

NEW ZEALAND DATA SHEET

1 UROMITEXAN

400mg tablet.

600mg film coated tablet.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient

Uromitexan tablets contain 400mg mesna.

Uromitexan film coated tablets contain 600mg mesna.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets and film coated tablets.

Appearance

Uromitexan tablets are white oblong, biconvex film-coated tablets, scored on one side and marked "M 4" or "M 6", containing 400mg or 600mg (respectively) of mesna.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Uromitexan tablets and film coated tablets are indicated for the reduction and prevention of urinary tract toxicity (haemorrhagic cystitis) of oxazaphosphorines (see section 4.8 of the cyclophosphamide [**Endoxan**] and ifosfamide [**Holoxan**] data sheets).

4.2 Dose and method of administration

Sufficient mesna must be given to protect the patient adequately from the urotoxic effects of the oxazaphosphorine. The duration of mesna treatment should equal that of the oxazaphosphorine treatment plus the time taken for the urinary concentration of oxazaphosphorine metabolites to fall to non-toxic levels. This usually occurs within 8 - 12 hours after the end of oxazaphosphorine treatment but may vary depending on the scheduling of oxazaphosphorine. When calculating the dose of mesna, the quantity should be rounded down to the nearest whole tablet. Urinary output should be maintained at 100mL/hr (as required for oxazaphosphorine treatment) and the urine monitored for haematuria and proteinuria throughout the treatment period.

For intermittent oxazaphosphorine therapy

Oral mesna, 40% (w/w) of the oxazaphosphorine dose, should be given 2 hours prior to the oxazaphosphorine dose, and repeated at 2 and at 6 hours after oxazaphosphorine administration. Alternatively, an initial intravenous dose of mesna (20% (w/w) of the oxazaphosphorine dose) can be given with the cytotoxic dose and additional oral mesna, 40% (w/w) of the oxazaphosphorine, given at 2 and 6 hours.

Example of administration for intermittent oxazaphosphorine therapy:

	-2 hrs	0 hrs	2 hrs	6 hrs
Oxazaphosphorine	-	1g IV	-	-
UROMITEXAN (oral only)	400mg po	-	400mg po	400mg po
UROMITEXAN (oral and IV)	-	200mg IV	400mg po	400mg po

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Following 24 hour infusion of ifosfamide and mesna

The first oral mesna dose of 40% (w/w) of the ifosfamide dose is given as the infusion is stopped, and the same dose is repeated after 2 and 6 hours.

Higher doses of mesna can be given if urothelial toxicity occurs.

Elderly

No specific information on the use of this product in the elderly is available. Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported.

Children

Due to increased micturition, children may require shorter intervals between doses and/or an increased number of individual doses.

High risk patients

Those who have had previous irradiation of the small pelvis, occurrence of cystitis during previous cyclophosphamide or ifosfamide therapy or a history of urinary tract lesions may require shorter intervals between doses and/or an increased number of doses.

4.3 Contraindications

Uromitexan is contraindicated in individuals with a known hypersensitivity to mesna or any of the excipients (see section 6.1) and other thiols.

4.4 Special warnings and precautions for use

The protective effect of mesna applies only to the urothelial toxic effect of oxazaphosphorines (*viz.* ifosfamide or cyclophosphamide) not to their renal and other toxic effects. Additional prophylactic or accompanying measures recommended during treatment with oxazaphosphorines are thus not affected and should not be discontinued.

Severe allergic symptoms, such as systemic anaphylactic reactions, have occurred with mesna, especially in patients suffering from autoimmune diseases.

Due to the possibility of anaphylactoid reactions, it should be ensured that adequate emergency medication is available.

Patients with autoimmune diseases who were treated with cyclophosphamide and **Uromitexan** appeared to have a higher incidence of hypersensitivity reactions: Skin and mucosal reactions of varying extent and severity (rash, itching, redness, severe bullous and ulcerative skin, vesiculation, Lyell Syndrome, Stevens-Johnson Syndrome), toxic epidermal necrolysis, erythema exudative multiforme), localised or generalised urticarial or other forms of exanthema, pruritus, burning, local tissue swelling (urticarial oedema), angioedema and/or flushing. Some reactions appeared to be consistent with a diagnosis of fixed drug eruption. Skin reactions were accompanied by one or more other symptoms (see section 4.8) such as:

- fever,
- conjunctivitis,
- cardiovascular symptoms (hypotension, in some cases reported as fluid refractory, associated with circulatory reactions and increased pulse rate above 100/min (tachycardia) hypertension, ST-segment elevation, ECG signs consistent with perimyocarditis),
- signs consistent with acute renal failure,

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- pulmonary symptoms (hypoxia, respiratory distress, bronchospasm, cough, bloody sputum and increased respiration rate (tachypnoea) due to severe acute hypersensitivity reactions,
- prolonged prothrombin time and partial prothrombin time, laboratory signs of disseminated intravascular coagulopathy,
- haematological abnormalities (leukopaenia, eosinophilia, lymphopaenia, thrombocytopenia, pancytopenia,
- pain in the extremities, arthralgia, myalgia, malaise,
- transient rise in certain liver function tests (e.g. transaminases),
- nausea, vomiting, stomatitis.

Photodistribution of a rash has also been reported. Some reactions have presented as anaphylaxis. Fever accompanied by, e.g. hypotension but no skin manifestations, has also been reported.

Severe as well as minor reactions were reported with the use of mesna in regimens to treat both severe systemic autoimmune disorders and malignancy. In most cases, reactions occurred during or after a first treatment occasion or after several weeks of mesna exposure. In other cases, the initial reaction was observed only after several months of exposure. In many cases, symptoms appeared on the day of exposure, with a tendency to shorter intervals following subsequent exposures.

In some patients, the occurrence and/or severity of reaction appeared to vary with the dose administered. Recurrence of reactions, in some cases with increasing severity, has been reported with re-exposure. However, in some cases, a reaction did not recur with re-exposure.

Some patients with a history of a reaction have shown positive delayed-type skin test results. However, a negative delayed reaction does not exclude hypersensitivity to mesna. Positive immediate-type skin test reactions have occurred in patients regardless of previous mesna exposure or history of hypersensitivity reactions, and may be related to the concentration of the mesna solution used for testing.

Protection of the urinary tract with mesna should therefore only be undertaken in such patients with autoimmune diseases following careful risk-benefit analysis and under medical supervision.

Prescribers should:

- be aware of the potential for such reactions and that reactions may worsen with re-exposure and may in some cases be life-threatening,
- be aware that hypersensitivity reactions to mesna were interpreted to resemble the clinical picture of sepsis and, in patients with autoimmune disorders, resemble an exacerbation of the underlying disease.

Thiol compounds

Mesna is a thiol compound, i.e. a sulfhydryl group-containing organic compound. Thiol compounds show some similarities in their adverse reaction profile, including a potential to elicit severe skin reactions. Examples of medicines that are thiol compounds include amifostine, penicillamine, and captopril.

It is not clear whether patients who experienced an adverse reaction to such a medicine are at increased risk for any reactions, or similar reactions, to another thiol compound. However, when considering subsequent use of another thiol compound in such patients, the possibility of an increased risk should be taken into account.

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Uromitexan does not prevent haemorrhagic cystitis in all patients. As a result, a morning specimen of urine should be examined for the presence of haematuria (microscopic evidence of red blood cells) and proteinuria each day prior to oxazaphosphorine therapy. If haematuria develops when **Uromitexan** is given with oxazaphosphorines according to the recommended dosage schedule, depending on the severity of the haematuria, dosage reduction or discontinuation of oxazaphosphorine therapy may be indicated.

Urinary output should be maintained at 100mL/hr (as required for oxazaphosphorine treatment). The urine should be monitored for haematuria and proteinuria throughout the treatment period.

Paediatric use

Safety and effectiveness of mesna in paediatric patients (< 16 years of age) have not been established in formal clinical studies, but its use in paediatric patients is referenced in the medical literature.

Geriatric use

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. The ratio of oxazaphosphorines to mesna should remain unchanged.

Effects on laboratory tests

A false positive test in nitroprusside sodium-based urine tests (including dipstick tests) for urinary ketones may arise in patients treated with **Uromitexan**. In this test, a red-violet (rather than purple) colour develops which is less stable, e.g. with the addition of glacial acetic acid, will return to violet.

Mesna treatment may cause false positive reactions in Tillman's reagent-based urine screening tests for ascorbic acid.

Mesna may cause false positive or false negative reactions in the dipstick test for erythrocytes in urine. To exactly determine erythrocytes in the urine, urinary microscopy is recommended.

In pharmacokinetics studies in healthy volunteers, serum creatine phosphokinase (CPK) values were lower in samples taken 24 hours after mesna dosing than in pre-dosing samples. While available data are insufficient to determine the cause of this phenomenon, it might be considered to represent a significant interference with thiol (e.g. N-acetylcysteine) dependent enzymatic CPK tests.

4.5 Interaction with other medicines and other forms of interaction

In vitro and *in vivo* animal tumour models have shown that mesna does not have any effect on the antitumour efficacy of concomitantly administered cytotoxic agents.

It may be necessary to replace oral mesna with intravenous mesna in patients treated with total body irradiation in combination with high dose cyclophosphamide.

Oral mesna should be replaced by intravenous mesna in patients experiencing vomiting.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Animal studies of potential toxicity in a fertility and general reproductive screen have not been carried out. It is not known whether Uromitexan can affect reproductive capacity.

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Pregnancy (Category B1)

Teratology studies with oral doses of mesna to rabbits at up to 1000mg/kg/day and to rats at up to 2000mg/kg/day have revealed no harm to the foetus. Animal studies of potential toxicity in a peri-/post-natal screen have not been carried out. It is not known whether **Uromitexan** can cause foetal harm when administered to a pregnant woman. **Uromitexan** should be given to a pregnant woman only if the benefits clearly outweigh any possible risks.

Breast-feeding

It is not known whether mesna or dimesna are excreted in human milk. Because many medicines are excreted in human milk and because of the potential for adverse reactions in breast-fed infants, a decision should be made whether to discontinue breast-feeding or discontinue the medicine, taking into account the importance of the medicine to the mother.

4.7 Effects on ability to drive and use machines

Patients undergoing treatment with mesna may experience undesirable effects (including, e.g. syncope, lightheadedness, lethargy/drowsiness, dizziness, and blurred vision) which could affect the ability to drive or use machines. The decision to drive or operate machinery should be made on an individual basis.

4.8 Undesirable effects

As **Uromitexan** is used in combination with oxazaphosphorine alkylating agents and other chemotherapeutic agents with documented toxicities, it is difficult to distinguish the adverse reactions which may be due to **Uromitexan** from those caused by the concomitantly administered cytotoxic agents. Consequently, the side effect profile of mesna has been assessed from studies in which oral mesna was given alone.

In an early dose-ranging study, 6 patients were given an oral solution of mesna at doses of 60 - 70mg/kg without concurrent chemotherapy. Diarrhoea (83%), headache (67%), fatigue (50%), nausea (33%), limb pain (50%), cardiovascular collapse (17%) and allergy (17%) were reported.

In 4 pharmacokinetic studies involving 72 subjects given mesna tablets (0.6 to 2.4g) on up to 10 occasions, the most common adverse events were diarrhoea (6%), headache (12%), nausea (5%), vomiting (2%) and fatigue (1%).

Frequently reported side effects from clinical studies and/or spontaneous reporting are nausea, vomiting, flatulence, diarrhoea, constipation, colic (e.g. abdominal pain), anorexia, influenza-like reactions, fever, rigors, flushing, cough, pharyngitis, lightheadedness/dizziness, lethargy/somnolence, headache, back pain, arthralgia.

Isolated cases of partially organ-related hypersensitivity reactions have been reported, e.g. in some cases associated with decreased platelet counts (thrombocytopenia), skin and mucosal reactions of varying extent and severity (rash, itching, redness, vesiculation, Lyell syndrome, Stevens-Johnson syndrome), local tissue swelling (urticarial oedema), conjunctivitis. Very rare cases of hypotension associated with circulatory reactions and increased pulse rate above 100/min (tachycardia), as well as increased respiration rate (tachypnoea) due to severe acute hypersensitivity reactions (anaphylactoid reactions), hypertension, ST-segment elevation, myalgia, and also a transient rise in certain liver function tests (e.g. transaminases) have been reported.

The most severe adverse reactions associated with use of mesna are: toxic epidermal necrolysis, Stevens-Johnson syndrome, anaphylaxis, and drug rash with eosinophilia and systemic symptoms (DRESS). The occurrence of hypersensitivity reactions (hyperergic reactions) following **Uromitexan**

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has been reported more frequently in patients with autoimmune disorders than in tumour patients (see sections 4.3 and 4.4).

Incidence of adverse effects

Primary System Organ Class (SOC)	Very common > 1/10	Common > 1/100 – < 1/10	Uncommon > 1/1000 – < 1/100	Rare > 1/10000 – < 1/1000	Very Rare < 1/10 000, incl. isolated reports
Infections and infestations		Pharyngitis			
Blood and lymphatic system disorders					Thrombocytopenia (hypersensitivity)
Immune system disorders					Hypersensitivity reactions Anaphylactoid reactions
Metabolism and nutrition disorders		Anorexia			
Nervous system disorders		Dizziness Somnolence Headache			
Eye disorders					Conjunctivitis
Cardiac disorders					ST segment elevation Tachycardia
Vascular disorders		Flushing			Circulatory reactions Hypotension Hypertension
Respiratory disorders		Coughing			Tachypnea
Gastrointestinal disorders		Nausea Vomiting Diarrhoea Constipation Colic Abdominal pain Flatulence			
Skin and subcutaneous tissue disorders					Skin and mucosal reactions: Rash Itching Redness Vesiculation Lyell syndrome Stevens-Johnson syndrome Urticarial edema Local tissue swelling
Musculoskeletal and connective tissue disorders		Arthralgia Back pain			Myalgia Limb and joint pain

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Primary System Organ Class (SOC)	Very common > 1/10	Common > 1/100 – < 1/10	Uncommon > 1/1000 – < 1/100	Rare > 1/10000 – < 1/1000	Very Rare < 1/10 000, incl. isolated reports
General disorders and administration site conditions		Fever Rigors Influenza-like reactions		Injection site reactions	Weakness Mucosal reactions Lack of energy Exhaustion
Investigations					Decreased platelet counts Increased respiration rate Rise in certain liver function tests Rise in transaminases

Time to onset

In these studies, some subjects experienced their events on first exposure to mesna and others after the second or third exposure. In general, the complete spectrum of symptoms experienced by a subject developed over a period of several hours.

Experience with re-exposure

Some subjects experienced no further reactions after their initial event while others experienced an exacerbation of events upon repeated dosing.

Cutaneous/mucosal reactions

Cutaneous and mucosal reactions were reported to occur after both intravenous and oral mesna. These reactions included rashes, pruritus, flushing, mucosal irritation, pleuritic pain, and conjunctivitis. Approximately one-quarter of subjects with any event experienced cutaneous/mucosal reactions in conjunction with other adverse symptoms, which included, dyspnoea, fever, headache, gastrointestinal symptoms, drowsiness, malaise, myalgia, and influenza-like symptoms.

Gastrointestinal reactions

Gastrointestinal reactions reported in healthy subjects included nausea, vomiting, diarrhoea, abdominal pain/colic, epigastric pain/burning, constipation, and flatulence and were reported to occur after intravenous and oral mesna administration.

In vivo effect on lymphocyte counts

In pharmacokinetics studies in healthy volunteers, administration of single doses of mesna was commonly associated with a rapid (within 24 hours) and in some cases marked decrease in lymphocyte count, which was generally reversible within 1 week of administration. Data from studies with repeated dosing over several days are insufficient to characterize the time course of lymphocyte count changes under such conditions.

In vivo effect on serum phosphorus levels

In pharmacokinetics studies in healthy volunteers, administration of mesna on single or multiple days was in some cases associated with moderate transient increases in serum phosphorus concentration. These phenomena should be considered when interpreting laboratory results.

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Post-marketing adverse reactions

The following adverse reactions have been identified from post-marketing reports of patients receiving mesna in combination with oxazaphosphorine cytostatics and other medications.

Many of the adverse reactions listed occurred as part of a syndrome suggestive of hypersensitivity reactions (see section 4.4).

BLOOD AND LYMPHATIC SYSTEM DISORDERS: Pancytopenia, Leukopenia, Lymphopenia, Thrombocytopenia, Eosinophilia

IMMUNE SYSTEM DISORDERS: Anaphylaxis, Hypersensitivity

NERVOUS SYSTEM DISORDERS: Convulsion

EYE DISORDERS: Periorbital oedema

CARDIAC DISORDERS: Electrocardiogram abnormal (consistent with perimyocarditis), Tachycardia

VASCULAR DISORDERS: Hypotension (in some cases fluid refractory), Hypertension

RESPIRATORY, THORACIC, MEDIASTINAL DISORDERS: Respiratory distress, Hypoxia, Oxygen saturation decreased, Tachypnoea, Haemoptysis

GASTROINTESTINAL DISORDERS: Stomatitis, Bad taste

HEPATOBIILIARY DISORDERS: Hepatitis, Gamma-glutamyl transferase increased, Blood alkaline phosphatase increased

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Toxic epidermal necrolysis, Stevens-Johnson syndrome, Erythema multiforme, Drug rash with eosinophilia and systemic symptoms, Ulcerations and/or bullae/blistering (mucocutaneous, mucosal, oral, vulvovaginal, anorectal), Angioedema, Fixed drug eruption, Rash (vesicular, exfoliative, maculo-papular, morbilliform), Photodistributed rash, Urticaria, Burning sensation, Erythema

RENAL AND URINARY DISORDERS: Acute renal failure

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Face oedema, Oedema peripheral, Asthenia, Infusion site reactions (thrombophlebitis, irritation)

INVESTIGATIONS: Laboratory signs of disseminated intravascular coagulation, Prothrombin time prolonged, Activated partial thromboplastin time prolonged

INJURY, POISONING AND PROCEDURAL COMPLICATIONS: Occupational sensitization to other mesna formulations used for inhalation (manifested as eczema, papulovesicular rash, erythema, pruritus).

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/>

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4.9 Overdose

No specific antidote for mesna is known. Overdosage should be managed with supportive measures to sustain the patient through any period of toxicity. Mesna has been administered at doses from 70 to 100mg/kg without any toxic effect on haematopoiesis, hepatic or renal function or the CNS.

Overdose may lead to the reactions observed in a tolerability study in healthy volunteers at single doses of 60 - 70mg/kg: nausea, vomiting, abdominal pain, colic, diarrhoea, headache, fatigue, paresthesia, fever, limb and joint pains, lack of energy like exhaustion and weakness, depression, irritability, rash, bronchospasm, flushing, hypotension, bradycardia and tachycardia.

For advice on the management of overdose please contact the National Poisons Centre on phone number: 0800 764 766 [0800 POISON] in New Zealand (or 131126 in Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group Detoxifying agents for antineoplastic treatment

ATC code V03AF

Mechanism of action

Uromitexan was developed as a prophylactic agent, used to prevent and reduce the urothelial toxicity (haemorrhagic cystitis) induced by oxazaphosphorine alkylating agents such as ifosfamide or cyclophosphamide.

The active ingredient, mesna, is a synthetic sulphhydryl compound designated as sodium 2-mercaptoethane sulphonate.

Chemical structure



Structural formula

HS-CH₂-CH₂-SO₃⁻Na⁺

Molecular formula

C₂H₅NaO₃S₂

Molecular weight

164.18.

CAS number

19767-45-4

Clinical trials

Evidence of the efficacy of oral mesna is based on studies with the drinking ampoule which was administered either following an initial dose of intravenous mesna or as the only form of mesna therapy. In 18 studies involving 320 patients and 700 courses of treatment, macroscopic haematuria was observed in 1.6% of courses. This may be compared with results from two other studies in which patients were hydrated instead of receiving mesna therapy. In these studies, the incidence of macroscopic haematuria after 65 courses of treatment was 45%.

5.2 Pharmacokinetic properties

Two bioavailability studies have been undertaken comparing mesna tablets with mesna injection. In one study, the urinary recovery of mesna 24 hours after 2 x 600mg tablets was 48% of that after 1200mg mesna given intravenously. In the second study, the corrected urinary recovery of mesna 24 hours after 2 x 600mg tablets was 80% of that after 600mg mesna given intravenously. The reason for the higher recovery of mesna in this study is not clear.

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Dosing regimens are based on the observation that the urinary excretion of mesna after tablet administration begins two hours later than after intravenous administration, and on the assumption that the bioavailability of the tablets is 50%, based on the two studies summarised above. Hence, the recommended dosing (see section 4.2) is that, when oral mesna is administered, tablets should be taken two hours before oxazaphosphorine therapy and then at 2 and 6 hours. If an initial intravenous dose of mesna is given with cytotoxic therapy, tablets should be taken 2 and 6 hours later. The dose of oral mesna should be double that of intravenous mesna (i.e. 40% of the oxazaphosphorine dose).

Metabolism

Analogous to the physiological cysteine-cystine system, mesna is rapidly and easily converted by autoxidation to its only metabolite, disodium 2,2'-dithio-bisethane sulphonate (mesna disulphide, dimesna) forming a disulphide link. Following intravenous injection, only a small portion of the administered dose is detected in the blood as a reduced thiol compound (mesna). Mesna disulphide remains in the intravascular space and is rapidly delivered to the kidney. In the renal tubular epithelium a considerable proportion of mesna disulphide is again reduced to a free thiol compound, presumably mediated by glutathione reductase. Acrolein or other urotoxic oxazaphosphorine metabolites are detoxified by chemical reaction with the free thiol compound i.e. mesna.

Excretion

The first and most important step towards detoxification is the reaction of mesna with the double bond of acrolein, resulting in the formation of a stable thioether which can be detected in the urine by chromatography. In the second step, mesna reduces the speed of degradation of the 4-hydroxy metabolite in the urine. A relatively stable, non-urotoxic condensation product from 4-hydroxy cyclophosphamide or 4-hydroxy ifosfamide and mesna is formed. As a result of this chemical interaction, mesna inhibits the degradation of 4-hydroxy cyclophosphamide or 4-hydroxy ifosfamide and hence the formation of acrolein. The presence of this intermediate chemical species can be detected by chromatographic urinalysis.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No long-term animal studies have been performed to evaluate the carcinogenic potential of mesna.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate, cellulose microcrystalline, lactose, magnesium stearate, maize starch, povidone.

Coating

Hypromellose, Macrogol 6000, simethicone, titanium dioxide.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

36 months. The expiry date can be found on the packaging.

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6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

Uromitexan (mesna) 400mg (tablets) in pack sizes of 10, 20 & 50.

Uromitexan (mesna) 600mg (film coated tablets) in pack sizes of 10, 20 & 50.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

Uromitexan is distributed in New Zealand by

Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060.

Baxter Healthcare Ltd
PO Box 14 062
Panmure
Auckland 1741

Phone (09) 574 2400.

Uromitexan is distributed in Australia by

Baxter Healthcare Pty Ltd
1 Baxter Drive
Old Toongabbie, NSW 2146.

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:

400mg tablet: 8 August 1996.

600mg film coated tablet: 8 August 1996.

10 DATE OF REVISION OF THE TEXT

17 September 2019.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
ALL	Headings and formatting made consistent throughout document.,
2	Active ingredient information made consistent with injection data sheet.
4.6, 4.8	Safety information updated.
5.1	Pharmacodynamic information relocated.

Based on Australian PI most recent amendment 29 August 2019; and CCDS 424 2015 0921.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.

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