AUSTRALIAN PRODUCT INFORMATION –

HIPREX® (METHENAMINE HIPPURATE) TABLET

1 NAME OF THE MEDICINE

Methenamine hippurate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 g of methenamine hippurate.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

White, oblong-shaped tablet, coded HX with score line on one surface and plain on the other face.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For prophylaxis or suppression of bacteriuria associated with chronic or recurrent infection of the urinary tract.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults and Children 12 years or older: 1 tablet twice daily, with or without food.

Not recommended for use in children under 12 years.

Method of Administration

For oral administration.

The tablets may be halved or crushed and taken with water if the patient is unable to swallow whole tablets.

Special populations

Renal impairment: No dose adjustments for patients with mild or moderate renal insufficiency.

Methenamine hippurate is not recommended for use by patients with neurogenic bladder, renal tract abnormalities or using long-term catheters. (see Section 4.3 Contraindications).

4.3 CONTRAINDICATIONS

1. Hypersensitivity or allergy to methenamine hippurate, formaldehyde or to any of the excipients listed in section 6.1 List of Excipients.
2. Severe renal failure (eGFR < 10 mL/min/1.73m^2), kidney infection, severe dehydration, or gout.
3. Severe hepatic impairment.
4. Metabolic acidosis.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The underlying causes and risk factors for urinary tract infections should be investigated, and changes to perineal hygiene, sexual practices, urinary voiding and diet to maintain the normal urinary tract flora may be indicated before pharmacological interventions.

The effectivity of methenamine hippurate as a prophylactic agent depends on the acidity of urine, the bacterial species and counts in urine, their susceptibility to methenamine, and the exposure interval to formaldehyde that is hydrolysed from methenamine (see Section 5.1 Pharmacodynamic Properties – Mechanism of Action). Methenamine may be ineffective when the urinary tract is colonised by new species,

when bacteria multiply quickly under certain conditions, or when bacteria migrate from the lower urinary tract to the kidneys, therefore patients should be encouraged to consult their doctor at the onset of signs and symptoms of infection.

Bacteriological analysis of a urine sample is recommended to confirm the clinical diagnosis. When antibiotic treatment of bacteriuria or urinary tract infection is indicated, prophylaxis with methenamine hippurate should be stopped until infection is cleared, and urine becomes sterile ($<10^4$ counts per mL).

Use in the elderly

The elderly are at higher risk of urinary tract infections because of changes in oestrogen levels (women), prostate problems (men), incontinence, increased use of medications, surgical or medical interventions including catheters, or decreased mobility and personal hygienic practices. No difference in the safety of methenamine hippurate in the elderly compared to the younger population has been observed.

Paediatric use

Hiprex is not recommended for children under 12 years of age (see Section 4.2 Dose and Method of Administration).

Effects on laboratory tests

In laboratory tests using acid hydrolysis of urine during pregnancy, the presence of methenamine or formaldehyde can result in unmeasurably low oestriol results. Enzymatic hydrolysis will provide more accurate results.

Methenamine can affect the determination of steroids, catecholamines and 5-hydroxyindole acetic acid in urine and give false results depending on the analytical method used.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

- Sulphonamides: Some sulphonamides may form an insoluble crystalline precipitate with formaldehyde in urine, therefore concurrent administration with methenamine should be avoided.
- Alkalising agents: Methenamine hydrolyses into the therapeutically active formaldehyde under acidic conditions in urine, therefore concomitant use with agents that make urine alkaline or urinary alkalising agents such as potassium citrate or acetazolamide reduce the effectivity of methenamine and should be avoided.
- Antacids might cause an increase of urine pH and hence decrease the effect of methenamine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no human data available on fertility. Data from studies in rats do not indicate any effects on female fertility, while effects on male fertility have not been adequately tested (see Section 5.3 Preclinical safety data).

Use in pregnancy – Pregnancy Category A

There is inadequate evidence of safety of methenamine hippurate in human pregnancy, but it has been in wide use for many years without apparent ill consequence. Animal studies are insufficient with respect to reproductive toxicity.

In limited studies in pregnant rabbits with methenamine hippurate at approximately 3 times the clinical dose based on body surface area, there was increased post-implantation loss resulting in lower litter sizes and a limited occurrence of foetal deformities including shortness of tail and malrotation of limbs. No effects on development were noted at doses equivalent to the clinical dose. Methenamine hippurate, administered at approximately 3 times the clinical dose, based on body surface area, did not adversely affect the fertility of female rats. Effects on male fertility have not been adequately studied.

As a precautionary measure, it is preferable to avoid the use of methenamine hippurate during pregnancy.

Use in lactation

Methenamine hippurate is excreted in human milk, but at therapeutic doses of Hiprex no effects on the breastfed newborn or infant are anticipated.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Hiprex has no, or negligible, effects on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety of methenamine hippurate is estimated from its well-established use and published literature on studies involving small numbers of patients. Adverse effect frequencies are defined as:

Very common (≥1/l0)

Common (≥1/100 to <1/10)

Uncommon (≥1/1000 to <1/100)

Rare (≥ 1/10 000 to <1/1000)

Very rare (<1/10 000)

Not known (cannot be estimated from the available data).

System Organ Class		
	Uncommon	*Not known*
Gastrointestinal disorders	Nausea, vomiting, gastric irritation	Diarrhoea, abdominal pain
Skin and subcutaneous tissue disorders	Rashes, pruritis	
Renal and urinary disorders	Irritation of the bladder, dysuria Albuminuria and haematuria have been reported with higher doses (4 to 8 grams daily for 3 to 4 weeks)	

Occasionally superinfection with yeast may occur. At high dosage, chemical cystitis leading to dysuria may occur.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: urinary antibacterial agent, ATC code: J01XX05

Mechanism of action

Hiprex contains methenamine hippurate, a salt of methenamine and hippuric acid, which is absorbed and excreted rapidly.

Methenamine hippurate is a urinary antibacterial agent with a wide spectrum covering both gram-positive and gram-negative organisms. Urinary antibacterial activity can be shown within 30 minutes of administration.

The antibacterial action of methenamine hippurate arises from the slow release of formaldehyde when methenamine is hydrolysed in acidic urine.

Formaldehyde denatures the proteins and nucleic acid of bacteria, in particular E. coli, enterococci and staphylococci. *Enterobacter aerogenes* is generally resistant while urea- splitting bacteria such as *Proteus* and *Pseudomonas* species are inhibited by methenamine only when urine is sufficiently acidic.

A formaldehyde concentration above 25 micrograms per mL of urine maintained for about 2 hours is effective as a bactericidal. Higher urinary pH, flow rates and frequency decrease the formation, concentration and exposure time of formaldehyde and therefore its effectivity.

Clinical trials

The authors of a Cochrane review of methenamine hippurate for prevention of urinary tract infections (Lee et al, 2012) concluded that methenamine hippurate may be effective for preventing UTI in patients without renal tract abnormalities, particularly when used for short term prophylaxis, but that it does not appear to work in patients with neuropathic bladder or in patients who have renal tract abnormalities.

In a randomised, double blind, long term, crossover study (Cronberg et al, 1987), 1 g twice daily of methenamine hippurate was compared with placebo for its preventive effect on recurrent attacks of acute cystitis. Methenamine hippurate and placebo were interchanged every six months for two years. Out of 21 enrolled patients, 14 completed the first year and 13 both years of treatment, which permitted the evaluation of 27 patient years. There were 52 episodes of acute cystitis caused by reinfection: 41 occurred during placebo treatment and only 11 during the methenamine hippurate regimen ($p<0.01$).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration, methenamine is rapidly absorbed from the gastrointestinal tract, with a peak plasma concentration of about 30 mg/L occurring approximately 1-2 hours after ingestion of a single dose. It then declines with a mean elimination half-life of about 4 hours.

The peak plasma concentration from twice daily dosing is about 35 mg/L at steady-state, indicating that no drug accumulation takes place.

Distribution

The average distribution volume was about 0.56 L/kg, which is similar to the total body water in adults.

Metabolism

A small proportion of methenamine is degraded by stomach acid to formaldehyde, which is absorbed and quickly converted to formic acid – which in turn is oxidised to carbon dioxide and water or eliminated quickly through the kidneys. The remaining methenamine is unchanged until excreted by the kidneys.

Excretion

Excretion is by both tubular secretion and glomerular filtration. About 82% of a single methenamine dose is recovered intact in urine within 24 hours, while about 88% is recovered from 1 g twice daily dosing after a 12-hour interval.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Limited in vitro tests indicate that methenamine is non-mutagenic to Salmonella typhyimurium strains in the presence of S9, but some mutagenic effects with metabolic activation were observed after nitrosation.

Carcinogenicity

In limited studies, no evidence of carcinogenic activity was found in mice and rats, and methenamine did not induce neoplasms.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Magnesium stearate, colloidal anhydrous silica, povidone.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine (See also Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 °C. Keep container tightly closed/airtight.

6.5 NATURE AND CONTENTS OF CONTAINER

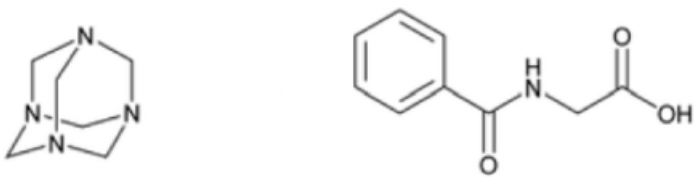
Bottle; 20 or 100 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Methenamine hippurate is a white to off-white powder. It is freely soluble in water.

Chemical name: 2-benzamidoacetic acid; 1,3,5,7-tetrazatricyclo[3.3.1.1^{3,7}] decane.

Molecular formula: $C_{15}H_{12}N_5O_{31}$

Molecular weight: 319.36 g/mol

CAS number: 5714-73-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

(S3) Pharmacist Only Medicine

8 SPONSOR

iNova Pharmaceuticals (Australia) Pty Limited

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Toll free: 1800 630 056

9 DATE OF FIRST APPROVAL

4th July 1991

10 DATE OF REVISION

7th April 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	New Product Information document