PATIENT INFORMATION LEAFLET
IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986
Available by doctor's prescription only

Macrobid
Capsules

Each capsule contains:
Nitrofurantoin (as macrocrystals) 25 mg
Nitrofurantoin (as anhydrous) 75 mg

For inactive ingredients and allergen information, please see Section 2, "Important information about some of the ingredients of this medicine", and Section 6 – "Further Information".

Read this leaflet carefully in its entirety before you start taking this medicine. This leaflet contains concise information about the medicine. If you have any further questions, please contact your doctor or pharmacist.

This medicine has been prescribed for your disease. Do not give it to other people. It may harm them, even if their disease seems to be the same as yours.

1. WHAT IS THIS MEDICINE INTENDED FOR?

This medicine is used to treat acute uncomplicated urinary tract infections (acute cystitis) caused by sensitive strains of *Escherichia coli* (*E. coli*) or *staphylococcus saprophyticus* in adults and children aged 12 years or older.
Nitrofurantoin is not indicated for the treatment of pyelonephritis (kidney infection) or abscesses in the area surrounding the kidneys.

Therapeutic group:
Systemic antibacterials, nitrofuran derivatives.

2. BEFORE USING THIS MEDICINE

Do not take Macrobid if:

- You are allergic to nitrofurantoin or any of the other ingredients of this medicine (listed in Section 6)

- You have a kidney disease which severely impairs their function (if you are unsure, please ask your doctor).
- You have anuria, oliguria or severe kidney function impairment (creatinine clearance < 60 ml/min, or clinically significant increased serum creatinine levels) – those are contraindications.
- You are 38-42 weeks pregnant, in labour, or about to give birth.
- You have a history of cholestatic jaundice / impaired liver function associated with nitrofurantoin treatment
- Do not use Macrobid in infants younger than 1 month old
- If you are unsure about any of the above, please contact your doctor.

Special warnings and precautions
Before using this medicine, please consult your doctor or pharmacist.

Tell your doctor if you develop acute, sub-acute or chronic pulmonary symptoms. If you have any such reaction, stop taking Macrobid and take appropriate action. There have been reports according to which pulmonary symptoms were part of the causes of death.

There have been rare cases of liver reactions including hepatitis, cholestatic jaundice, active chronic hepatitis and liver necrosis. There have been reports of deaths. The onset of active chronic hepatitis can be hard to identify; therefore, patients must be periodically monitored to identify changes in biochemical examinations that may indicate liver damage. If you develop hepatitis, stop taking the medicine immediately and take appropriate action.

There have been cases of peripheral neuropathy, which may worsen or become irreversible. There have been reports of deaths. Conditions such as kidney failure (creatinine clearance < 60 ml/min, or clinically significant increased serum creatinine levels), anemia, diabetes, electrolyte imbalance, Vitamin B deficiency and debilitating diseases may increase the prevalence of peripheral neuropathy. Patients on long-term treatment must be periodically monitored for changes in their kidney function.

There have been some rare post-marketing reports of inflammation of the optic nerve with various formulations of nitrofurantoin.

Clostridium difficile associated diarrhea (CDAD) has been reported after use of nearly all antibiotics, including nitrofurantoin, and may vary from mild diarrhea to life-threatening colitis. Antibiotic treatment changes the normal intestinal flora, resulting in overproliferation of the *clostridium difficile* bacteria. The possibility of CDAD should be taken into consideration for every patient experiencing diarrhea after antibiotic

treatment. It is important to collect precise medical history, as there have been reports of CDAD occurring more than 2 months after the antibiotic treatment.

Use in children and adolescents
Macrobid is contraindicated for infants under 1 month of age (see section 2 “Do not take Macrobid”). Efficacy and safety in children under 12 years of age have not been established yet.
This medicine is not suitable for children under 12 years of age.
There is no efficacy or safety data regarding the use of this medicine in children under 12 years of age.

Drug interactions
Please tell your doctor or pharmacist if you are taking, or have recently taken, any other medicines, including over-the-counter products and dietary supplements. Some of these products may alter the effect of Macrobid, particularly if you are using the following:

- Antacids containing magnesium trisilicate, when taken concomitantly with nitrofurantoin, reduce its absorption extent and rate.
- If you are taking gout medications such as probenecid or sulfinpyrazone, please tell your doctor.
- Some of these medications may decrease Macrobid’s effect.
- This medicine may affect the results of urine glucose tests.

If you are unsure about any of the above medications, please contact your doctor or pharmacist.

Macrobid with food and drink
Macrobid should be taken with food during the meal. This helps improve absorption and avoid abdominal discomfort.

Pregnancy, breastfeeding and fertility
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
This medicine may be used during pregnancy only if necessary. However, it should not be used during labor and delivery, because at that stage it might affect the baby. Always follow your doctor’s instructions precisely.

Breastfeeding

If you would like to breastfeed, you should consult your doctor first, because this medicine passes into breast milk. Because of nitrofurantoin's potential to cause severe adverse reactions during breastfeeding of babies under 1 month old, a decision must be made whether to stop breastfeeding or stop taking the medication.

Driving and machinery operation
This medicine may cause dizziness or drowsiness. If you are affected this way, do not drive or operate machinery until after such symptoms have disappeared.

Important information about some of the ingredients of this medicine
Macrobid contains lactose and sucrose.
This medicine contains lactose and sucrose, which are 2 types of sugars. If your doctor has told you that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains Allura Red dye (FD&C Red 40), which may cause an allergic reaction.

3. HOW TO TAKE THIS MEDICINE?

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure about the dose or how to take it.

Macrobid is taken by mouth. Capsules should be swallowed whole, with a meal or some milk or yogurt. In this way, the medicine is better tolerated and leads to better results.

The dosing and administration schedule should be determined by the doctor only. The usual standard dosing is:
The recommended dose for adults and children aged 12 years or older is 2 capsules per day, 1 in the morning and 1 in the evening (1 capsule every 12 hours).

Once you start treatment, the symptoms may improve quickly – usually within half a day to 2 days – and then disappear completely. Nevertheless, you must complete the entire treatment course, because even if the discomfort goes away, it does not mean that all the bacteria have been destroyed. Stopping treatment too soon may cause the infection to return, which would be inconvenient for you and clinically undesirable. If the discomfort does not go away after 3 days, you should speak to your doctor.

Do not exceed the recommended dose

Chewing/crushing/breaking
There is no information available about opening the capsules and dispersing their contents. Therefore, it is not recommended to open the capsules. The capsules should be swallowed whole.

If you took too much Macrobid
If you have taken more Macrobid than you should, or if a child has accidentally swallowed the medicine, go to a doctor or an emergency room immediately and take the medicine package with you.

If you forget to take Macrobid
The usual dosing schedule is 1 capsule twice a day. If you missed a dose, try to take it as soon as possible. However, if it is nearly time for the next dose, you should skip the forgotten dose and continue with your usual dosing schedule. Never take a double dose to make up for a missed capsule.
If you forgot to take a few consecutive doses, you should talk to your doctor. He will probably prescribe you a new treatment.
You should keep taking Macrobid as recommended by your doctor.

If you stop taking Macrobid
You doctor will tell you how long you should keep taking this medicine. Do not stop treatment sooner, even if you feel better. Stopping treatment too soon may cause the symptoms to return quickly, causing you more discomfort. It is very important to complete the treatment course.

If you have any further questions concerning the use of this medicine, please ask your doctor or pharmacist.

Never take medicines in the dark! Check the label and dose <u>each time</u> you take a medicine. Wear glasses if you need to. If you have any further questions concerning the use of this medicine, please ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Macrobid can cause side effects in some patients. Do not be alarmed when reading the list of side effects. You will not necessarily have any of them. If you experience any of the side effects listed below or any other side effects, stop taking this medicine and consult your doctor or pharmacist.

All medicines can cause allergic reactions, although serious allergic reactions are rare. If you experience any sudden wheeziness, difficulty in breathing, swelling of the eyelids, face or lips, rash or itching (especially affecting your whole body), stop taking the medicine and go to a doctor immediately.

Taking Macrobid may cause your urine to become dark yellow or brown. This is normal and is no cause for stopping the medicine.

Contact your doctor immediately if you notice any of the following:

- Your lungs may react to Macrobid. This may develop quickly, within a week of starting treatment, or very slowly, especially in elderly patients. This may cause fever, chills, cough and shortness of breath associated with pneumonia and tissue damage.
- In rare cases, Macrobid may cause inflammation of the liver and jaundice (yellowing of the skin or whites of the eyes).
- In some patients, Macrobid may affect blood cells, causing internal hemorrhage, slower blood clotting, sore throat, fever, anemia, sensitivity to cold or feeling cold all the time.
- Increased intracranial pressure, which causes severe headache.
- Severe allergic skin reactions (DRESS syndrome).
- There have been reports of severe skin reactions such as flaking skin, red skin rash or fever accompanied by increased heart rate and severe rash with blistering.

The most frequently reported clinical adverse events were:
Nausea, headache, flatulence, eosinophilia, increased AST (SGOT) levels, increased ALT (SGPT) levels, decreased hemoglobin levels, increased serum phosphorus levels, G6PD deficiency associated anemia, agranulocytosis, leukopenia, granulocytopenia, hemolytic anemia, thrombocytopenia, megaloblastic anemia.

Below is a list of additional adverse events, reported in less than 1% of patients, sorted by organ systems:

Gastrointestinal system: Diarrhea, indigestion, abdominal pain, constipation, vomiting, inflammation of salivary glands, pancreatitis, pseudomembranous colitis.

Nervous system: Dizziness, drowsiness, lazy eye, peripheral neuropathy which may worsen or become permanent, death, asthenia, vertigo, flickering eyes, benign (pseudotumor cerebri) intracranial hypertension, confusion, depression, inflammation of

the optic nerve and psychotic reactions are rarely reported. There have been rare reports of raised fontanelle as indication of benign intracranial hypertension in infants.

Respiratory system: Acute, sub-acute or chronic pulmonary hypersensitivity reactions.

Signs of chronic pulmonary reactions:
General sickness, shortness of breath on exertion, cough, changes in lung function, and pneumonitis and/or fibrosis are common. Rarely, fever may appear.

The severity of chronic pulmonary symptoms and their degree of recovery seem to be associated with the length of treatment after the onset of the first signs. Lung damage may be permanent, even after treatment is stopped. The risk is greater if the chronic pulmonary reactions are not recognized early.

Signs of sub-acute pulmonary reactions:
Fever and eosinophilia appear less frequently in their acute form.

Signs of acute pulmonary reactions:
Fever, chills, cough, chest pain, shortness of breath, pulmonary infiltration with consolidation or pleural effusion on x-ray, and eosinophilia.

Acute reactions usually appear during the first week of treatment and can be reversed by stopping the medicine. They usually go away quickly.

There have been reports of EKG changes associated with pulmonary reactions.
There have been rare reports of cyanosis (bluish skin hue).

Liver: There have been rare cases of reactions of the liver including hepatitis, cholestatic jaundice, active chronic hepatitis and liver necrosis.

Allergies: they include itching, hives, lupus-like symptoms, angioedema; maculopapular, erythematous or eczematous eruptions; anaphylaxis, joint pain; muscle pain; drug-associated fever; chills; vasculitis, hypersensitivity reactions.

Dermatologic: Hair loss, exfoliative dermatitis and erythema multiforme (including Stevens-Johnson syndrome).

Hematological: Cyanosis secondary to methemoglobinemia.

Other: Fever, chills, general sickness, superinfections caused by resistant microorganisms such as strains of *Pseudomonas* or *Candida*.
Aplastic anemia.

If you experience a side effect, if any side effect is worsening, or if you are experiencing a side effect not mentioned in this leaflet, please consult your doctor.

Reporting side effects
Side effects can be reported to the Ministry of Health by clicking on the link "Reporting side effects following medicinal treatment" on the home page of the Ministry of Health (www.health.gov.il), which will lead you to the online form for reporting side effects, or by following the link: https://sideeffects.health.gov.il.

5. HOW TO STORE MACROBID?

- Avoid poisoning! This and all other medicines must be kept in a closed space, out of the sight and reach of children and/or infants, to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use this medicine after the expiry (exp.) date printed on the package. The expiry date refers to the last day of the indicated month.

Store below 25°C.
After opening: Store below 25°C for 7 weeks.

Do not flush medicines down the sink or toilet or dispose of them via the household waste. Ask your pharmacist how to dispose of medicines you no longer use. These measures will help protect the environment.

6. FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains:
Each capsule contains: lactose monohydrate, gelatin, povidone, corn starch, compressible sugar, talc, carbomer 934P, magnesium stearate, titanium dioxide, D&C Yellow No. 10, FD&C Red No. 40, FD&C Blue No. 1, gray ink, purified water.

What Macrobid looks like and the contents of the package

Yellow capsules with “(band) Macrobid (band)” imprinted on one side, and the number “52427-285” imprinted on the other.

Macrobid is sold in a white HDPE 150 ml vial with a wide opening and a childproof cap, which contains 100 capsules and a sachet of moisture absorber.

Manufacturer name and address:
Alvogen Malta Operations Ltd.,
Malta Life Sciences Park, Building I Level 4, Sir Temi Zammit Building,
San Gwann, San Gwann 3000, Malta.

License holder’s name and address:
K.S. Kim International (SK-Pharma) Ltd., 94 Igal Alon St., Tel-Aviv 6789139, Israel.

Drug registration number in the state drug register with the Ministry of Health: 170-53-36483

This leaflet was made in September 2022 in accordance with the MoH guidelines