MEDSAFE
New Zealand Medicines and Medical Devices Safety Authority

Classification of Methenamine hippurate

Submission to the Medicines Classification Committee

Medsafe
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Te Kāwanatanga o Aotearoa
New Zealand Government

1. Background

Methenamine hippurate (also known as hexamine hippurate) is a urinary antibacterial agent intended for 'suppression or elimination of urinary tract bacteria' [1]. Methenamine hippurate is a prodrug that converts to formaldehyde in an acidic environment. Formaldehyde is the active substance that exerts bactericidal activity in the urine [2].

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 [3]. Methenamine hippurate had therefore not undergone a rigorous benefit-risk evaluation consistent with current standards prior to the recent review by the MARC.

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 [4, 5].

Medsafe considered 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. The Medicines Adverse Reactions Committee (MARC) reviewed the benefits and risks of methenamine hippurate at their 190th meeting on 9 June 2022.

The MARC considered that, on balance, the benefit-risk profile for methenamine hippurate is favourable, but expressed concern that the general sale classification may not be appropriate for the indication. The MARC recommended that Medsafe ask the Medicines Classification Committee (MCC) to review the classification of methenamine hippurate.

2. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the medicine

Methenamine hippurate

3. Classification sought

On the recommendation of the MARC, Medsafe requests that the MCC consider whether products containing methenamine hippurate should be upscheduled from general sale medicines to a more restrictive classification.

4. Classification status in other countries (especially Australia, UK, USA, Canada)

Methenamine hippurate is not a scheduled substance in Australia. Methenamine hippurate products are registered medicines in Australia, making them equivalent to general sale medicines in New Zealand [6].

In the UK, methenamine hippurate products are classified as pharmacy medicines.

In Canada, methenamine hippurate is scheduled as an ethical drug. Ethical drugs do not require a prescription, but are generally prescribed by a medical practitioner. Ethical products are unscheduled non-prescription professional use products [7].

In the USA, methenamine hippurate is a human prescription drug. A similar product, methenamine sodium salicylate, is available as an over-the-counter (OTC) product.

5. Reasons for requesting the classification

The Medicines Adverse Reactions Committee (MARC) reviewed the benefit-risk balance of methenamine hippurate at the 190th MARC meeting on 9 June 2022. The MARC expressed concern that the current general sale classification for this medicine may not be appropriate. The Committee recommended that Medsafe should ask the MCC to review the classification of methenamine hippurate and advise whether it should be upscheduled from a general sale medicine to a more restrictive classification.

The MARC considered that the current evidence supporting the efficacy of methenamine hippurate for the suppression or elimination of urinary tract bacteria is weak. Methenamine hippurate may have a role in antimicrobial stewardship by providing an alternative to antibiotics for preventing urinary tract infection. On balance, the MARC considered methenamine hippurate to have a favourable benefit-risk profile.

Consultation with a healthcare professional is advisable for patients with symptoms of recurrent urinary tract infection to ensure accurate diagnosis and appropriate treatment. Upscheduling of these products may improve patient outcomes by ensuring appropriate consultation with a healthcare professional who will assess the patient's condition and whether methenamine hippurate is an appropriate therapeutic choice.

On the recommendation of the MARC, Medsafe has also requested the sponsor for Hiprex (methenamine hippurate) provide a data sheet and consumer medicines information.

Usage
Hiprex (methenamine hippurate) is available in 20-tablet and 100-tablet pack sizes. Hiprex 1g tablet (100 tablet bottle) is fully funded on the Pharmaceutical Schedule and is included in the Hospital Medicines List. PHARMAC does not fund the 20-tablet pack size.

The use of Hiprex has increased significantly following PHARMAC's decision in November 2019 to increase the pharmaceutical subsidy for the 100-tablet pack size from 1 December 2019.

The Ministry of Health's Pharmaceutical Collection contains information on subsidised pharmaceutical dispensings. Dispensing data for methenamine hippurate for the period 2017 to 2019 indicates that there was a steady increase in usage prior to the change in funding (Figure 1). Pharmaceutical Collection data includes PHARMAC funded medicines dispensed from community pharmacies. The data does not include pharmaceutical products dispensed at hospitals, non-funded medicines, medicines purchased over-the-counter or prescriptions that

were not dispensed. Figure 1 shows number of first dispensings for methenamine hippurate for the period 2016 to 2020.

Figure 1: Number of initial dispensings of methenamine hippurate tablets, 2016-2020.

Type	FormID	ChemForm	DHB	YearDisp	NumDisps	Qty	NumPpl	NHIComp	BaseUnits
Initial dispensings	159401	Methenamine (hexamine) hippurate - Tab 1 g	New Zealand	2016	2505	162041.5	988	99.8	tab
Initial dispensings	159401	Methenamine (hexamine) hippurate - Tab 1 g	New Zealand	2017	3651	252500.5	1575	99.9	tab
Initial dispensings	159401	Methenamine (hexamine) hippurate - Tab 1 g	New Zealand	2018	4458	317641	1895	99.9	tab
Initial dispensings	159401	Methenamine (hexamine) hippurate - Tab 1 g	New Zealand	2019	5485	412319.5	2438	99.9	tab
Initial dispensings	159401	Methenamine (hexamine) hippurate - Tab 1 g	New Zealand	2020	14839	1182695.5	6950	99.9	tab

Source: Pharmaceutical Collection (Ministry of Health).

Safety

Medsafe reviewed the available information on the safety of methenamine hippurate in the report prepared for the MARC meeting in June 2022. **A copy of the report is provided as an annex to this submission**.

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. Section 4.8 of the Australian product information lists gastric irritation, nausea, vomiting, rash, pruritus, irritation of the bladder and dysuria as uncommon adverse events. Diarrhoea and abdominal pain are listed with an unknown frequency. Albuminuria and haematuria have been reported with high doses (4 to 8 grams daily for 3 to 4 weeks).

The most commonly reported adverse effects to CARM 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).

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.

Furthermore, information about the safety of methenamine hippurate in pregnancy is lacking. The consumer-oriented website for Hiprex states that Hiprex is safe in pregnancy but advice should be sought from a healthcare professional [8]. The Australian product information for Apohealth Urinary Tract Antibacterial classifies methenamine hippurate as pregnancy category A but recommends against use in pregnancy [9]. In the US, the Hiprex label states '*In early pregnancy the safe use of methenamine hippurate is not established. In the last trimester, safety is suggested, but not definitely proved'* [10].

It is unclear if Hiprex can be used in children in New Zealand. The New Zealand Hiprex website states that Hiprex may be used in children from 6 years of age,

while the Australian product information states that Hiprex is not recommended in children less than 12 years [8, 9].

In New Zealand, the label claim for methenamine is *'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'* [1, 9].

6. Published literature

The report prepared for the MARC includes a description of the available data on effectiveness in section 3, Scientific Information. **A copy of the report is provided as an annex to this submission**.

The literature review identified a Cochrane review and one systematic review and meta-analysis and two randomised controlled trials (RCTs) that were published after the Cochrane review. An earlier study, by Cronberg et al was also reviewed as it is cited as evidence of efficacy in the Australian product information for methenamine hippurate.

Overall, the evidence for efficacy of methenamine hippurate for the suppression or elimination of urinary tract bacteria is weak. 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.

7. Discussion and conclusions

Methenamine hippurate is currently classified as a general sale medicine. On the recommendation of the MARC, Medsafe requests the MCC to review the classification of methenamine hippurate.

The MARC was concerned that the general sale classification may not be appropriate for methenamine hippurate. Consultation with a healthcare professional is advisable for patients with symptoms of recurrent urinary tract infection to ensure accurate diagnosis and appropriate treatment. Upscheduling methenamine hippurate to a more restrictive classification that requires consultation with a healthcare professional would enable consumers to assess whether methenamine hippurate is an appropriate therapeutic choice.

Reclassification of methenamine hippurate as prescription only would ensure that patients see their GP for treatment but would reduce access to the medicine. A pharmacist only classification would maintain access to the medicine through pharmacies. However, pharmacists may not be fully equipped with the information and resources they need to recommend treatment for recurrent urinary tract infections.

The Committee are kindly asked to review the current classification and consider if should be changed and if so to consider which would be the most appropriate classification.

References

1. Medsafe. 2019. Medsafe Product Detail: Hiprex 31 May 2019. URL: https://medsafe.govt.nz/regulatory/ProductDetail.asp?ID=1248 (accessed 25 July 2022).
2. National Center for Biotechnology Information. 2022. PubChem Compound Summary for CID 21945, Methenamine hippurate URL: https://pubchem.ncbi.nlm.nih.gov/compound/Methenamine-hippurate (accessed 25 July 2022).
3. Medsafe. 2019. History of medicines and medical device regulation in New Zealand 18 March 2019. URL: https://medsafe.govt.nz/about/HistoryRegulation/HistoryRegulationContents.asp (accessed 25 July 2022).
4. Harding C, Mossop H, Homer T, et al. 2022. Alternative to prophylactic antibiotics for the treatment of recurrent urinary tract infections in women: multicentre, open label, randomised, non-inferiority trial. BMJ 376: e068229. DOI: 10.1136/bmj-2021-0068229 (accessed 25 July 2022).
5. Hoffmann TC, Bakhit M and Del Mar C. 2022. Methenamine hippurate for recurrent urinary tract infections. BMJ 376: o533. DOI: 10.1136/bmj.o533 (accessed 25 July 2022).
6. Therapeutic Goods Administration. 2019. How we regulate medicines 20 June 2019. URL: https://www.tga.gov.au/how-we-regulate-medicines (accessed 25 July 2022).
7. Government of Canada. 2022. Drug Product Database (DPD): Terminology 15 March 2022. URL: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database/terminology.html (accessed 25 July 2022).
8. Radiant Health Ltd. 2022. About Hiprex URL: https://www.hiprex.co.nz/about-hiprex/ (accessed 28 July 2022).
9. Micro Labs Pty Ltd. 2021. Australian Product Information– Apohealth Urinary Tract Antibacterial 3 December 2021. URL: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2021-PI-02482-1&d=20220728172310101 (accessed 28 July 2022).
10. Validus Pharmaceuticals LLC. 2022. Hiprex: Drug Label Information 2 February 2022. URL: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c8ddaa11-5753-46eb-8bd4-8f1d874a3ec4 (accessed 28 July 2022).
11. Protano C, Buomprisco G, Cammalleri V, et al. 2022. The Carcinogenic Effects of Formaldehyde Occupational Exposure: A Systematic Review. Cancers 14(1): 165. URL: https://www.mdpi.com/2072-6694/14/1/165(accessed 25 July 2022).