidal silicone dioxide, Hydrogenated castor oil, Talc, Methacrylic acid copolymer, Sodium hydroxide, Triethyl citrate.

The medicine contains lactose:
Arthrotec® 50 mg: 13 mg lactose.
Arthrotec® 75 mg: 19.5 mg lactose.

What the medicine looks like and the contents of the package:
Arthrotec® 50 mg: Round, white, biconvex tablet, imprinted with "SEARLE 1411" on one side and 4 'A's on the other side.
Arthrotec® 75 mg: Round, white tablet, imprinted with "SEARLE 1421" on one side and 4 'A's on the other side.

Manufacturer: Piramal Healthcare UK, Ltd.

License holder: Pfizer Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya Pituach 46725.

This leaflet was checked and approved by the Ministry of Health in June 2014.

Registration numbers of the medicine in the National Drug Registry of the Ministry of Health:
Arthrotec® 50 mg: 139 73 28553 00
Arthrotec® 75 mg: 130 98 29104 00