Medicines Adverse Reactions Committee

Meeting date	9/06/2022	Agenda item	3.2.4
Title	**Methenamine: benefit-risk review**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	**Product name**	**Pack size**	**Sponsor**
Methenamine	Hiprex 1 g tablet	100 tablets	iNova Pharmaceuticals (New Zealand) Limited
		20 tablets	
	U-Tract 1 g tablet	100 tablets	Miro Healthcare Limited
PHARMAC funding	Hiprex 1g tablet (100 tablet bottles) is fully funded on the Pharmaceutical Schedule and is included in the Hospital Medicines List.		
Previous MARC meetings	none		
International action	none		
Prescriber Update	none		
Classification	General sale medicine		
Usage data	[redacted]. U-Tract has not been marketed in New Zealand.		
Advice sought	**The Committee is asked to advise:** • Whether the benefit-risk profile of methenamine hippurate for prevention of recurrent urinary tract infection is favourable • Whether any regulatory action such as a change in the classification is recommended • Whether any communication in addition to MARC's Remarks is needed to inform consumers and healthcare professionals about the benefit-risk profile of methenamine hippurate.		

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1 PURPOSE

Methenamine hippurate (also known as hexamine hippurate) is a urinary antibacterial agent intended for 'suppression or elimination of urinary tract bacteria' [1].

Methenamine hippurate (Hiprex) is a 'grandfathered' medicine that was available in New Zealand before the 1969 Food and Drug Act and subsequent Medicines Act 1981 came into force. Medicines that were already on the market prior to 1969 were accepted without evaluation [2]. Methenamine hippurate has therefore not undergone a rigorous benefit-risk evaluation consistent with today's standards.

There is renewed interest in the use of methenamine hippurate as an alternative to low-dose daily antibiotic prophylaxis for the prevention of recurrent urinary tract infection (UTI) in women [3, 4].

Medsafe therefore considers it timely to review the efficacy and safety of methenamine hippurate to ensure that the benefit-risk balance of this historically approved medicine is favourable.

2 BACKGROUND

2.1 Methenamine hippurate

Methenamine (also known as hexamine, hexamethylenetetramine, urotropine, aminoform) was discovered in 1859 and was first used as a urinary antiseptic medicine in 1894 [5, 6].

Methenamine hippurate is the salt formed from methenamine ($C_6H_{12}N_4$) and hippuric acid ($C_9H_9NO_3$).

Figure 1. Chemical structure of methenamine (left) and hippuric acid (right). Source: PubChem [7]

A related medicine, methenamine mandelate, the salt formed from methenamine and mandelic acid, is available in other countries.[1]

2.1.1 Mechanism of action

Methenamine is a prodrug that converts to formaldehyde and ammonia in an acidic environment [5, 8]. (Box 1, Figure 1)

[1] Mandelamine (methenamine mandelate) was previously available in New Zealand but the approval lapsed in 1991.

Box 1. Chemical equation showing the conversion of methenamine to ammonia and formaldehyde

Figure 2. Molecular structure of methenamine and its decomposition products formaldehyde and ammonia [5]

Formaldehyde denatures bacterial proteins and nucleic acid [5, 7] by forming an irreversible -CH2 cross-link between the primary amine groups of proteins and nearby nitrogen atoms in protein or DNA. [5, 7].

Hippuric acid maintains a low urine pH, driving the conversion of methenamine to formaldehyde and ammonia. A formaldehyde concentration above 25 micrograms per mL of urine maintained for about 2 hours is needed to provide bactericidal activity. Higher urinary pH, flow rates and frequency decrease the formation, concentration and exposure time of formaldehyde and therefore reduce its antibacterial effect [9, 10].

Methenamine hippurate has activity against both gram-positive and gram-negative organisms, including *E. coli*, enterococci, and staphylococci. Urea-splitting bacteria such as *Proteus* and *Pseudomonas* species are inhibited by methenamine only when urine is sufficiently acidic. *Enterobacter aerogenes* is generally resistant. [9, 10]

2.1.2 Pharmacology

The usual dose of methenamine hippurate for adults and children 12 years or older is 1g twice daily taken by mouth. [9, 10]

The following information on the pharmacological properties of methenamine hippurate is available in the Australian product information. [9, 10]

Absorption: Methenamine is rapidly absorbed after oral administration. Peak plasma concentration from twice daily dosing is about 35 mg/L at steady state, indicating that there is no drug accumulation.

Distribution: The average volume of distribution is about 0.56 L/kg, 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 is then oxidised to carbon dioxide and water, or eliminated via the kidneys.

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

2.2 Data sheets

2.2.1 New Zealand

Methenamine hippurate is classified as a 'general sale' medicine. The Medicines Regulations 1984 do not require the sponsor to provide a data sheet for general sale medicines.

The sponsor provides consumer information about Hiprex on a dedicated website: www.hiprex.co.nz/about-hiprex/. The Hiprex website includes the following information:

- Hiprex is suitable for adults and children over the age of 6 years for protection from recurrent UTIs
- Hiprex is suitable for use in pregnancy – but always speak to your Healthcare Professional before use
- Hiprex is not recommended if you have kidney disease, liver disease, gout or severe dehydration
- Infrequently, people taking Hiprex have reported nausea, vomiting, diarrhoea, rash and painful or difficult urination – consult your Healthcare Professional for full list of side effects

The Hiprex website encourages consumers to see their healthcare professional for advice on whether Hiprex is suitable for them, for a full list of side effects, if they have kidney disease, liver disease, gout or severe dehydration or if pregnant.

Health Navigator provides patient information derived from NZ Formulary and the UK Electronic Medicines Compendium (eMC) patient information leaflet (PIL) for Hiprex (www.healthnavigator.org.nz/medicines/h/hiprex/).

2.2.2 Australia

Ten products containing methenamine hippurate are included on the Australian Register of Therapeutic Products (including Hiprex). An Australian Product Information (PI) is available for two of these products: *ApoHealth Urinary Tract Antibacterial methenamine hippurate* [9] and *Hexamine Micro methenamine hippurate* [10]. These Australian PIs state that methenamine hippurate is indicated for '*prophylaxis or suppression of bacteriuria associated with chronic or recurrent infection of the urinary tract*'.

The Australian PIs also state that methenamine hippurate is not recommended for children under 12 years, and is not recommended for patients with neurogenic bladder, renal tract abnormalities or using long-term catheters. [9, 10]

In Australia, methenamine hippurate is contraindicated in patients with severe hepatic dysfunction, severe renal impairment (eGFR < 10 ml/min/1.73m^2), severe dehydration, metabolic acidosis or gout.

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

Fertility, pregnancy and lactation: Methenamine hippurate is classified as Category A in the Australian categorisation system for prescribing medicines in pregnancy [11]. Category A is defined as *'drugs that have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed'*. The assumption of safety in pregnancy is based on '*wide use for many years without apparent ill consequence'*. Given the lack of data, the Australian PI states 'As a precautionary measure, it is preferable to avoid the use of methenamine hippurate during pregnancy'.

No human data is available on fertility.

Methenamine is excreted in breast milk but the quantities are considered insignificant to the infant.

The Australian PIs for methenamine hippurate list gastrointestinal, dermatological and urological adverse effects, which are reported as either uncommon (between 1/100 and 1/1000) or frequency unknown [9, 10]. (Table 1).

Table 1. Adverse effects listed in the Australian product information for methenamine hippurate [9, 10]

Adverse effect	Frequency
Gastrointestinal disorders	
Gastric irritation Nausea Vomiting	Uncommon
Diarrhoea Abdominal pain	Not known
Skin and subcutaneous disorders	
Rash Pruritis	Uncommon
Renal and urinary disorders	
Irritation of the bladder Dysuria	Uncommon
Albuminuria and haematuria have been reported with high doses (4 to 8 grams daily for 3 to 4 weeks)	

2.3 Usage data

Hiprex (methenamine hippurate) is available as a general sale medicine in 20-tablet and 100-tablet bottles.

[redacted]

[redacted] reflects the change in the Pharmaceutical Subsidy for Hiprex (100-tablet pack size only), which increased from partially to fully funded in December 2019.[2]

[2] PHARMAC consulted on the proposal to increase the subsidy for Hiprex in October 2019. The main themes identified in the consultation were:

- Support for greater use of methenamine hippurate in the context of increasing antimicrobial resistance
- Need for consistency in the naming of the active pharmaceutical ingredient (methenamine *vs* hexamine).
  PHARMAC changed name to methenamine (hexamine) hippurate in the Pharmaceutical Schedule

The [redacted] provide additional insights on the usage of methenamine hippurate in New Zealand.

The **Pharmaceutical Dispensings** app contains usage data for PHARMAC funded medicines dispensed from community pharmacies. The data is sourced from the New Zealand Pharmaceutical Collection data warehouse [12] for the period 1 January 2017 to 31 December 2019. Information on pharmaceutical products dispensed at hospitals, non-funded medicines, and prescriptions that were not dispensed (ie, a medicine was prescribed but patient did not take the prescription to the pharmacy to have it filled) are not included. Self-purchased medicines that are available over the counter without prescription are not included in the Pharmaceutical Collection data.

Figure 3 shows the age and sex distribution of first dispensings for methenamine hippurate for the period 2017 to 2019. As expected, women are more likely to be dispensed methenamine hippurate than men

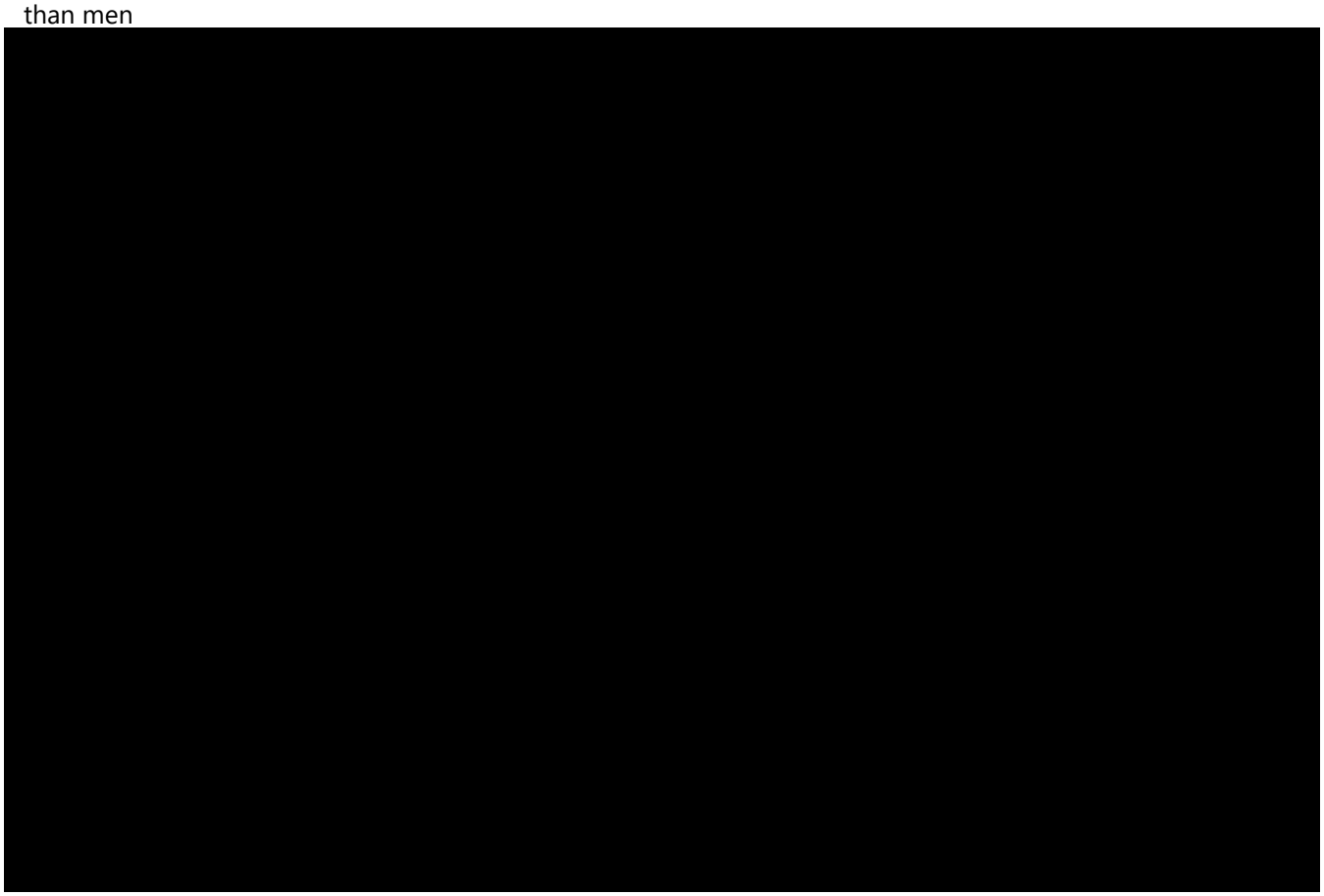


Figure 3. Age and sex distribution of people who were dispensed methenamine hippurate at least once during the year, for the period 2017 to 2019. (Source: Ministry of Health)

Figure 4 shows the ethnicity distribution of first dispensings for methenamine hippurate for the period 2017 to 2019. People who identify as New Zealand European were dispensed methenamine hippurate significantly more than people who identify as other ethnicities. Dispensings increased from 2017 to

- Concern about the evidence supporting the use of methenamine hippurate and the risk of adverse events. Suggestion that guidance be given to prescribers regarding appropriate use of this medicine.
  PHARMAC would consider the possibility of providing prescribers guidance on the appropriate use of this medicine as part of their work promoting responsible use of medicines.

2019 in all groups with known ethnicity, with the greatest proportional increases among MELAA and Pacific Peoples (usage in these groups more than doubled, but the absolute numbers remained low).

Figure 4. Ethnicity of people who were dispensed methenamine hippurate at least once during the year, for the period 2017 to 2019. (Source: Ministry of Health)

The [redacted] combines data from three national collections: National Maternity Collection (MAT), Pharmaceutical Collection (PHARMS) and National Minimum dataset (NMDS). The dataset contains 10 complete years of data on pregnancies (by year of delivery) from 2010-2019, the corresponding information on community dispensed, PHARMAC subsidised medicines, and information on congenital conditions diagnosed during publicly funded inpatient hospitalisations within the first year of the baby's life. The dataset does not include medicines that were dispensed from hospital pharmacies or purchased over the counter. The MAT data includes only pregnancies that resulted in a live birth or a still birth that delivered either in a health care facility (hospital or birthing unit) or at home involving a lead maternity carer (LMC).

Table 3. Number of pregnancies* in which the mother was dispensed methenamine hippurate for years 2010 to 2019, by trimester***.**

[redacted]

3 SCIENTIFIC INFORMATION

3.1 Published literature on efficacy and safety of methenamine hippurate

The Ministry of Health Library performed a comprehensive literature search on 5 April 2022 for evidence on the efficacy and safety of methenamine hippurate in the treatment/prevention of urinary tract infection. The search strategy (Box 2) was modelled on a Cochrane review on the same topic conducted by Lee et al in 2012 [13].

The search identified 149 citations dating from 1946 to 2022. This review focused on 51 citations that were published after the 2012 Cochrane review. The title and abstract for each of these 51 citations was reviewed to identify:

- systematic reviews & meta-analyses that compared methenamine hippurate with either active control or placebo
- prospective randomised controlled trials (RCTs) of methenamine hippurate vs active control or placebo

Studies that examined the efficacy and/or safety of methenamine hippurate in combination with another therapeutic agent were not considered in this benefit-risk evaluation. Studies that were conducted in specific patient groups such as post-catheterisation for gynaecological surgery or in patients with spinal injury were also excluded from further review as such studies do not align with the approved indication. Studies that had only been published as a conference abstract or poster were also not considered.

The review identified one systematic review & meta-analysis [14]) and two RCTs [4, 15]. These studies and the 2012 Cochrane review [13] are summarised below.

An earlier study, by Cronberg et al [16], is also reviewed as it is cited as evidence of efficacy (together with the 2012 Cochrane review [13]) in the Australian product information for methenamine hippurate [9, 10].

Box 2. Strategy for literature search performed on 5 April 2022 (MOH Library)

[redacted]

3.1.1 Systematic reviews and meta-analyses

3.1.1.1 Lee et al (2012)

Methenamine hippurate for preventing urinary tract infections [13]

Objective: This 2012 Cochrane review updated two previous reviews, published in 2002 and 2007, on the benefits and harms of methenamine hippurate for prevention of UTI.

Methods: The authors conducted a literature search in June 2012 involving the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (from 1950), EMBASE (from 1980), and reference lists of articles and abstracts from conference proceedings without language restriction. Manufacturers of methenamine salts were also contacted for unpublished study data. The search included all randomised controlled trials (RCT), randomised cross-over trials and quasi-RCTs of methenamine hippurate used for UTI prophylaxis. Trials evaluating curative treatment were excluded. All at-risk populations for UTI were included in the search, without restriction on age, sex, or underlying condition.

Only studies of methenamine hippurate vs. placebo or 'no treatment' were included. There was no restriction on dose or duration of therapy.

The outcomes of interest were symptomatic UTI with a positive urine culture, quantitative urine culture, and adverse reactions.

Risk of bias was assessed based on allocation concealment, generation of randomisation sequence, inclusion of all randomised participants in the analysis, intention-to-treat analysis, and blinding.

Pooled analysis using a random effects model was conducted to assess symptomatic bacteriuria and bacteriuria. Heterogeneity was assessed on pooled analyses.

Results: The search identified 13 studies that met the inclusion/exclusion criteria, comprising 2032 participants in total [17-29].

Among the 13 included studies, the methenamine hippurate total daily dose ranged from 1 g to 4 g. Two of the studies combined methenamine hippurate with acidification agents (Vitamin C and sodium acid phosphate, respectively)[26, 28].

The study populations were heterogeneous, including people with renal tract calculi [25], women following gynaecological operations [21, 23, 27-29], men undergoing prostate operations [26], pregnant women [17], patients (predominantly women) with recurrent UTI [18], post-menopausal women [19], pre-menopausal women [20] and patients with spinal injury [22, 24].

Six studies involved follow-up of one month or less [21, 23, 25, 26, 28, 29] and seven studies had follow-up periods longer than one month [17-20, 22, 24, 27].

Outcome measures:

- Eight studies measured symptomatic UTI [17-19, 21, 24, 25, 27, 29]. None used the same criteria.
- Twelve studies assessed urine culture, but the threshold level for significant bacteriuria varied between studies.
- Adverse events were poorly described in most studies. One study on pregnant women specifically reported on birth weight, maturity at delivery and foetal mortality and abnormalities [17]. This was the only study to provide a methodology for collecting adverse event data. Five other studies collected AE data at follow-up [18-21, 26], but the methodology was not well described or standardised.
- Four studies [18-20, 22] counted recurrent events, so that a participant could potentially make multiple contributions to the numerator. These studies were not included in the pooled analysis.

Efficacy:

- Symptomatic bacteriuria: six studies with 853 participants in total were included in the analysis [17, 21, 24, 25, 27, 29].
    - RR 0.53 (95% CI 0.24 to 1.18).
    - Heterogeneity was significant (Chi^2 = 17.74, df = 5, P = 0.003; I^2 = 71.8%).
    - Sensitivity analysis did not reveal any difference in overall effect when missing urine tests were assumed to be positive (RR 0.53, 95% CI 0.24 to 1.17; I^2 = 72.4%).
- Bacteriuria: eight studies with 1114 participants in total [21, 23-29].
    - RR 0.67 (95% CI 0.45 to 0.99).
    - Q test was significant using a random effects model (Chi^2 = 28.55, df = 7, P = 0.0002; I^2 = 75.5%), indicating heterogeneity.
- Subgroup analyses: methenamine hippurate may have some benefit in patients without renal tract abnormalities (symptomatic UTI: RR 0.24, 95% CI 0.07 to 0.89; bacteriuria: RR 0.56, 95% CI 0.37 to 0.83), but not in patients with known renal tract abnormalities (symptomatic UTI: RR 1.54, 95% CI 0.38 to 6.20; bacteriuria: RR 1.29, 95% CI 0.54 to 3.07).
- For short-term treatment duration (1 week or less) there was a significant reduction in symptomatic UTI in those without renal tract abnormalities (RR 0.14, 95% CI 0.05 to 0.38).

Safety:

- Adverse events:
    - Nausea was the most common symptom and was noted in 12 patients from a total of six studies
    - In pregnancy, no obvious differences in birth weight, maturity at delivery, foetal abnormality or abortion were noted between treated and untreated patients [17]
    - Other reported AEs were constipation (1 report), rash (4 reports), and diarrhoea, sore throat and stinging in the bladder, each reported once.

Quality of evidence: The authors note that overall, the studies were of poor quality, although more recent studies were better. The two most recent studies [24, 27] demonstrated adequate allocation concealment while the others did not. Most of the other studies were unblinded. These study characteristics are associated with exaggerated treatment effects. Publication bias cannot be completely excluded, as the number of studies available for the pooled analysis was too small to be interpreted using methods such as funnel plots. The number of studies available for the pooled analysis was limited by methodological problems in four studies.

The overall pooled estimates for the major outcome measures were not interpretable because of underlying heterogeneity.

Conclusion: Methenamine hippurate may be effective for preventing UTI in patients without renal tract abnormalities, particularly when used for short-term prophylaxis. It does not appear to work in patients with neuropathic bladder or in patients who have renal tract abnormalities. The rate of adverse events was low, but poorly described. There is a need for further large well-conducted RCTs to clarify this question, particularly for longer term use for people without neuropathic bladder.

Comments:

This Cochrane review is cited as evidence of efficacy in the Australian PI.

The review found no statistically significant difference in symptomatic bacteriuria in the pooled analysis of six studies with 853 participants in total (RR 0.53, 95% CI 0.24 to 1.18). In the pooled analysis of eight studies with 1114 participants in total, there was a reduction in the risk of bacteriuria for methenamine compared to placebo that only just met statistical significance (RR 0.67, 95% CI 0.45 to 0.99). Subgroup analyses suggested that methenamine hippurate may have some benefit in patients without renal tract abnormalities (symptomatic UTI: RR 0.24, 95% CI 0.07 to 0.89; bacteriuria: RR 0.56, 95% CI 0.37 to 0.83), but not in patients with known renal tract abnormalities. When analysed by treatment duration, there was a statistically significant reduction in symptomatic UTI with short-term treatment duration (1 week or less) in those without renal tract abnormalities (RR 0.14, 95% CI 0.05 to 0.38).

Based on these study findings, use of methenamine hippurate should be limited to short-term use in people without renal tract abnormalities. However, the evidence for efficacy is weak due to the heterogeneity of the studies in the pooled analyses.

The approved label claim in New Zealand does not specify duration of treatment or use only in patients without renal tract abnormalities.

3.1.1.2 Bakhit et al (2021)

Use of methenamine hippurate to prevent urinary tract infections in community adult women: A systematic review and meta-analysis [14]

Objective: To conduct a systematic review of methenamine hippurate focusing on RCTs of adult women in the community with a history of UTIs who used methenamine hippurate as treatment or prophylaxis

Method: PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception until 13 July 2020.

Inclusion criteria: RCTs of adult women (aged ≥18 years) with a history of recurrent or confirmed UTIs from the community that compared methenamine hippurate with placebo/no treatment or compared with any antibiotic.

Exclusion criteria: Studies involving women with spinal cord injuries or those with catheters (long-term or short-term after surgery) were excluded as these groups may experience UTI at different rates from the general population. Studies of males and mixed-gender studies for which separate results for women were not available were excluded.

Studies that reported the use of an acidifying agent for the urine (eg, ascorbic acid or sodium dihydrogen phosphate) combined with methenamine hippurate were excluded unless given to both the control and intervention arms.

Primary outcome: UTI manifested by any combination of dysuria, nocturia, urgency, fever, burning, pyuria, frequency, suprapubic pain, loin pain.

Secondary outcomes: adverse events, bacteriuria, antibiotic use, antibiotic resistance.

The Cochrane Risk of Bias Tool was used to assess risk of bias. Treatment effect was calculated using Review Manager 5.

Rate ratios were used for results reporting the number of events only, and risk ratios (RRs) or odds ratios (ORs) were used for results reporting the number of patients with an event. Meta-analysis using a random-effects model was performed when two or more studies or comparisons reported the same outcome.

The I^2 statistic was used to measure heterogeneity among the included trials.

Results: Six RCTs met the study criteria, five of which were more than 30 years old (Table 4). Risk of bias was unclear as the older studies lacked information such as sequence generation, allocation concealment and blinding. Five of the included studies were published RCTs, and one was a clinical trial registry record with results provided. The latter has since been published [30].

A total of 557 participants were included in the trials, of which 447 were analysed. In three studies the comparator was a placebo or control, and in the remaining three studies methenamine hippurate was compared with an antibiotic (trimethoprim in two trials and nitrofurantoin in one trial). One study included an antiseptic perineal wash (povidone-iodine solution) as a second non-antibiotic comparator.

Prevention of UTI:

- Patients remaining asymptomatic after 6- or 12-months treatment[3]:
    - Methenamine hippurate vs. antibiotics showed no significant difference (RR 0.65, 95% confidence interval [CI] = 0.40 to 1.07).
    - Methenamine hippurate versus control (placebo or antiseptic iodine perineal wash) showed no significant difference between groups (RR 1.0, 95% CI = 0.27 to 3.66). Figure 5
- Patients remaining abacteriuric after 12 months:
    - Methenamine hippurate vs. any antibiotic showed no significant difference (RR 0.80, 95% CI = 0.62 to 1.03)
- Number of symptomatic UTI episodes after 6 or 12 months:
    - Methenamine hippurate vs. any antibiotic showed no statistically significant difference (RR 1.95, 95% CI = 0.87 to 4.38).
    - Methenamine hippurate vs. control (placebo or antiseptic iodine perineal wash) showed no statistically significant difference between groups (RR 0.56, 95% CI = 0.13 to 2.35).
- Number of bacteriuric episodes after 12 months:

[3] Participants were treated continuously for 12 months in 3 studies and for 6 months in two studies . Information on the duration of treatment was not available for one study.

    - Methenamine hippurate vs. any antibiotic showed no statistically significant difference between groups (RR 2.09, 95% = CI 0.72 to 6.09).

Adverse events:

- The most common adverse events reported in all studies were nausea, headache, and abdominal pain.
- No statistically significant difference in the number of patients experiencing any adverse events when methenamine hippurate was compared with any antibiotic (odds ratio [OR] 0.77, 95% CI = 0.11 to 5.46), or with control (OR 1.32, 95% CI 0.23 to 7.77).
- No overall difference between methenamine hippurate and any comparator (total OR 0.89, 95% CI = 0.21 to 3.67).

*Strengths: S*tudies at high risk of bias due to confounding variables (such as post-surgery preventive studies and those involving women with indwelling catheters), thereby rendering the results more relevant to women in the community.

Limitations: The literature search identified only six studies that met the inclusion/exclusion criteria for this review, five of which were more than 30 years old, and the most recent study was a clinical trial record. The included studies had considerable clinical and statistical heterogeneity, poor reporting of bacterial resistance and unclear risk of bias. One report included use of methenamine mandelate. Sub-group analyses were not possible due to the paucity of available data.

Table 4 Studies included in review by Bakhit et al [14]

Study Country RCT type	Randomised participants, *n* mean age, years	Intervention, dose, frequency, duration	Comparator, dose, frequency	Follow-up
Brumfitt *et al* (1981) [31] UK Two-arm, parallel	110 (intervention: 35.9; comparator: 31.3)	methenamine hippurate, 1 g, twice daily, 12 months	Nitrofurantoin, 50 mg, twice daily	12 months
Brumfitt *et al* (1983) [32] UK Three-arm, parallel	67 intervention: 38.2; comparator 1: 39.9; comparator 2: 31.7	methenamine hippurate, 1 g, twice daily, 12 months	1: trimethoprim, 100 mg, once nightly; 2: povidone iodine, 10% solution diluted 15 mL to 240 mL water/antiseptic perineal wash, minimum twice daily	12 months
Furness *et al* (1975) [17] Australia Three-arm, parallel	206 all of childbearing age	1: methenamine hippurate, 1 g, twice daily, NR; 2: methenamine mandelate, 1 g, four times daily, NR	no treatment	24 months
Gundersen *et al* (1986) [18] Norway Two-arm, parallel	30 intervention: 74.5; comparator: 74.0	methenamine hippurate, 1 tablet (dose NR), twice daily, 6 months	Placebo, one tablet, twice daily	6 months
Høivik *et al* (1984) [19] Norway Three-arm, cluster	52 intervention 1: 19.1; intervention 2: 28.9; comparator: 29.3	1: methenamine hippurate, 1 tablet (dose NR), twice daily, 12 months 2: methenamine hippurate, 1 tablet (dose NR), once nightly, with one placebo tablet per 12 months	Placebo, two tablets, twice daily	12 months
Botros (2020) [30] US Two-arm, parallel	92 intervention: 70; comparator: 73	methenamine hippurate (dose NR)	Comparator: trimethoprim (dose NR)	12 months

NR not reported

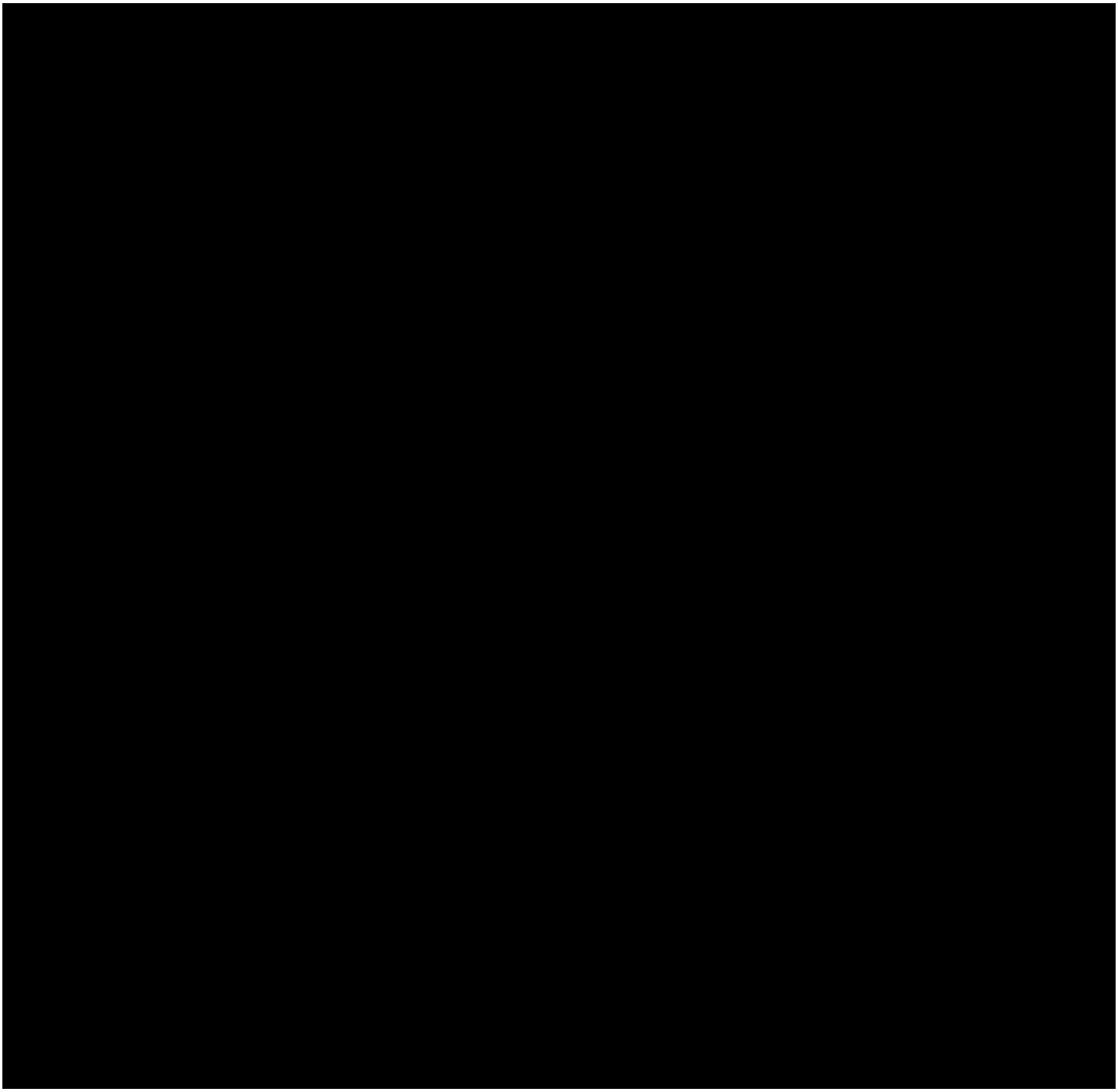


Figure 5. Prevention of UTI meta-analysed outcomes.

[a] Risk of bias: A = random sequence generation (selection bias); B = allocation concealment (selection bias); C = blinding of participants and personnel (performance bias); D = blinding of outcome assessment (detection bias); E = incomplete outcome data (attrition bias); F = selective reporting (reporting bias); and G = other bias. df = degrees of freedom. CI = confidence interval. IV = inverse variance. Log = natural logarithm. RR = rate ratio. SE = standard error. UTI = urinary tract infection.

Figure 6 Number of patients with adverse outcomes: methenamine hippurate versus comparator – sub-grouped by comparator type (any antibiotic, control)

[a] Risk of bias: A = random sequence generation (selection bias); B = allocation concealment (selection bias); C = blinding of participants and personnel (performance bias); D = blinding of outcome assessment (detection bias); E = incomplete outcome data (attrition bias); F = selective reporting (reporting bias); and G = other bias. CI = confidence interval. df = degrees of freedom.

Conclusion: The authors made no firm recommendation about the use of methenamine hippurate for prophylaxis in women but considered that further investigation of methenamine hippurate is warranted given the observed 'trend towards benefit in reducing recurrent UTI' and the minimal reporting of harms.

Comments:
This study was limited by a small number of poorly documented studies most of which were more than 30 years old. The pooled analyses showed no statistically significant difference between methenamine hippurate and either antibiotic, placebo or non-antibiotic comparator when used for 6 -12 months in adult women to prevent UTI.

3.1.2 Randomised controlled trials

3.1.2.1 Harding et al (2022)

Alternative to prophylactic antibiotics for the treatment of recurrent urinary tract infections in women: multicentre, open label, randomised, non-inferiority trial [4]

Objective: To test and compare the efficacy of methenamine hippurate for prevention of recurrent UTI with the current standard prophylaxis of daily low dose antibiotics.

Methods: The ALTAR trial (ALTernative to prophylactic Antibiotics for the treatment of Recurrent urinary tract infections in women) was a pragmatic, multicentre, randomised, open label, non-inferiority trial comparing clinical effectiveness of low dose antibiotic prophylaxis with methenamine hippurate. The study recruited women from eight secondary care urology and urogynaecology centres in the UK from June 2016 to June 2018. (**Error! Reference source not found.**)

Inclusion criteria: Women aged 18 years or older with recurrent UTI requiring prophylactic treatment. Recurrent UTI was defined as at least three episodes of symptomatic UTI in the previous 12 months or at least

two episodes in the past six months. Women who were already taking antibiotic prophylaxis or methenamine hippurate were required to have a three-month washout period without preventive treatment before randomisation.

Exclusion criteria: Women with correctable urinary tract abnormalities.

Intervention: Women were randomised (1:1) to receive antibiotic prophylaxis or methenamine hippurate for 12 months. Patients were stratified by menopausal status (pre- vs peri-/post-menopausal) and UTI frequency (<4 vs ≥4 in the preceding year). Treatment allocation was not masked.

For those randomised to receive antibiotic prophylaxis, nitrofurantoin (50 or 100 mg), trimethoprim (100 mg), or cefalexin (250 mg) given orally once daily was selected, depending on previous urine culture results and individual history of allergy or intolerance. Methenamine hippurate was prescribed as a twice daily oral dose (1 g). Crossover between arms was allowed.

Participants who experienced symptomatic UTI were advised to seek antibiotic treatment in their usual way.

Follow-up: Patients were assessed every three months until 18 months (12 months on treatment and 6 months of follow-up). Assessments included UTI episodes, kidney and liver function tests, urine samples (3-monthly and in the event of symptomatic UTI). Optional perineal swabs at baseline and 6-monthly routine visits. Symptom questionnaires 3-monthly and in the event of symptomatic UTI)

Primary outcome: incidence of self-reported symptomatic, antibiotic-treated UTI over the 12-month treatment period. A UTI was defined as the presence of at least one symptom from a predefined list produced by Public Health England, together with a discrete treatment course of antibiotics.

Statistical analysis: The trial was powered to assess non-inferiority of the absolute difference in UTI incidence over the 12-month treatment period. The non-inferiority margin was a difference of one UTI episode per year.

For the primary outcome, the incidence rate in each group was the total number of UTI episodes divided by the total follow-up (exposure) time, reported with 95% confidence intervals calculated using a resampling procedure (bootstrap). The absolute difference between groups was calculated and reported with a 90% bootstrap confidence interval. Non-inferiority would be concluded if the upper limit of the confidence interval was below one UTI episode/year.

Analysis was conducted using a modified intention-to-treat (ITT) population, which included all participants observed for at least six months.

Prespecified sensitivity analyses were conducted in ITT and per protocol populations (participants achieving ≥90% adherence with preventive treatment; switching between treatment strategies was considered adherent). A *post hoc* sensitivity analysis was conducted in a strict per protocol population that included only those participants achieving ≥90% adherence with initially randomised treatment.

Sensitivity analyses also excluded periods in which participants took therapeutic antibiotics for UTI.

Results:

Self-reported symptomatic, antibiotic-treated UTI over the 12-month treatment period: In the modified ITT, 90 symptomatic, antibiotic treated UTI episodes were reported over 101 person years of follow-up in the antibiotic group, and 141 episodes over 102 person years of follow-up in the methenamine hippurate group. Incidence: 0.89 episodes per person year (95% confidence interval 0.65 to 1.12) in the antibiotic group and 1.38 (1.05 to 1.72) in the methenamine hippurate group (absolute difference 0.49 (90% confidence interval 0.15 to 0.84)). With the upper limit of the 90% confidence interval below the non-inferiority limit of one, methenamine hippurate was found to be non-inferior to antibiotic prophylaxis. The result was confirmed in all sensitivity analysis populations. (Table 5)

Table 5. Incidence of episodes of symptomatic, antibiotic treated, urinary tract infection during 12-

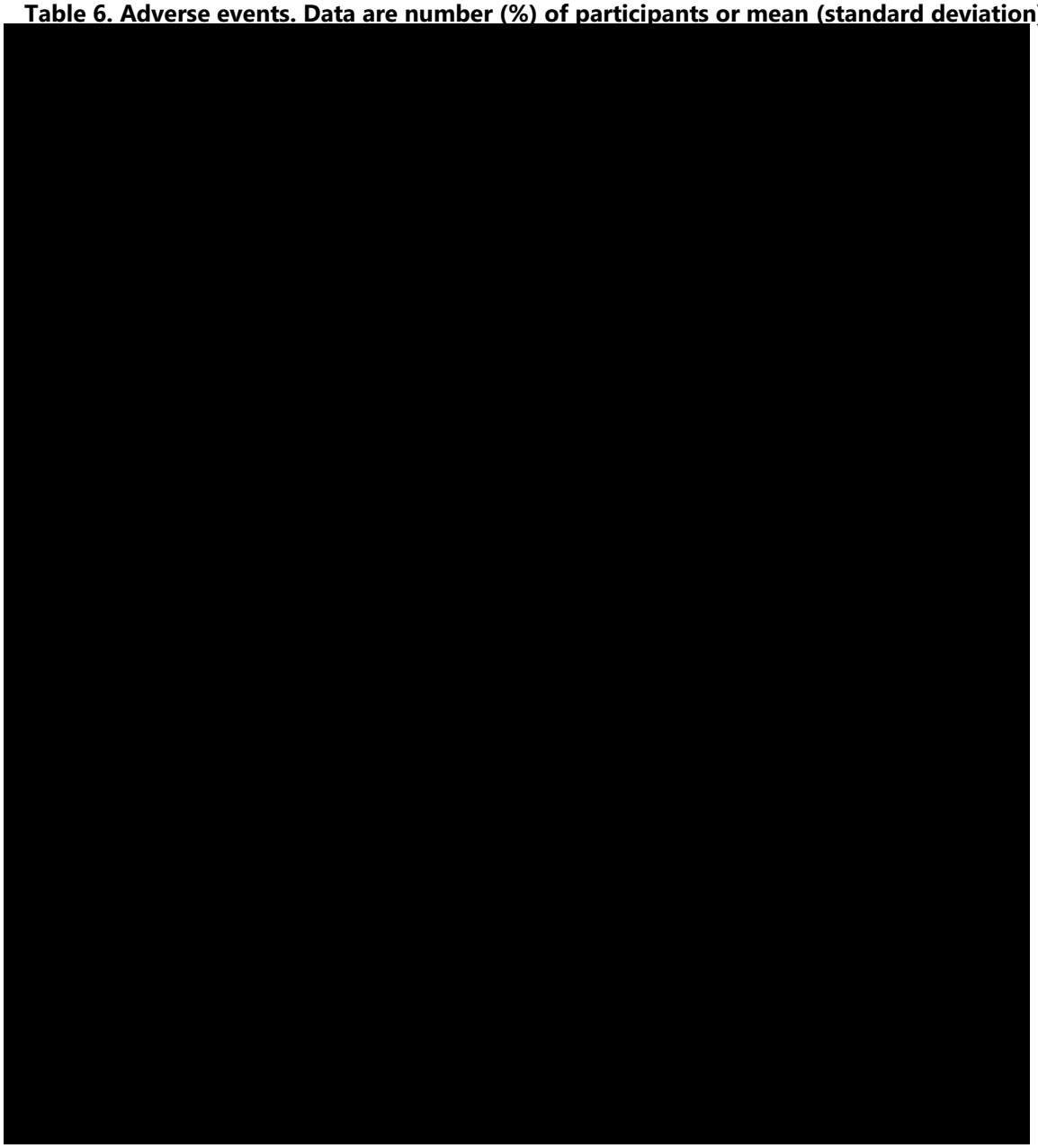
Adverse events: Rates of adverse events and adverse reactions were low and comparable across treatment groups. Two serious adverse reactions (severe abdominal pain and raised alanine transaminase) were reported, both in participants allocated to antibiotic prophylaxis. Kidney and liver function was assessed by blood tests taken every three months. Little difference was observed in the distribution of these measurements between treatment groups or over time. Over the 18-month trial period, four participants allocated to methenamine hippurate were admitted to hospital because of UTI. Six participants who were allocated to methenamine hippurate reported a fever of ≥38°C during a UTI episode (febrile UTI). Table 6

Strengths: The pragmatic trial design allowed for widespread applicability and generalisability. A broad range of eligible participants accurately represented women with recurrent UTI seen regularly in routine clinical practice. Women from a range of geographical and socioeconomic areas were included in the trial Shared decision making between patients and clinicians about the choice of antibiotic was in line with good clinical practice. Patients could crossover between trial arms, reflecting usual care.

Limitations: The unblinded treatment allocation reduced the certainty of the results. The range of prophylactic antibiotics prescribed, and the wide inclusion criteria prevented meaningful subgroup analysis to identify differences in efficacy of individual antibiotic drugs or specific groups of patients who might benefit from either of the trial treatments. The long-term safety of methenamine hippurate was outside of the scope of this trial.

Conclusion: The authors concluded that the trial demonstrated a high level of efficacy for methenamine hippurate for UTI prevention, comparable to low dose antibiotic treatment recommended in current guidelines.

Table 6. Adverse events. Data are number (%) of participants or mean (standard deviation)



Comments:

The primary outcome in this trial was the incidence of symptomatic UTI (requiring treatment with antibiotic over) the 12-month study period, based on the modified ITT analysis. The incidence of antibiotic treated UTI in the antibiotic group was 0.89 compared to 1.38 episodes per person year in the methenamine hippurate group (absolute difference 0.49 episodes [90% CI 0.15 to 0.84]).

The prespecified non-inferiority margin was one episode of symptomatic UTI per person year. This measure was guided by a series of patient focus group meetings to determine a meaningful difference in treatment outcome. As the difference between treatments was less than one episode, the study reported that methenamine hippurate was no worse than antibiotics at preventing urinary tract infection.

However, in each of the primary outcome analyses (modified ITT, ITT and per protocol), the incidence of UTI was significantly higher for patients allocated to methenamine hippurate vs antibiotic prophylaxis (Table 5). For example, in the modified ITT analysis, the incidence rate ratio was 1.52 (1.16 to 1.98).

An editorial by Hoffmann et al [3] published in the same issue of the BMJ notes that the non-inferiority margin used in the trial is likely to inspire debate. However, the study will help to inform discussions with patients on the benefits and harms of preventive treatment options for recurrent UTI, and facilitate shared decision making.

3.1.2.2 Botros et al (2021)

Methenamine hippurate compared with trimethoprim for the prevention of recurrent urinary tract infections: a randomized clinical trial [30]

Objective: To evaluate the difference in rates of recurrent urinary tract infection (UTI) within 1 year when treated with methenamine hippurate for prophylaxis compared with trimethoprim.

Methods: open-label, single-centre, randomized trial comparing the efficacy of methenamine hippurate to trimethoprim for prevention of recurrent UTI at 12 months after starting treatment. Patients were enrolled at one tertiary female pelvic medicine and reconstructive surgery practice from June 2016 to May 2018.

Inclusion criteria: Women over 18 years who had at least two UTIs in the previous 6 months or three in the previous year that were culture positive (growth of colony forming units per millilitre [CFU/mL]). The patients must have had symptoms, in addition to a documented positive urine culture, with any UTI episodes, including acute dysuria, suprapubic pain, fever, worsening urinary urgency, frequency, and urinary incontinence. Women who had received previous prophylaxis for recurrent UTI but had not taken it for a minimum of 30 days were eligible for enrolment.

Exclusion criteria: Pregnancy, urinary tract abnormalities (eg, kidney stones), acute pyelonephritis, renal impairment, allergy to medications *(sic)*, or on prophylaxis for post-coital recurrent UTI.
Intervention: Women were randomized 1:1 to receive prophylaxis with either methenamine hippurate 1 g twice daily or trimethoprim 100 mg nocte for a minimum of 6 months. Prophylaxis was continued for 6 months after initiation and patients were encouraged to discontinue the medicine if they did not develop recurrent UTI.

Randomization was via computer-generated block randomization. Patients were seen at 6 and 12 months after enrolment or in the event of UTI symptoms.

If the patient had acute UTI symptoms at enrolment, a urine culture was obtained, and a full course of antibiotics given if indicated. Prophylaxis then began after treatment of the acute UTI

Patients could switch randomly assigned groups if they experienced adverse effects after starting trial medicine, if a drug interaction was discovered after randomisation, if they were unable to afford one of the trial medicines due to lack of insurance coverage, or if they were concerned about adverse reactions after reading the package insert of the trial medicine.

Primary outcome: culture proven UTI recurrence by 12 months after initiating prophylaxis

Secondary outcomes: time from enrolment to first UTI, number of UTIs in 1 year after starting prophylaxis, adverse effects.

Statistical analysis: ITT and per protocol analyses were performed to account for potential crossover between study medicines. Student's t test was used to assess the difference is recurrence rate and incidence of adverse events between the two groups.

Results: 92 of 104 consecutive patients met the eligibility criteria and were randomised to receive methenamine hippurate (47) or trimethoprim(45). Four patients in the methenamine hippurate group did not complete the study (2 were lost to follow-up and 2 were non-adherent with the study medicine). Two patients in the trimethoprim group were lost to follow-up. The remaining 86 patients were included in the analysis.

The ITT analysis comprised 43 patients in each group. The per protocol analysis was performed on 40 patients in the trimethoprim group and 46 in the methenamine group after 11 patients were reassigned based on

actual drug taken during the trial (7 changed from trimethoprim to methenamine hippurate, and 4 changed from methenamine hippurate to trimethoprim).

No difference in recurrent UTI was observed between the two groups in either the ITT or per protocol analyses. (Table 7)

Table 7. Recurrent UTI during prophylaxis with either methenamine or trimethoprim - primary and secondary outcome measures (ITT and per protocol analyses)

[redacted]

Adverse effects: 10 out of 92 patients (10.9%) experienced an adverse effect that warranted stopping the medication, including diarrhoea, rash, and weakness (Table 8). The most common adverse effect reported was diarrhoea and this was seen in 1 patient in the trimethoprim group and 2 patients in the methenamine hippurate group. One patient experienced abdominal pain, and one patient had an acute episode of nephrolithiasis thought to be unrelated. One patient developed a Clostridium difficile infection 2 weeks after initiating antibiotic therapy and the medication was discontinued for that reason. In these cases, if patients were willing to try the alternative study medicine, they were reassigned to the opposite group.

Table 8. Adverse effects in patients randomised to take either methenamine (n=47) or trimethoprim (n=45)

[redacted]

Conclusion: The authors concluded that methenamine hippurate may be an alternative for the prevention of recurrent UTI, with similar rates of recurrence and adverse effects to trimethoprim.

Comments:

The study showed no significant difference between methenamine hippurate and trimethoprim prophylaxis in the recurrence of UTI at 1 year. However, this open-label, single-centre, effectively non-randomised study has significant methodological flaws that make the results unreliable.

- Although randomised at the start, patients could cross over from one treatment group to the other after randomisation.
- Baseline demographics are compared at randomisation, but there is no subsequent comparison of the groups to determine whether crossing over biased the treatment allocation.
- The ITT analysis does not include patients who were LTFU or who were non-adherent to the study protocol
- Rather than excluding patients who crossed-over after randomisation, the per-protocol analysis compares the groups based on the medicine that was actually taken (ie, takes into account those who crossed over).

3.1.2.3 Cronberg et al (1987)

Prevention of recurrent acute cystitis by methenamine hippurate: double blind controlled crossover long term study.

Objective: To evaluate the effectiveness of methenamine hippurate, with and without extra fluid intake, in preventing acute recurrent cystitis.

Method: Randomised, double blind, placebo controlled, cross-over study. Twenty-one women aged 40-80 years with recurrent acute cystitis were randomised to receive either methenamine hippurate 1 g twice daily (11 women) or placebo (10 women) for 6 months. The drugs were swapped every six months for two years. During one of these periods, patients were also prescribed 250 ml of extra fluid every morning and evening.

Urine culture and sensitivity was at two-monthly follow-ups and if symptomatic. UTI was defined as 10^8 colony forming units/L. Patients with UTI were treated with appropriate antibiotics for a week.

Only new infections (not relapses) were included for analysis. Differences in the frequency of cystitis for the individual patients during treatment were analysed by Wilcoxon's matched pairs rank sum test.

Results: Of the 21 women who entered the study, 14 completed the first year and 13 completed both years. Two patients (one from each group) withdrew soon after the start complaining of urgency – both had been allocated to take extra fluid. The remaining patients withdrew due to loss of motivation. In 27 patient-years of follow-up there were 52 episodes of acute cystitis due to reinfection (23 in the first year and 29 in the second year), 11 in patients taking methenamine and 41 in patients taking placebo. The authors reported that methenamine hippurate therefore reduced the incidence of cystitis by 73%. There were 2.1 infections per patient/year with placebo compared to 0.8 infections per patient/year with methenamine hippurate ($p<0.01$).

Ten patients had fewer attacks while taking methenamine hippurate than placebo. One patient had a single episode of infection while taking methenamine hippurate but was otherwise free of infection.

No difference was observed between patients taking extra fluid than those with normal fluid intake (28 vs 24 attacks), and extra fluid did not reduce the efficacy of methenamine hippurate (six vs five attaches).

Conclusion: The authors concluded that methenamine hippurate seems to be a suitable prophylactic agent against recurrent acute cystitis in women.

Comments:

This study is one of two studies cited in the Australian Product Information as evidence of efficacy. The other study is the 2012 Cochrane review by Lee et al [13].

The quality of this study is poor and should not be cited as evidence of efficacy. The study enrolled only 21 patients in total, of which 14 completed one year of follow-up and 13 remained for the full 2-year study period. The numbers are too small to provide meaningful results, even with the cross-over design.

The risk of bias is high as women who experienced UTI symptoms may have chosen to withdraw early from the study due to lack of effect.

There is no ITT analysis to examine efficacy in patients who were randomised to each group prior to cross-over.

3.2 CARM data

Adverse reactions that are reported to CARM are not necessarily causally related to the suspect medicine. The reports come from a variety of sources, and the probability that the reported adverse effect is drug-related is not the same in all cases.

Methenamine is recorded as the synonym 'hexamine' in the CARM database. From April 1965 to March 2022 (inclusive), the Centre for Adverse Reactions Monitoring (CARM) received a total of 20 reports for methenamine hippurate, of which 12 identified hexamine (methenamine) as a suspect medicine,

The 12 reports in which hexamine is reported as a suspect medicine are summarised in Table 9.

All 12 reports concerned female patients aged 19-93 years (median age 53.5 years).

Hexamine was the only suspect medicine in 10 reports, was co-suspected with isopropamide iodide in one report, and was reported as interacting with ferrous sulphate in the remaining report.

Hexamine was the only reported medicine in seven reports. Concomitant medicines reported in the remaining five reports included: simvastatin, solifenacin and evening primrose oil; norfloxacin; ascorbic acid and oxybutynin; and oestriol and fluticasone/salmeterol.

Seven of the reports were about skin reactions, including acne, urticaria, angioedema, rash, pruritis, skin disorder, and cheilitis. Other reported adverse effects were abdominal pain, haemoptysis, drug interaction, medicine ineffective, vomiting, micturition frequency, urinary tract disorder, and candidiasis. (Table 9)

Table 9. CARM case reports in which methenamine is identified as a suspect (including interacting) medicine

Report	Date	Sex	Age	Medicine(s)	Adverse effect(s)
001359	Jun-68	F	54	Hexamine (S)	Abdominal pain
010485	Oct-81	F	22	Isopropamide iodide (S) Hexamine (S)	Acne
100831	Apr-12	F	70	Hexamine (S) Simvastatin (C) Solifenacin (C) Evening primrose oil (C)	Urticaria Angioedema Rash
105080	Dec-12	F	49	Hexamine (S) Norfloxacin (C)	Haemoptysis
126135	Sep-17	F	53	Hexamine (S)	Pruritis

126136	Sep-17	F	87	Hexamine (S)	Skin disorder
126137	Sep-17	F	86	Hexamine (S)	Rash pruritic
134047	Aug-19	F	27	Hexamine (I) Ferrous sulphate (I) Ascorbic acid (C) Oxybutinin (C)	Drug interaction Medicine ineffective
134630	Oct-19	F	26	Hexamine (S)	Vomiting Urinary tract disorder
140040	Mar-21	F	63	Hexamine (S) Oestriol (C) Fluticasone/Salmeterol (C)	Micturition frequency
140506	Apr-21	F	93	Hexamine (S)	Candidiasis Cheilitis
142721	Nov-21	F	19	Hexamine (S)	Urticaria

Abbreviations: (C) Concomitant, (I) Interacting, (S) Suspect

[redacted]

3.4 Formaldehyde toxicity

Formaldehyde is the active ingredient in methenamine hippurate. Ingestion may cause corrosive injury to the gastrointestinal mucosa, with nausea, vomiting, pain, bleeding, and perforation. Systemic effects include metabolic acidosis, CNS depression and coma, respiratory distress, and renal failure.

In 2004, the International Agency for Research of Cancer (IARC) classified formaldehyde as a Group 1 carcinogen[5]. A recent meta-analysis of epidemiological studies over the past 20 years aimed to update the evidence on occupational exposure to formaldehyde and cancer onset. The study found that the evidence of correlation between formaldehyde occupational exposure and the occurrence of cancer is limited and could neither confirm nor refute the IARC classification. [33]

[redacted]

[5] The IARC Group 1 category is 'carcinogenic to humans' (monographs.iarc.who.int/agents-classified-by-the-iarc/).

4 DISCUSSION AND CONCLUSIONS

Current guidelines recommend the use of a low dose antibiotic for 6-12 months to prevent recurrent UTI in women [4, 34]. With the increasing global burden of antimicrobial resistance, there is renewed interest in methenamine hippurate, a urinary antiseptic medicine that was first used to treat UTI more than a century ago.

Despite its long history of use, the benefit-risk profile of methenamine hippurate is not well described. Many of the studies examining the safety and efficacy of this medicine are more than 30 years old and lack methodological rigour and statistical power.

Methenamine hippurate is a 'grandfathered medicine' that was approved in New Zealand prior to current legislation and has not been subject to a robust benefit-risk evaluation. Hiprex 1 g tablets are fully funded on the Pharmaceutical Schedule and are available over the counter as a 'general sale' medicine. In line with current requirements for general sale medicines, Hiprex does not have a data sheet.

The New Zealand dedicated product website for Hiprex (www.hiprex.co.nz/) states that Hiprex is suitable for adults and children over 6 years for protection from recurrent UTIs, and that it is suitable for use in pregnancy. The website displays a diagram illustrating the conversion of 'hexamine hippurate' to hippuric acid and hexamine, which in turn is converted to 'bactericidal agent' and ammonia. It is notable that the term 'formaldehyde' is not used in the consumer-oriented information.

A comprehensive literature search for evidence of efficacy and safety of methenamine hippurate identified a Cochrane review published in 2012 and one recent systematic review (with meta-analysis) published in2021.

Lee et al (2012) [13] conducted a systematic review of methenamine hippurate vs placebo/no treatment. The review included 13 studies, many of which were found to be of poor quality. Although the total number of patients was large (2032), the study populations were heterogeneous, including patients with renal tract calculi, men undergoing prostate operations, pregnant women and patients with spinal injury. Only seven of the studies had a follow-up period longer than one month. This is important as methenamine hippurate is intended for long-term prophylaxis of UTI.

The pooled analysis found no significant reduction in symptomatic bacteriuria (RR 0.53, 95% CI 0.24 to 1.18) for methenamine hippurate vs placebo/no treatment, and a reduction in bacteriuria that only just reached significance (RR 0.67, 95% CI 0.45 to 0.99). However, significant heterogeneity in the pooled analyses limited interpretation of the results.

Subgroup analyses found methenamine hippurate may have some benefit in patients without rental tract abnormalities (symptomatic UTI: RR 0.24, 95% CI 0.07 to 0.89; bacteriuria: RR 0.56, 95% CI 0.37 to 0.83), but not in patients with known renal tract abnormalities. For treatment duration of one week or less, there was a significant reduction in symptomatic UTI in those without renal tract abnormalities (RR 0.14, 95% CI 0.05 to 0.38), but this may represent a chance finding.

The recent systematic review by Bakhit et al (2021) [14] focused on RCTs of adult women in the community with a history of UTI who used methenamine hippurate as treatment or prophylaxis. The review identified six RCTs, but only one study was less than 30 years old. The review included comparisons with either active treatment (antibiotic) or placebo. The study found no statistically significant difference in the number of patients remaining asymptomatic after 6 or 12 months for methenamine hippurate when compared to either antibiotics or placebo. Other findings were no significant difference in patients remaining abacteriuric after 12 months (methenamine hippurate vs antibiotic), number of symptomatic UTI episodes after 6 or 12 months (methenamine hippurate vs antibiotic or placebo), or the number of bacteriuric episodes after 12 months (methenamine hippurate vs antibiotic).

Two recent RCTs compared methenamine hippurate with an antibiotic to prevent recurrent UTI.

Harding et al (2022) [4] conducted a pragmatic, multicentre, randomised, open-label non-inferiority trial to compare the clinical effectiveness of methenamine hippurate vs low dose antibiotic prophylaxis (the current standard of care for recurrent UTI). The primary outcome measure was the incidence of self-reported symptomatic antibiotic-treated UTI over the 12-month treatment period. The non-inferiority margin was a

difference of one UTI episode per year, which was predetermined in consultation with consumers. The study found an absolute difference in self-reported symptomatic, antibiotic treated UTI over the 12-month treatment period to be 0.49 (90% confidence interval 0.15 to 0.84)). With the upper limit of the 90% confidence interval below the non-inferiority limit of one, methenamine hippurate was found to be non-inferior to antibiotic prophylaxis.

Botros et al (2021) [30] compared the difference in rates of recurrent UTI within one year when treated with methenamine hippurate vs. trimethoprim for prophylaxis. The study showed no significant difference between the treatment groups. However, the study had significant methodological flaws that make the results difficult to interpret.

Finally, a study by Cronberg et al (1987) [16] which is cited as evidence of efficacy in the Australian product information, was also found to have significant methodological flaws, small number of participants, a high LTFU, which make the results difficult to interpret.

A review of the safety data from CARM found reported adverse events to be consistent with the known adverse effects listed on the sponsors dedicated website and in the Australian product information [9, 10]. The most commonly reported adverse effects were dermatological /allergic reactions (urticaria, angioedema, rash, pruritis) and gastrointestinal symptoms (abdominal pain, vomiting). Adverse effects that may suggest lack of efficacy were also reported (medicine ineffective, UTI, micturition frequency). Given the volume of methenamine hippurate sold in New Zealand over the 5-year period 2017-2021, and the relatively low number of reports submitted to CARM over this period, the safety profile appears to be acceptable.

The possibility of harm associated with long term exposure to formaldehyde has not been evaluated in the literature, and the question of long-term safety remains unanswered.

A further issue to consider is the information about use in pregnancy. The consumer-oriented website for Hiprex states that Hiprex is safe in pregnancy (although advice should be sought from a healthcare professional). The Australian PI classifies methenamine hippurate as pregnancy category A but recommends against use in pregnancy.

In the US, the Hiprex label includes the following precaution concerning use in pregnancy:

> *'Use in Pregnancy: In early pregnancy the safe use of methenamine hippurate is not established. In the last trimester, safety is suggested, but not definitely proved. No adverse effects on the fetus were seen in studies in pregnant rats and rabbits. Methenamine hippurate taken during pregnancy can interfere with laboratory tests of urine estriol (resulting in unmeasurably low values) when acid hydrolysis is used in the laboratory procedure. This interference is due to the presence in the urine of methenamine and/or formaldehyde. Enzymatic hydrolysis, in place of acid hydrolysis, will circumvent this problem'*.

A further discrepancy between the information provided by the sponsor on the New Zealand Hiprex website and both the Australian PI is the recommendations about use in children. The New Zealand information states that Hiprex may be used in children from 6 years of age, while the Australian PI states that Hiprex is not recommended in children less than 12 years. The US product label states the dose for children aged 6-12 years should be 0.5 to 1g twice daily.

In summary, the evidence for efficacy of methenamine hippurate for the suppression or elimination of urinary tract bacteria is weak. The medicine has been used by a large number of patients in New Zealand over many years with little apparent evidence of harm (based on reports to CARM), but long-term safety data is lacking.

There remains a need for further large well-conducted RCTs to assess the safety and efficacy of methenamine hippurate for the prevention of recurrent UTI in women.

In New Zealand, methenamine is approved for *'suppression or elimination of urinary tract bacteria'*. In Australia, the approved indication is more specific: *'prophylaxis or suppression of bacteriuria associated with chronic or recurrent infection of the urinary tract'*. Furthermore, there are important differences between the information provided on the dedicated product website for New Zealand consumers and the approved Australian Product Information for methenamine hippurate. These differences concern use in children and safety in pregnancy.

5 ADVICE SOUGHT

The Committee is asked to advise:

- Whether the benefit-risk profile of methenamine hippurate for prevention of recurrent urinary tract infection is favourable
- Whether any regulatory action such as a change in the classification is recommended
- Whether any communication in addition to MARC's Remarks is needed to inform consumers and healthcare professionals about the benefit-risk profile of methenamine hippurate.

6 ANNEXES

None

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