NEW ZEALAND DATA SHEET
HIPREX

1 PRODUCT NAME
HIPREX 1 g tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 1 g of methenamine hippurate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
White, oblong-shaped tablet, coded HX with score line on one surface and plain on the other face. Score line is not an aid for breaking the tablet.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Methenamine hippurate tablets are indicated for prophylaxis or suppression of bacteriuria associated with 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.

In cases of alkaline urine pH, supply of acidifying agent could be needed.

Use in patients with structural urinary tract abnormalities: Methenamine hippurate has not been shown to be effective in patients with structural urinary tract abnormalities.

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.

4.3 Contraindications
- Hypersensitivity or allergy to methenamine hippurate, formaldehyde or to any of the excipients listed in section 6.1.
- Severe renal failure (eGFR < 10 mL/min/1.73m2), kidney infection, severe dehydration, and gout.
- Severe hepatic impairment.
- 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).

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 Interaction with other medicines and other forms of interaction

- Alkaline agents reduce the effect of methenamine and should be avoided, antacids might cause an increase of urine pH and hence decrease the effect of methenamine.
- Concurrent use with sulphonamides increases the risk of crystalluria.
- Depending on analytical procedure, methenamine might affect the determination of steroid, catecholamine and 5-hydroxyindole acetic acid leading to incorrect results.
- HIPREX should not be given concurrently with sulphonamides because of the possibility of crystalluria.
  Alkaline agents reduce the effect of methenamine and should be avoided, as antacids might cause an increase of urine pH and hence decrease the effect of methenamine.

4.6 Fertility, pregnancy, and lactation

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.

A moderate amount of data on pregnant women (between 300-1000 pregnancies) has not shown signs of malformations or foetal/neonatal toxicity. Animal studies do not indicate reproductive toxicity (see section 5.3). The use of HIPREX may be considered during pregnancy, if the benefits outweigh the risks.

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.

Fertility

There are no human studies regarding fertility and methenamine hippurate.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

4.7 Effects on ability to drive and use machines

HIPREX has no, or negligible, influence 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	**Frequency**	
	Uncommon	*Not known*
Gastrointestinal disorders	Nausea, vomiting, gastric irritation	Diarrhoea, abdominal pain
Skin and subcutaneous tissue disorders	Rashes, pruritus	
Renal and urinary disorders	Irritation of the bladder, dysuria, Albuminuria and haematuria have been reported with high 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 of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose
Toxicity: 8 g to a 2½-year old child resulted in moderate intoxication.

Symptoms: Nausea, vomiting, vertigo, tinnitus, and metabolic acidosis may occur. Irritating effect on the urinary tract with albuminuria and haematuria.

Treatment: The treatment is symptomatic and supportive, the use of an anti-emetic and drinking copious quantities of water. Bladder symptoms can be treated by the consumption of copious quantities of water and 10 – 15 g of bicarbonate of soda.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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.

Pharmacodynamic effects

HIPREX is active against microorganisms, which usually cause urinary tract infection, e.g., *Escherichia coli* and *Aerobacter aerogenes*. The substance has decreased effect on urea-degrading bacteria, e.g., *Pseudomonas* and some strains of *Proteus*. Urea-degrading bacteria hydrolyse the urea to

ammonium hydroxide, which is basic and increases urinary pH. This results in reduced hydrolysis of methenamine to formaldehyde.

Clinical trials

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 urinary tract infections in patients without renal tract abnormalities, particularly when used for short term prophylaxis. Efficacy in patients with neuropathic bladder or in patients who have renal tract abnormalities was not established.

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. Of the 21 enrolled patients, 14 patients completed the first year and 13 patients completed 2 years of treatment, which permitted the evaluation of 27 patient years. Fifty-two (52) episodes of acute cystitis caused by reinfection were reported. Forty-one (41) occurred during placebo treatment and 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

Non- clinical data reveal no special hazard for humans based on repeated dose toxicity studies. No carcinogenicity or genotoxicity data are available for methenamine hippurate. Methenamine did not demonstrate any carcinogenic potential in long term studies in rodents.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate, povidone.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from date of manufacture.

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container.

Bottle; 20 or 100 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MEDICINE SCHEDULE

General Sale

8 SPONSOR

iNova Pharmaceuticals (New Zealand), Ltd
c/- Simpson Grierson
88 Shortland Street,
Auckland 1141

Telephone: Toll-free 0508 375 394

9 DATE OF FIRST APPROVAL

31 December 1969

10 DATE OF REVISION OF THE TEXT

15 June 2023

SUMMARY TABLE OF CHANGES

Date	Changes
15th June 2023	New