SAMENVATTING VAN DE PRODUCTKENMERKEN

1. NAAM VAN HET GENEESMIDDEL

Nitrofurantoine Adalvo 100 mg harde capsules met gereguleerde afgifte

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified-release capsule contains 25 mg of nitrofurantoin in the macrocrystalline form and 80.7 mg in the monohydrate form, corresponding to 75 mg of anhydrous nitrofurantoin.

Excipients with known effect:
Each capsule contains 73.50 mg lactose and 34.56 mg confectioner's sugar (containing 32.84 mg sucrose).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified release hard capsule

Each capsule is 19.4 mm long and 6.91 mm wide and has a blue opaque cap with imprinted "NTRF" in white ink and a yellow opaque body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nitrofurantoin Adalvo is indicated for use in adults and children over 12 years old for treatment of acute uncomplicated lower urinary tract infections caused by nitrofurantoin sensitive microorganisms (see section 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Dosage
Adults and children above 12 years old
Adults and children above 12 years old should take 2 capsules per day: 1 in the morning and 1 in the evening (1 capsule every 12 hours).
The general use is for 7 days or at least 3 days after no more infection is detectable in the urine.

Children under 12 years old
Nitrofurantoin Adalvo is a fixed dosage and is not suitable for young children. For small children, the use of other medicinal products containing nitrofurantoin available on the market should be considered.
Nitrofurantoin is contraindicated in neonates.

Method of administration
For oral use

Nitrofurantoin Adalvo is best taken during or right after a meal or with milk or yogurt. This is to ensure the greatest possible bioavailability and to aim for an optimal gastrointestinal tolerance.

4.3 Contraindications

Nitrofurantoin Adalvo is contraindicated in:
- patients with known hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- patients with renal impairment (eGFR below 45 ml/min) or increased serum creatinine;
- patients with G6PD deficiency;
- patients with acute porphyria;
- infants less than 3 months of age due to the theoretical possibility of haemolytic anaemia in the foetus or neonate due to immature erythrocyte enzyme systems;
- patients who previously had pulmonary or hepatic reaction or a peripheral neuropathy after using nitrofurantoin or other nitrofurans.

4.4 Special warnings and precautions for use

Long-term use of nitrofurantoin is not recommended. Lung and liver complications that can be life-threatening can occur during nitrofurantoin treatments (see section 4.8). In the event of occurrence, the treatment should be stopped immediately and the necessary measures should be taken.

Acute, subacute and chronic pulmonary reactions were observed in patients treated with nitrofurantoin. If these reactions occur, nitrofurantoin must be discontinued immediately.

Chronic pulmonary reactions (including pulmonary fibrosis and diffuse interstitial pneumonitis) may develop insidiously, often in elderly patients. Close monitoring of the lung conditions of patients receiving long-term therapy is indicated (especially in the elderly).

Hepatotoxicity
Patient should be monitored closely for signs of hepatitis (particularly in long term use). Hepatic reactions, including hepatitis, autoimmune hepatitis, cholestatic jaundice, chronic active hepatitis, and hepatic necrosis, occur rarely. Fatalities have been reported. The onset of chronic active hepatitis may be insidious, and patients should be monitored periodically for changes in biochemical tests that would indicate liver injury. If hepatitis occurs, the drug should be withdrawn immediately and appropriate measures should be taken.

Existing conditions may mask pulmonary and hepatic side effects. Caution should be exercised when nitrofurantoin is used in patients with pulmonary disease, impaired hepatic function, neurological disorders or allergic diathesis.

During long-term treatment, the patient should be monitored for hepatic or pulmonary symptoms and other signs of toxicity. Discontinue nitrofurantoin if unexplained pulmonary, hepatotoxic, haematological or neurological symptoms occur.

Nitrofurantoin is not effective in the treatment of parenchymal infections of a unilaterally functioning kidney. Infection due to surgery must be ruled out in recurrent or severe cases.

Peripheral neuropathy, which may become severe or irreversible, has occurred (usually develops within 2 months of treatment) and may become life-threatening. Therefore, treatment should be discontinued at the first sign of neural damage (paraesthesia, weakness). Conditions such as renal insufficiency, anaemia, diabetes mellitus, alcoholism, electrolyte disorder, vitamin B deficiency (especially folate deficiency) or debilitating conditions increase the risk of developing peripheral neuropathy.

Urine may be coloured yellow or brown after taking nitrofurantoin. Patients taking nitrofurantoin are susceptible to false positive urinary glucose (if tested for reducing substances).

Nitrofurantoin should be discontinued at signs of haemolysis in subjects with suspected glucose-6-phosphate dehydrogenase deficiency (10% of black people of Black descent and a small percentage of Mediterranean and Near Eastern ethnic groups suffer from G6PD deficiency).

Gastrointestinal reactions can be minimized by taking this medicinal product with food or milk, or by adjusting the dosage.

Excipients
Nitrofurantoin Adalvo contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Nitrofurantoin Adalvo contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interactions with other medicinal products and other forms of interaction

Effects of other medicinal products on nitrofurantoin:
- Foods or agents that delay gastric emptying increase the bioavailability of nitrofurantoin, probably through better dissolution in the gastric juice.
- Carbonic anhydrase inhibitors and urine alkalizing agents can reduce the antibacterial activity of nitrofurantoin.
- Magnesium trisilicate, co-administered with nitrofurantoin, reduces the absorption of nitrofurantoin.
- There may be an antagonism between quinolones and nitrofurantoin: concomitant use is not recommended.
- Probenecid and sulfinpyrazone may decrease the renal excretion of nitrofurantoin.

Effects of nitrofurantoin on other medicinal products/ laboratory tests:
- Typhoid fever vaccine (oral): antibacterial agents inactivate the oral typhoid vaccine.
- Nitrofurantoin may affect certain laboratory tests. False positive results or false high readings may occur with urinary glucose tests based on copper sulfate reduction, such as Benedict's reagent and Clinitest (Ames). However, there is no interference with the Clinistix test.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy
A large amount of data in pregnant women has not demonstrated teratogenicity or foetal/ neonatal toxicity. Animal studies do not indicate reproductive toxicity at clinically relevant doses.

If prescribed by a physician, nitrofurantoin can be used during pregnancy.
However, due to the potential risk of haemolysis of the immature red blood cells in infants, it should not be administered during labour and delivery.

Breastfeeding
Nitrofurantoin is excreted in human milk. The small amounts in milk are unlikely to cause haemolytic anaemia in a G6PD-deficient infant. Nitrofurantoin can be used during breastfeeding.

Fertility
A transient arrest in spermatogenesis and decreased sperm counts were observed in men at supratherapeutic doses. Clinical dosages have not been associated with male infertility. No decreased fertility was found in animal studies. A temporary halt in spermatogenesis was observed in rats at high doses.

4.7 Effects on ability to drive and use machines

Nitrofurantoin can cause dizziness and drowsiness. In case any of this occurs, the patient should not drive or operate machinery until symptoms disappear.

4.8 Undesirable effects

The list of adverse reactions for nitrofurantoin are presented below by system organ class. The frequency of adverse reactions, is defined according to the following convention: Very common (≥1/10), Rare (≥1/10,000 to <1/1,000), Not known (cannot be estimated from the available data)

Table 1: Adverse reactions reported with nitrofurantoin

MedDRA System Organ Class	Frequency	Adverse reactions
Infections and infestations	Not known	sialoadenitis
Blood and lymphatic system disorders	Rare	agranulocytosis, eosinophilia, leukopenia, granulocytopenia, thrombocytopenia. aplastic anaemia, megaloblastic anaemia[1]
Immune system disorders	Rare	exfoliative dermatitis, erythema multiforme (including Stevens-Johnson syndrome).
	Not known	allergic skin reactions such as maculopapular, erythematous or eczematous eruptions, urticaria, rash, angioedema. Lupus-like syndrome (associated with lung reactions), anaphylactic reactions, cutaneous vasculitis.
Metabolism and nutrition disorders	Rare	anorexia
Psychiatric disorders[2]	Not known	depression, euphoria, confusion, psychotic reactions, headache[2].
Nervous system disorders	Very common	idiopathic intracranial hypertension
	Not known	peripheral neuropathy (including optic neuritis) with symptoms involving both sensory and motor implications, which may become severe or irreversible, optic neuritis, nystagmus, dizziness, somnolence.
Cardiac disorders	Rare	collapse, cyanosis
Respiratory, thoracic and mediastinal disorders	Not known	acute lung reactions[3] including fever, chills[4], chest pain, dyspnoea, cough, lung infiltration with consolidation or pleural effusion[5] in the chest indicated by *x*-rays, eosinophilia; subacute lung reactions including fever, eosinophilia; chronic lung reactions including fever, cold chills, cough, dyspnoea[6], DRESS-syndrome.
Gastrointestinal disorders	Rare	nausea

MedDRA System Organ Class	Frequency	Adverse reactions
	Not known	vomiting, abdominal pain, diarrhoea, pancreatitis
Hepatobiliary disorders	Rare	cholestatic jaundice, chronic active hepatitis[7].
	Not known	autoimmune hepatitis
Skin and subcutaneous tissue disorders	Very common	alopecia (short term)
	Not known	cutaneous vasculitis
Renal and urinary disorders	Very common	superinfections due to fungi or resistant organisms (such as *Pseudomonas*[8])
	Not known	interstitial nephritis
Congenital, familial and genetic disorders	Rare	haemolytic anaemia / G6PD-deficiency-anaemia
General disorders and administration site conditions	Not known	asthenia, arthralgia

[1] Treatment should be stopped after which blood counts generally return to normal
[2] Treatment should be discontinued at the first sign of neurological and/or psychological implication.
[3] If any of the following respiratory reactions occur, this medicinal product should be discontinued.
[4] Acute pulmonary reactions usually occur within the first week of treatment and are reversible upon discontinuation of treatment.
[5] Demonstrated by x-ray diagnosis.
[6] Chronic pulmonary reactions are rare in patients receiving continuous treatment for 6 months or more, and are more common in elderly patients. Pulmonary reactions are sometimes accompanied by changes in the ECG. Lung function can be permanently damaged even after discontinuation of treatment.
[7] Fatalities were reported. Cholestatic jaundice is generally associated with short-term treatment (usually up to 2 weeks). Chronic active hepatitis, occasionally leading to necrosis, is generally associated with long-term treatment (usually 6 months). Treatment should be discontinued at the first sign of hepatotoxicity. See section 4.4.
[8] These are limited to the genitourinary tract, because the suppression of normal bacterial flora does not occur elsewhere in the body.

Reporting of suspected side effects

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

Symptoms and signs of overdose include stomach irritation, nausea and vomiting.

Management

There is no specific antidote, however, nitrofurantoin can be haemodialysed if necessary. Standard treatment consists in the induction of emesis or gastric lavage in cases of recent ingestion (within one hour). Monitoring of full blood count, hepatic function and pulmonary function tests are recommended. A high fluid intake should be maintained to promote urinary excretion of nitrofurantoin.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinfectives for systemic use, ATC code: J01XE01

Mechanism of action
Nitrofurantoin belongs to the nitrofurans group. Therapeutic active concentrations are only reached in the urine. The antibacterial activity of nitrofurantoin is highest in acidic urine, and pH values above 8 may cause the loss of its effect. The exact mechanism of action is unknown. Several mechanisms of action are described. Nitrofurantoin inhibits a number of bacterial enzymes. It also inhibits bacterial ribosomal proteins and thus causes complete inhibition of bacterial protein synthesis. Nitrofurantoin may also cause damage in the DNA.

Resistance
Resistance rarely develops during the treatment with nitrofurantoin, possibly because nitrofurantoin has different modes of action. Resistance may occur in case of long-term treatment. Plasmid-encoded resistance has been reported in *E.coli*. Reduced sensitivity has been observed among ESBL-producing gut bacteria. Resistance may be due to the loss of nitrofuran reductases that generates the active intermediates.

Breakpoints
European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for MIC testing are presented below.

	MIC breakpoint (mg/L)
Staphylococcus saprophyticus (uncomplicated urinary tract infections only)	S ≤64, R >64 mg/L
Enterococcus faecalis (uncomplicated urinary tract infections only)	S ≤64, R >64 mg/L
Streptococcus agalactiae (uncomplicated urinary tract infections only)	S ≤64, R >64 mg/L
Escherichia coli (uncomplicated urinary tract infections only)	S ≤64, R >64 mg/L.

The following lists contain an overview of relevant microorganisms for the indication:
Usually sensitive species:
Staphylococcus aureus
Staphylococcus epidermis
Staphylococcus saprophyticus
Enterococcus faecalis
Escherichia coli

Species in which acquired resistance may be a problem:
Citrobacter spp
Enterobacter spp
Klebsiella spp

Inherently resistant organisms
Proteus spp
Pseudomonas spp
Serratia spp

5.2 Pharmacokinetic properties

Clinical Pharmacology
Each Nitrofurantoin Adalvo capsule contains two forms of nitrofurantoin. 25% of the dose is macrocrystalline nitrofurantoin, which has slower dissolution and absorption than the nitrofurantoin microcrystals. The remaining 75% of the dose is microcrystalline nitrofurantoin contained in a powder mixture which on exposure to gastrointestinal fluids, forms a gel matrix resulting in a modified release of active ingredient over time.

Absorption
Nitrofurantoin is rapidly absorbed in the upper part of the small intestine. Intake with food or milk increases absorption. Plasma concentrations are low at therapeutic doses with peak levels usually less than 1 μg/ml.

Distribution
Nitrofurantoin is 60-77% bound to plasma albumin. Distribution takes place over intra- and extracellular tissue components. Small amounts of nitrofurantoin may cross the placenta.

Biotransformation
Approximately 60% of the administered dose of nitrofurantoin is primarily metabolised by enzymatic route to microbiologically inactive aminofurans, which may cause changes in urine colour to brown.

Elimination
The half-life in blood or plasma is estimated to be approximately 60 minutes. Approximately 20-25% of the 2 daily doses of nitrofurantoin is recovered unchanged from the urine. On average, peak concentrations of over 100 μg/ml are reached in the urine.

5.3 Preclinical safety data

Nitrofurantoin was not carcinogenic when fed to female Holtzman rats for 44.5 weeks or to female Sprague-Dawley rats for 75 weeks. Two chronic rodent bioassays utilising male and female Sprague-Dawley rats and two chronic bioassays in Swiss mice and in BDF1 mice revealed no evidence of carcinogenicity.

Nitrofurantoin presented evidence of carcinogenic activity in female B6C3F1 mice as shown by increased incidences of tubular adenomas, benign mixed tumors, and granulosa cell tumors of the ovary. In male F344/N rats, there was an increased incidence of uncommon kidney tubular cell neoplasms, osteosarcomas of the bone, and neoplasms of the subcutaneous tissue. In one study involving subcutaneous administration of 75 mg/kg nitrofurantoin to pregnant female mice, lung papillary adenomas of unknown significance were observed in the F1 generation.

Nitrofurantoin has been shown to induce point mutations in certain strains of *Salmonella typhimurium* and forward mutations in L5178Y mouse lymphoma cells. Nitrofurantoin induced increased numbers of sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells but not in human cells in culture. Results of the sex-linked recessive lethal assay in Drosophila were negative after administration of nitrofurantoin by feeding or by injection. Nitrofurantoin did not induce heritable mutation in the rodent models examined.

The significance of the carcinogenicity and mutagenicity findings relative to the therapeutic use of nitrofurantoin in humans is unknown.

The administration of high doses of nitrofurantoin to rats causes temporary spermatogenic arrest; this is reversible on discontinuing the medicine. Doses of 10 mg/kg/day or greater in healthy human males may, in certain unpredictable instances, produce a slight to moderate spermatogenic arrest with a decrease in sperm count.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Talc (E 553b)
Maize starch
Carbomer 971P

Povidone K30 (E 1201)
Lactose monohydrate
Sucrose
Magnesium stearate (E 470b)

Capsule shell:
Iron oxide yellow (E 172)
Iron oxide black (E 172)
Titanium dioxide (E 171)
Gelatin
Indigo Carmine (E 132)

Printing ink
Shellac (E 904)
Propylene glycol (E 1520)
Strong ammonia solution (E 527)
Water, purifed
Potassium hydroxide (E 525)
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Do not store above 25° C.

6.5 Nature and contents of the packaging

Carton box containing PVC-Aclar/Aluminium blisters.

Pack sizes of 2 capsules, 14 capsules or 20 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other instructions

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORIZATION HOLDER

Adalvo Limited
Malta Life Science Park,
Level 1, Building 4,
Sir Temi Zammit Buildings,
San Gwann, SGN 3000,
Malta

8 NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

RVG 129327

9 DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 20 maart 2023

10 DATUM VAN HERZIENING VAN DE TEKST