URIFAST Capsules (Nitrofurantoin monohydrate/macrocrystals)

Composition

URIFAST is a hard gelatin capsule shell containing the equivalent of 100 mg of nitrofurantoin in the form of 25 mg of nitrofurantoin macrocrystals and 75 mg of nitrofurantoin monohydrate.

Dosage Form

Capsules

Pharmacology

Pharmacodynamics

Mechanism of Action

The mechanism of the antimicrobial action of nitrofurantoin is unusual among antibacterials. Nitrofurantoin is reduced by bacterial flavoproteins to reactive intermediates which inactivate or alter bacterial ribosomal proteins and other macromolecules. As a result of such inactivations, the vital biochemical processes of protein synthesis, aerobic energy metabolism, DNA synthesis, RNA synthesis and cell wall synthesis are inhibited. Nitrofurantoin is bactericidal in urine at therapeutic doses.The broad-based nature of this mode of action may explain the lack of acquired bacterial resistance to nitrofurantoin, as the necessary multiple and simultaneous mutations of the target macromolecules would likely be lethal to the bacteria.

Interactions with Other Antibiotics

Antagonism has been demonstrated *in vitro* between nitrofurantoin and quinolone antimicrobials. The clinical significance of this finding is unknown.

Development of Resistance

Development of resistance to nitrofurantoin has not been a significant problem since its introduction in 1953. Cross-resistance with antibiotics and sulfonamides has not been observed and transferable resistance is, at most, a very rare phenomenon.

Nitrofurantoin has been shown to be active against most strains of the following bacteria both *in vitro* and in clinical infections:

Aerobic and facultative Gram-positive microorganisms:

Staphylococcus saprophyticus

Aerobic and facultative Gram-negative microorganisms:

Escherichia coli

At least 90 percent of the following microorganisms exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for nitrofurantoin. However, the efficacy of nitrofurantoin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled trials.

Aerobic and facultative Gram-positive microorganisms:

Coagulase-negative staphylococci (including Staphylococcus epidermidis)

Enterococcus faecalis

Staphylococcus aureus

Streptococcus agalactiae

Group D streptococci

Viridans group streptococci

Aerobic and facultative Gram-negative microorganisms:

Citrobacter amalonaticus

Citrobacter diversus

Citrobacter freundii

Klebsiella oxytoca

Klebsiella ozaenae

Nitrofurantoin is not active against most strains of *Proteus* species or *Serratia* species. It has no activity against *Pseudomonas* species.

Susceptibility Test Methods:

When available, the clinical microbiology laboratory should provide cumulative results of the *in vitro* susceptibility test results for antimicrobial drugs used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth or agar) (1) or equivalent with standardized inoculum concentrations and standardized concentrations of nitrofurantoin powder. The MIC values should be interpreted according to the criteria provided in Table 1.

Diffusion Technique: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure (2) requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 300 µg of nitrofurantoin to test the susceptibility of

microorganisms to nitrofurantoin. The disk diffusion interpretive criteria are provided in Table 1.

Table 1. Susceptibility interpretive criteria for nitrofurantoin

Pathogen	Susceptibility Interpretive Criteria					
	Minimum Inhibitory Concentrations (µg/mL)			Disk Diffusion (zone diameter in mm)		
	S	I	R	S	I	R
Enterobacteriaceae	δ32	64	ε128	ε17	15-16	δ14
Staphylococcus spp.	δ32	64	ε128	ε17	15-16	δ14

A report of *Susceptible* indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the urine reaches the concentrations usually achievable. A report of *Intermediate* indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone, which prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the urine reaches the concentrations usually achievable; other therapy should be selected.

Quality Control: Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard nitrofurantoin powder should provide the following range of values noted in Table 2.

Table 2. Acceptable quality control ranges for nitrofurantoin

QC Strain	Acceptable Quality Control Ranges	
	Minimum Inhibitory Concentration (µg/mL)	Disk Diffusion (zone diameter in mm)
Escherichia coli ATCC 25922	4 – 16	20-25
Enterococcus faecalis ATCC 29212	4 – 16	NA[a]
Staphylococcus aureus ATCC 29213	8 – 32	NA[a]
Staphylococcus aureus ATCC 25923	NA[a]	18-22

[a]Not applicable

Pharmacokinetics

Each **URIFAST** capsule contains two forms of nitrofurantoin. Twenty-five percent is macrocrystalline nitrofurantoin, which has slower dissolution and absorption than nitrofurantoin monohydrate. The remaining 75% is nitrofurantoin monohydrate contained in a powder blend which, upon exposure to gastric and intestinal fluids, forms a gel matrix that releases nitrofurantoin over time. Based on urinary pharmacokinetic data, the extent and rate of urinary excretion of nitrofurantoin from the 100 mg **URIFAST** capsule are similar to those of the 50 mg or 100 mg nitrofurantoin macrocrystals capsule. Approximately 20-25% of a single dose of nitrofurantoin is recovered from the urine unchanged over 24 hours.

Plasma nitrofurantoin concentrations after a single oral dose of the 100 mg nitrofurantoin monohydrate/macrocrystals capsule are low, with peak levels usually less than 1 mcg/mL.

Nitrofurantoin is highly soluble in urine, to which it may impart a brown colour. When nitrofurantoin monohydrate/macrocrystals capsule is administered with food, the bioavailability of nitrofurantoin is increased by approximately 40%.

Indications

URIFAST is indicated only for the treatment of acute uncomplicated urinary tract infections (acute cystitis) caused by susceptible strains of *Escherichia coli* or *Staphylococcus saprophyticus.*

Nitrofurantoin is not indicated for the treatment of pyelonephritis or perinephric abscesses.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of **URIFAST** and other antibacterial drugs, **URIFAST** should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Nitrofurantoins lack the broader tissue distribution of other therapeutic agents approved for urinary tract infections. Consequently, many patients who are treated with nitrofurantoin are predisposed to persistence or reappearance of bacteriuria. Urine specimens for culture and susceptibility testing should be obtained before and after completion of therapy. If persistence or reappearance of bacteriuria occurs after treatment with **URIFAST**, other therapeutic agents with broader tissue distribution should be selected. In considering the use of **URIFAST**, lower eradication rates should be balanced against the increased potential for systemic toxicity and for the development of antimicrobial resistance when agents with broader tissue distribution are utilized.

Dosage and Administration

URIFAST capsules should be taken with food.

Adults and paediatric patients over 12 years: One 100 mg capsule every 12 hours for seven days.

Contraindications

Anuria, oliguria or significant impairment of renal function (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine) are contraindications. Treatment of this type of patient carries an increased risk of toxicity because of impaired excretion of the drug.

Because of the possibility of hemolytic anemia due to immature erythrocyte enzyme systems (glutathione instability), the drug is contraindicated in pregnant patients at term (38-42 weeks gestation), during labor and delivery, or when the onset of labor is imminent. For the same reason, the drug is contraindicated in neonates under one month of age.

URIFAST is contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with nitrofurantoin.

URIFAST is also contraindicated in those patients with known hypersensitivity to nitrofurantoin.

Warnings and Precaution

General

Prescribing **URIFAST** in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Drug Interactions

Antacids containing magnesium trisilicate, when administered concomitantly with nitrofurantoin, reduce both the rate and extent of absorption. The mechanism for this interaction probably is absorption of nitrofurantoin onto the surface of magnesium trisilicate.

Uricosuric drugs, such as probenecid and sulfinpyrazone, can inhibit renal tubular secretion of nitrofurantoin. The resulting increase in nitrofurantoin serum levels may increase toxicity and the decreased urinary levels could lessen its efficacy as a urinary tract antibacterial.

Drug/Laboratory Test Interactions

As a result of the presence of nitrofurantoin, a false positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions but not with the glucose enzymatic test.

Pulmonary Reactions

Acute, subacute or chronic pulmonary reactions have been observed in patients treated with nitrofurantoin. If these reactions occur, **URIFAST** should be discontinued and appropriate measures taken. Reports have cited pulmonary reactions as a contributing cause of death.

Chronic pulmonary reactions (diffuse interstitial pneumonitis or pulmonary fibrosis or both) can develop insidiously. These reactions occur rarely and generally in patients receiving therapy for six months or longer. Close monitoring of the pulmonary condition of patients receiving long-term therapy is warranted and requires that the benefits of therapy be weighed against potential risks.

Hepatotoxicity

Hepatic reactions, including 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.

Neuropathy

Peripheral neuropathy, which may become severe or irreversible, has occurred. Fatalities have been reported. Conditions such as renal impairment (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine), anemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency and debilitating disease may enhance the occurrence of peripheral neuropathy. Patients receiving long-term therapy should be monitored periodically for changes in renal function.

Optic neuritis has been reported rarely in post-marketing experience with nitrofurantoin formulations.

Hemolytic Anemia

Cases of hemolytic anemia of the primaquine-sensitivity type have been induced by nitrofurantoin. Hemolysis appears to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients. This deficiency is found in 10% of Blacks and a small percentage of ethnic groups of Mediterranean and Near-Eastern origin. Hemolysis is an indication for discontinuing **URIFAST**; hemolysis ceases when the drug is withdrawn.

Clostridium difficile-associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including nitrofurantoin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Information for Patients

Patients should be advised to take **URIFAST** with food (ideally breakfast and dinner) to further enhance tolerance and improve drug absorption. Patients should be instructed to complete the full course of therapy; however, they should be advised to contact their physician if any unusual symptoms occur during therapy.

Patients should be advised not to use antacid preparations containing magnesium trisilicate while taking **URIFAST.**

Patients should be counseled that antibacterial drugs including **URIFAST** should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When **URIFAST** is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by **URIFAST** or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Lactation

Nitrofurantoin has been detected in human breast milk in trace amounts. Because of the potential for serious adverse reactions from nitrofurantoin in nursing infants under one month of age, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Paediatric Use

URIFAST is contraindicated in infants below the age of one month. Safety and effectiveness in paediatric patients below the age of twelve years have not been established.

Geriatric Use

Clinical studies of nitrofurantoin monohydrate/macrocrystal did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Spontaneous reports suggest a higher proportion of pulmonary reactions, including fatalities, in elderly patients; these differences appear to be related to the higher proportion of elderly patients receiving long-term nitrofurantoin therapy. As in younger patients, chronic pulmonary reactions generally are observed in patients receiving therapy for six months or longer. Spontaneous reports also suggest an increased proportion of severe hepatic reactions, including fatalities, in elderly patients.

In general, the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy in elderly patients should be considered when prescribing **URIFAST**. This drug is known to be substantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Anuria, oliguria or significant impairment of renal function (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine) are contraindications. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

Undesirable Effects

In clinical trials of nitrofurantoin monohydrate/macrocrystals, the most frequent clinical adverse events that were reported as possibly or probably drug-related were nausea (8%), headache (6%) and flatulence (1.5%). Additional clinical adverse events reported as possibly or probably drug-related occurred in less than 1% of patients studied and are listed below within each body system in order of decreasing frequency:

Gastrointestinal: Diarrhea, dyspepsia, abdominal pain, constipation, emesis

Neurologic: Dizziness, drowsiness, amblyopia

Respiratory: Acute pulmonary hypersensitivity reaction

Allergic: Pruritus, urticaria

Dermatologic: Alopecia

Miscellaneous: Fever, chills, malaise

The following additional clinical adverse events have been reported with the use of nitrofurantoin:

Gastrointestinal: Sialadenitis, pancreatitis. There have been sporadic reports of pseudomembranous colitis with the use of nitrofurantoin. The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment.

Neurologic: Peripheral neuropathy, which may become severe or irreversible, has occurred. Fatalities have been reported. Conditions such as renal impairment (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine), anemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency and debilitating diseases may increase the possibility of peripheral neuropathy.

Asthenia, vertigo and nystagmus also have been reported with the use of nitrofurantoin.

Benign intracranial hypertension (pseudotumor cerebri), confusion, depression, optic neuritis and psychotic reactions have been reported rarely. Bulging fontanels, as a sign of benign intracranial hypertension in infants, have been reported rarely.

Respiratory: Chronic, subacute or acute pulmonary hypersensitivity reactions may occur with the use of nitrofurantoin.

Chronic pulmonary reactions generally occur in patients who have received continuous treatment for six months or longer. Malaise, dyspnea on exertion, cough and altered pulmonary function are common manifestations which can occur insidiously. Radiologic and histologic findings of diffuse interstitial pneumonitis or fibrosis, or both, are also common manifestations of the chronic pulmonary reaction. Fever is rarely prominent.

The severity of chronic pulmonary reactions and their degree of resolution appear to be related to the duration of therapy after the first clinical signs appear. Pulmonary function may be impaired permanently, even after cessation of therapy. The risk is greater when chronic pulmonary reactions are not recognized early.

In subacute pulmonary reactions, fever and eosinophilia occur less often than in the acute form. Upon cessation of therapy, recovery may require several months. If the symptoms are not recognized as being drug-related and nitrofurantoin therapy is not stopped, the symptoms may become more severe.

Acute pulmonary reactions are commonly manifested by fever, chills, cough, chest pain, dyspnea, pulmonary infiltration with consolidation or pleural effusion on x ray and eosinophilia. Acute reactions usually occur within the first week of treatment and are reversible with cessation of therapy. Resolution often is dramatic.

Changes in EKG (e.g., non-specific ST/T wave changes, bundle branch block) have been reported in association with pulmonary reactions. Cyanosis has been reported rarely.

Hepatic: Hepatic reactions, including hepatitis, cholestatic jaundice, chronic active hepatitis and hepatic necrosis occur rarely.

Allergic: Lupus-like syndrome associated with pulmonary reaction to nitrofurantoin has been reported. Also, angioedema; maculopapular, erythematous or eczematous eruptions; anaphylaxis; arthralgia; myalgia; drug fever and chills have been reported. Hypersensitivity reactions represent the most frequent spontaneously-reported adverse events in worldwide postmarketing experience with nitrofurantoin formulations.

Dermatologic: Exfoliative dermatitis and erythema multiforme (including Stevens-Johnson syndrome) have been reported rarely.

Hematologic: Cyanosis secondary to methemoglobinemia has been reported rarely.

Miscellaneous: As with other antimicrobial agents, superinfections caused by resistant organisms, e.g., *Pseudomonas* species or *Candida* species can occur.

In clinical trials of nitrofurantoin monohydrate/macrocrystals, the most frequent laboratory adverse events (1-5%), without regard to drug relationship, were as follows: eosinophilia, increased AST (SGOT), increased ALT (SGPT), decreased hemoglobin, increased serum phosphorus. The following laboratory adverse events also have been reported with the use of nitrofurantoin: glucose-6-phosphate dehydrogenase deficiency anemia, agranulocytosis, leukopenia, granulocytopenia, hemolytic anemia, thrombocytopenia, megaloblastic anemia. In most cases, these hematologic abnormalities resolved following cessation of therapy. Aplastic anemia has been reported rarely.

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the National Pharmacovigilance Programme of India by calling on 1800 180 3024.

By reporting side effects, you can help provide more information on the safety of this product.

Overdosage

Occasional incidents of acute overdosage of nitrofurantoin have not resulted in any specific symptoms other than vomiting. Induction of emesis is recommended. There is no specific antidote, but a high fluid intake should be maintained to promote urinary excretion of the drug. Nitrofurantoin is dialyzable.

Storage and Handling Instructions

Store at controlled room temperature (59° to 86°F or 15° to 30°C).

Packaging Information

URIFAST: Strip of 10 Capsules

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