Monuril®

Abbreviated Summary Product Characteristics

Name of Medicinal Product:
Monuril 3g granules for oral solution
Each single-dose sachet contains 5.631g fosfomycin – trometamol (1:1) equivalent to 3g fosfomycin. It is a white granular powder for oral solution with a characteristic odour and flavour of mandarin. **Therapeutic Indications: Monuril is indicated for;** the treatment of acute, uncomplicated cystitis in women and female adolescents and perioperative antibiotic prophylaxis for transrectal prostate biopsy in adult man.
Posology and administration: Posology: Acute, uncomplicated cystitis in women and female adolescents (>12years of age): 3 g fosfomycin once Perioperative antibiotic prophylaxis for transrectal prostate biopsy: 3 g fosfomycin 3 hours prior to the procedure and 3 g fosfomycin 24 hour safter the procedure. **Renal impairment:** Use of Monuril is not recommended in patients with renal impairment (creatinin clearance < 10 ml/min, see section 5.2 of the SmPC). **Paediatric population:** The safety and efficacy of Monuril in children aged below 12 years of age have not been established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SmPC. **Warnings and special precautions for use:** Hypersensitivity reactions, including anaphylaxis and anaphylactic shock, may occur during fosfomycin treatment and may be life-threatening (see section 4.8 of the SmPC). If such reaction occurs, fosfomycin should never be re-administered and an adequate medical treatment is required. Clostridioides difficile-associated diarrhea, Clostridioides difficile-associated colitis and pseudo-membranous colitishave been reported with fosfomycin and may range inseverity from mild to life-threatening (see section 4.8 of the SmPC). Therefore, it is important to consider this diagnosis in patients who present with diarrhea during or subsequent to the administration of fosfomycin. Discontinuation of therapy with Fosfomycin and the administration of specifictreatment for Clostridioides difficile should be considered. Medicinal products that inhibit peristalsis should not be given. Paediatric population, The safety and efficacy of Monurilin children below 12 years of age have not been established. Therefore, this medicine should not be used in this age group (see section 4.2 of the SmPC).Persistent infections and male patients, In case of persistent infections, a thorough examination and a re-evaluation of the diagnosis is recommended as this is often due to complicated urinary tractinfections or the prevalence of resistant pathogens (e.g. Staphylococcus saprophyticus, see section 5.1 of the SmPC). In general, urinary tract infections in male patients have to be considered as complicated UTIs for which this medicinal product is not indicated (see section 4.1 of the SmPC). **Interactions:** Metoclopramide: Concomitant administration of metoclopramide has been shown to lower serum and urinary concentrations of fosfomycin and should be avoided. Other medicinal products that increase gastrointestinal motility may produce similar effects. **Food effect:** Food may delay the absorption of fosfomycin, with consequent slight decrease in peak plasma levels and urinary concentrations. It is therefore preferable to take the medicinal product on an empty stomach or about 2 – 3 hours after meals. Specific problems concerning the alteration in INR: Numerous cases of increased oral anticoagulant activity have been reported in patients receiving antibiotic therapy. Risk factors include severe infection or inflammation, age and poor general health. Under these circumstances, it is difficult to determine whether the alteration in INR is due to the infectious disease or its treatment. However, certain classes of antibiotics are more often involved and in particular: fluoroquinolones, macrolides, cyclins, cotrimoxazole andcertain cephalosporins. **Paediatric population:** Interaction studies have only been performed in adults. Fertility, pregnancy and lactation: **Pregnancy:** Only limited data on the safety of fosfomycin treatment during 1st trimester of pregnancy (n=152) are available. These data do not raise any safety signal forteratogenicity so far. Fosfomycin crosses the placenta. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3 of theSmPC). Monuril should only be used during pregnancy, if clearly necessary. **Breast-feeding:** Fosfomycin is excreted in human milk in low quantities. If clearly necessary, a single dose of oral fosfomycin can be used during breast-feeding. Fertility: No data in humans are available. Driving and using machinery: Monuril oral solution to date, has had noinfluence on the ability to drive and use machines but patients should be informed that dizziness has been reported. **Undesirable effects:** Common (≥1/100 to <1/10): Headache,Dizziness, Diarrhea, Nausea, Vulvovaginitis, Dyspepsia, abdominal pain. UNCOMMON (≥ 1/1,000 to <1/100): Vomiting, rash, Uritcaria, Pruritus. Not KNown: (<1/10,000)Anaphylactic reactions: including anaphylactic shock & hypersensitivity, Antibiotic-associated colitis, Angioedema. **Overdose:** Experience regarding the overdose of oral fosfomycin is limited. Cases of hypotonia, somnolence, electrolytes disturbances, thrombocytopenia and hypoprothrombinemia have been reported with parenteral use of fosfomycin. In the event of overdose, the patient must be monitored (particularly for plasma/serum electrolyte levels), and treatment should be symptomatic and supportive. Rehydration is recommended to promote urinary elimination of the active substance. Fosfomycin is effectively cleared from the body by haemodialysis with a mean elimination half-life of approximately 4 hours.
Legal category: POM

MARKETING AUTHORISATION HOLDER: Zambon S.p.A. via Lillo del duca, 10 20091-Bresso, Milano, Italy
MARKETING AUTHORISATION NUMBER: PA1441/2/2
Marketed in Ireland by: Fannin Ltd, Fannin House, Leopardstown, Dublin 18
Reporting of suspected adverse reactions For a copy of the SmPC or further medical information, please contact medical@dccvital.com
Adverse events should be reported. Reporting forms and information can be found on the HPRA website (www.hpra.ie) or by emailing medsafety@hpra.ie. Adverse events should also be reported to Fannin Ltd, Tel 01 1290 7000. Alternatively, send via email to medical@dccvital.com Date of last PI revision: Aug 2020 IE20/001/SmPC-Jul 20. SmPC Jul 2020 EXPIRY DATE: Jul 2023.

FIRST LINE AGAINST UTI[1]

Monuril 93.8% efficacy. Low resistance.[1]

Treatment of acute lower uncomplicated urinary tract infections caused by pathogens sensitive to Fosfomycin in females above 12 years of age.[4]

Perioperative antibiotic prophylaxis for transrectal prostate biopsy in adult men.[4]

Fannin

Zambon 1906

MONURIL®: therapeutic indications and posology[4]

3g

INDICATION

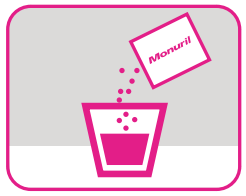
- Treatment of ***acute lower uncomplicated urinary tract infections*** caused by pathogens sensitive to Fosfomycin in ***females above 12 years of age*** [4]
- Prioperative antibiotic prophylaxis for transrectal prostate biopsy in adult man [4]

POSOLOGY

single ***3 g*** sachet

one ***3 g*** sachet 3 hours before surgery and one ***3 g*** sachet 24 hours after surgery [4]

Take one sachet, 3 hours before procedure



Dissolve one sachet into a glass of water

Swallow solution

- Fosfomycin 3g granules for oral solution is for oral administration and should be taken on an empty stomach [4]
- The contents of a sachet should be dissolved in a glass of water and taken immediately after preparation [4]

The advantages of Monuril®

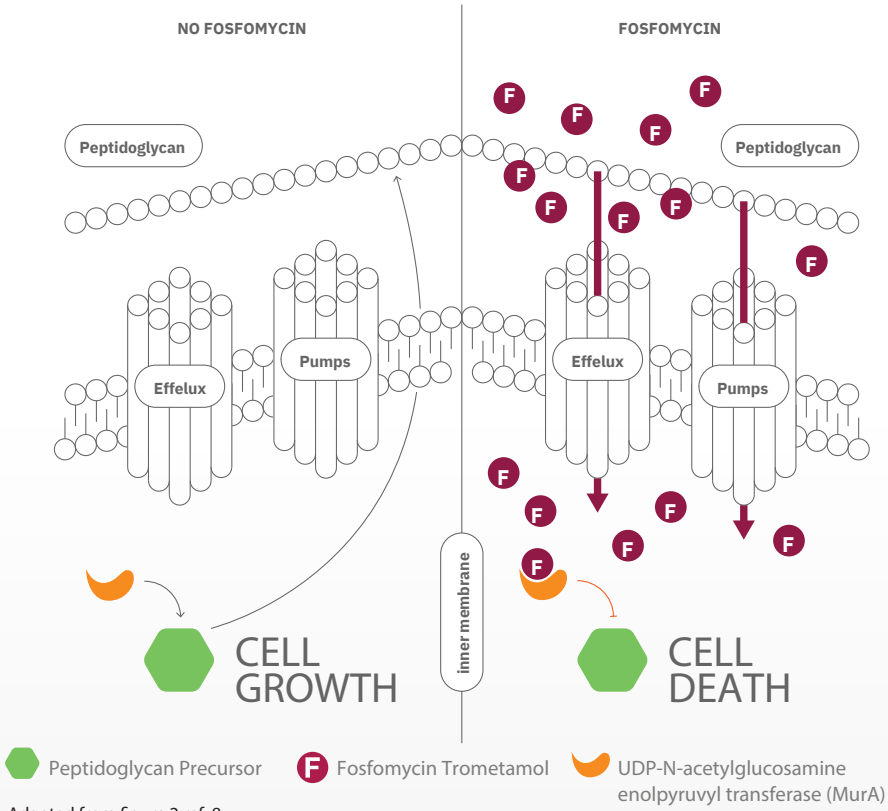
Compared with multi-day regimens, single-dose Fosfomycin Trometamol therapy offers[5]:

Low resistance[9]	without cross- or parallel-resistance to other frequently used antibiotics[9]
Effective treatment[9]	in the antibiotic prophylaxis of TR-PB2[9]
Good tolerability[10]	with a low rate of adverse events[10]
Unique mechanism of action[11]	irreversibly inhibit at an early stage of bacterial cell wall biosynthesis[11]
Better compliance[12]	compared with multi-day regimens[12]

References

1. EAU Guidelines. Edn. presented at the EAU Annual Congress Copenhagen 2018. ISBN 978-94-92671-01-1
2. https://emedicine.medscape.com/article/233101-overview#a2. Accessed on Dec. 2018
3. https://emedicine.medscape.com/article/233101-overview#a3. Accessed on Dec. 2018
4. SmPC Monuril
5. Foxman B, Dis Mon 2003; 49:53-70
6. Concia et al. Therapeutic recommendations for antibiotic prophylaxis in urology. Col 26 Suppl 1, 2014
7. Webb NB, Woo HH BJU International 2002; 89, 824–828
8. Castañeda-García A et al. Antibiotics 2013; 2: 217-236
9. Cai T et al. J Urol 2017 35: 221–228
10. Webb NB, Woo HH BJU International 2002; 89, 824–828
11. Castañeda-García A et al. Antibiotics 2013; 2: 217-236
12. Michalopoulos AS et al. Int J Infect Dis 2011; 15 (11): e732-e739
13. Rosen DA et al. PloS Medicine 2007; 4(12):e329
14. Mezzatesta ML et al. Int J Antimicrob Agents 2017; 49: 763-766

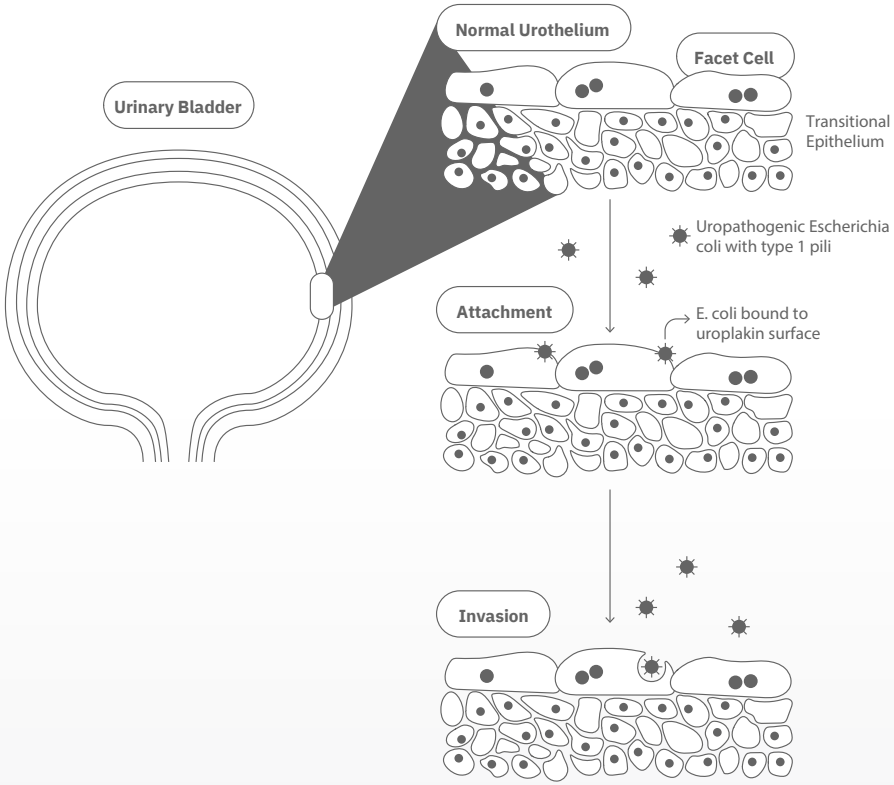
Fosfomycin Trometamol has a unique Mechanism of Action (MoA)[8]



Adapted from figure 2 ref. 8

Fosfomycin Trometamol inhibits the phosphoenolpyruvate transferase enzyme, thereby **irreversibly blocking the condensation of uridine diphosphate-N-acetylglucosamine with p-enolpyruvate,** one of the first steps in bacterial cell wall synthesis. [4]

Fosfomycin Trometamol has a unique Mechanism of Action (MoA)[8]



Adapted from figure 1 ref. 13

Fosfomycin Trometamol can also **reduce bacterial adhesion to bladder mucosa**, which can be **a predisposing factor for recurring infections.**[2]

Antimicrobial prophylaxis for TR-PB*: Fosfomycin Trometamol

Cai T et al. World J Urol 2017; 35(2): 221-8

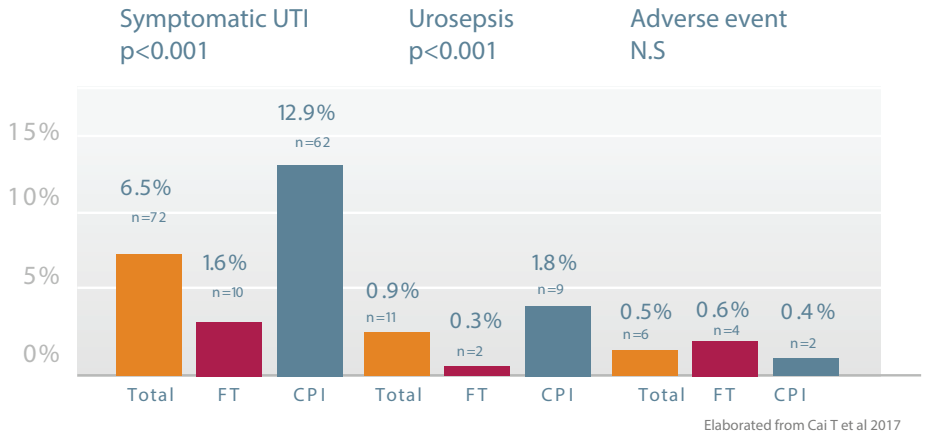
- TR-PB is one of the most commonurological interventions worldwide for prostate cancer diagnosis
- Even after 40 years of clinical use, fosfomycin maintains its full and excellent bactericidal activity against both the Gram-positive bacteria and, the Gram-negatives[6]

UTI is one of the most common complications with a range of 13-20%[7]

*TR-PB=transrectal ultrasound-guidedprostate biopsy.

Main Results

Main outcome measures: rate of symptomatic UTIs–rate of ADRs



Elaborated from Cai T et al 2017

73.6% **of symptomatic UTIs were caused by fluorquinolone-resistant strains N= 53 (out of 72 total symptomatic UTIs)**

Fosfomycin Trometamol antibacterial activity

In vitro antibacterial activity of antimicrobial agents by gradient test method against 106 urinary isolates. [14]

Species	Susceptibility rate (%)								
	n	Fosfomycin		Nitrofurantoin		Amoxicillin/ clavulanic acid		Ciprofloxacin	
		MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S
ESBL *Escherichia coli*	24	4	100	32	92	>256	50	>32	0
KPC *Klebsiella pneumoniae*	56	48	82	>512	28	>256	0	>32	0
Proteus mirabilis	10	1	100	>512	0	1	100	0.02	100
Meticillin-resistant *Staphlococcus saprophyticus*	16	12	100	12	100	4	NA	>32	50

ESBL, extended-spectrum β-lactamase-producing; MIC_{90}, minimum inhibitory concentration required to inhibit the growth of 90% of organisms; %S, percentage susceptibility.

Conclusions

Antibiotic prophylaxis with Fosfomycin Trometamol for TR-PB had a lower rate of adverse events and a lower rate of symptomatic UTIs as compared with CIP. Fosfomycin Trometamol appears as an attractive alternative prophylactic regimen in prostate biopsies.