

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Uromitexan 100mg/ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Mesna 100 mg/ml

Each 4 ml ampoule contains 400 mg mesna

Each 10 ml ampoule contains 1 g mesna

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.(Oral solution)

Clear, colourless aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the prevention of urothelial toxicity including haemorrhagic cystitis, microhaematuria and macrohaematuria in patients treated with ifosfamide and cyclophosphamide, in doses considered to be urotoxic.

4.2 Posology and method of administration

Sufficient mesna must be given to adequately protect the patient 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. Urinary output should be maintained at 100 ml/hr (as required for oxazaphosphorine treatment) and the urine monitored for haematuria and proteinuria throughout the treatment period.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration.

Any solutions which are discoloured, hazy, or contain visible particulate matter should not be used.

Where ifosfamide or cyclophosphamide is used as an iv bolus: Mesna is given by intravenous injection over 15-30 minutes at 20% of the simultaneously administered oxazaphosphorine on a weight for weight basis (w/w). The same dose of mesna is repeated after 4 and 8 hours. The total dose of mesna is 60% (w/w) of the oxazaphosphorine dose. This is repeated on each occasion that the cytotoxic agents are used.

Example dosage schedule:

	0 hrs	4 hrs	8 hrs
Cyclophosphamide/Ifosfamide	2 g	-	-
Uromitexan	400 mg	400 mg	400 mg

If necessary the dose of mesna can be increased to 40% of the oxazaphosphorine dose given four times at three hourly intervals (0, 3, 6 and 9 hours). (Total dose = 160% (w/w) of the oxazaphosphorine dose).

This larger dose is recommended in children, in patients whose urothelium may be damaged from previous treatment with oxazaphosphorine or pelvic irradiation, or in patients who are not adequately protected by the standard dose of mesna.

Example dosage schedule:

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	0 hrs	3 hrs	6 hrs	9 hrs
Cyclophosphamide/Ifosfamide	2 g	-	-	
Uromitexan	800 mg	800 mg	800 mg	800 mg

Where cyclophosphamide is used orally: The same dose regimen of mesna applies as though cyclophosphamide were used as an i.v. bolus.

Where ifosfamide is used as a 24-hour infusion: Mesna can be used as a concurrent infusion. An initial 20% (w/w) of the total ifosfamide dose is given as an i.v. bolus, then an infusion of 100% (w/w) of the ifosfamide over 24 hours, followed by a further 12-hour infusion of 60% (w/w) of the ifosfamide dose. Total mesna dose = 180% of the ifosfamide dose.

Example dosage schedule:

	0 hrs	0-24 hrs	24 hrs	28 hrs		32 hrs		36 hrs	
Ifosfamide	-	5 g/m ² infusion	-	-		-		-	
Uromitexan	1 g/m ² iv	5 g/m ² infusion	3g/m ² infusion						
					1 g/m ² iv		1 g/m ² iv		1 g/m ² iv

Where ifosfamide is used as a long-term infusion: An initial 20% (w/w) of the first 24 hours ifosfamide dose is given as an i.v. bolus as the ifosfamide infusion starts. Then each 24 hour infusion of ifosfamide is given with a concurrent 24 hour infusion (100% w/w) of mesna. A 12 hour infusion of mesna (60% (w/w) of the final 24 hour dose of ifosfamide) should be commenced as the ifosfamide-mesna infusion finishes.

Example dosage schedule:

	Day 1		Day 2			Day 3		Day 4		
	0 hrs	0-24 hrs		0-24 hrs	0-24 hrs		24 hrs	4 hrs	8 hrs	12 hrs
Ifosfamide	-	2 g/m ² infusion		2 g/m ² infusion	2 g/m ² infusion		-	-	-	-
Uromitexan	0.4g/m ² iv	2 g/m ² infusion		2 g/m ² infusion	2 g/m ² infusion		1.2 g/m ² infusion			
								0.4 g/m ² iv	0.4 g/m ² iv	0.4 g/m ² iv

The final 12-hour infusion of mesna, after long-term or 24 hour infusion of ifosfamide, may be replaced by boluses at 28, 32 and 36 hours, each of 20% (w/w) of the ifosfamide dose, or by oral mesna.

Mesna can be mixed in the same infusion bag as the ifosfamide.

Oral use of mesna ampoules: Mesna has been shown to be effective when taken orally. Compared with intravenous administration, overall availability of mesna in urine after oral administration is approximately 50%; the onset of urinary excretion is delayed by up to 2 hours and is more prolonged than following intravenous dosing.

With the exception of continuous long-term infusions of oxazaphosphorines with mesna, intravenously administered mesna may be replaced by oral administration of mesna. The dosage should be 40% w/w of the dosage of the oxazaphosphorines. The contents of the ampoule should be added to a flavoured soft drink (e.g. orange juice, cola). This mixture is stable when refrigerated in a sealed container for 24 hours.

For intermittent oxazaphosphorine therapy following an initial intravenous injection of mesna at a dose of 20% (w/w) of the oxazaphosphorine dose, oral mesna (40% w/w) should be administered at 2 hours and again at 6 hours after the initial intravenous dose. Alternatively, three oral doses of mesna may be administered, replacing the i.v. dose with an oral dose (40% w/w) 2 hours prior to administration of oxazaphosphorines.

Example dosage schedule:

	- 2 hrs	0 hrs	2 hrs	6 hrs
Cyclophosphamide/Ifosfamide	-	1 g iv	-	-
Uromitexan	400 mg po	-	400 mg po	400 mg po
		200 mg iv	400 mg po	400 mg po

Where ifosfamide is used as a long-term continuous infusion with concomitant mesna, oral mesna may be taken as the infusion of ifosfamide and mesna finishes, then at 2 hours and 6 hours after the time at the finish of the infusion. All oral mesna doses should be 40% (w/w) of the final 24 hour ifosfamide dose.

Example dosage schedule:

	0 hrs	0-24 hrs	24 hrs	26 hrs	30 hrs
Ifosfamide	-	5 g/m ² infusion	-	-	-
Uromitexan	1 g/m ² iv	5 g/m ² infusion	2 g/m ² po	2 g/m ² po	2 g/m ² po

Mesna is also available for oral administration as Uromitexan Tablets. For further information see the Summary of Product Characteristics for Uromitexan Tablets or contact Baxter Healthcare Ltd.

Children

Safety and effectiveness of Mesna in paediatric patients (<16 years of age) have not been established in clinical studies performed by Baxter. However, the use of mesna in paediatric patients is referenced in the medical literature, see section 4.4.

Children generally micturate more frequently than adults and therefore it may be necessary to shorten the interval between doses and/or to increase the number of individual doses.

Elderly

No specific information is available. Clinical trials have included patients over 65 and no adverse reactions specific to this age group have been reported.

4.3 Contraindications

Known hypersensitivity to mesna or any of the excipients.

4.4 Special warnings and precautions for use

WARNINGS

Hypersensitivity

Hypersensitivity reactions to mesna have been reported following administration of mesna as an uroprotectant. These include:

Various skin and subcutaneous tissue symptoms (see Section 4.8)

Cases of severe bullous and ulcerative skin and mucosal reactions were reported. Some reactions were considered to be consistent with Stevens-Johnson Syndrome, toxic epidermal necrolysis, or erythema exudativum multiforme.

In some cases, skin reactions were accompanied by one or more other symptoms, such as

- fever,
- cardiovascular symptoms (see Section 4.8)
- signs consistent with acute renal impairment,
- pulmonary symptoms (see Section 4.8)
- laboratory signs of disseminated intravascular coagulopathy (DIC)
- haematological abnormalities (see Section 4.8),
- increased liver enzymes,
- nausea, vomiting,

- pain in the extremities, arthralgia, myalgia, malaise,
- stomatitis, and
- conjunctivitis.

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.

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 (SH) group-containing organic compound. Thiol compounds show some similarities in their adverse reaction profile, including a potential to elicit severe skin reactions. Examples of drugs that are thiol compounds include amifostine, penicillamine, and captopril.

It is not clear whether patients who experienced an adverse reaction to such a drug 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.

PRECAUTIONS

Mesna does not prevent haemorrhagic cystitis in all patients. Patients should be monitored accordingly.

Sufficient urinary output should be maintained, as required for oxazaphosphorine treatment.

Sodium content

Mesna solution for injection contains approximately 59 mg of sodium per 400 mg mesna.

Lab test interferences

Mesna treatment may cause false positive reactions in nitroprusside sodium-based urine tests (including dipstick tests) for ketone bodies. The addition of glacial acetic acid can be used to differentiate between a false positive result (cherry-red colour that fades) and a true positive result (red-violet colour that intensifies).

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

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.

See also Section 4.8 for information on laboratory test abnormalities observed in pharmacokinetic studies.

Paediatric use

Safety and effectiveness of Mesna in paediatric patients (<16 years of age) have not been established in clinical studies performed by Baxter. However, the use of mesna in paediatric patients is referenced in the medical literature.

4.5 Interaction with other medicinal products and other forms of interactions

The systemic effects of oxazaphosphorines are not affected by mesna. In clinical trials it was shown that overdoses of mesna did not diminish the acute toxicity, subacute toxicity, leucocytic activity, and immunosuppressive efficacy of oxazaphosphorines. Animal studies with ifosfamide and cyclophosphamide on a variety of tumours have also demonstrated that mesna does not interfere with their antineoplastic activity.

Mesna also does not affect the antineoplastic efficacy of other cytostatics (e.g. adriamycin, BCNU, methotrexate, vincristine), nor the therapeutic effect of other drugs such as digitalis glucosides.

Food does not influence the absorption and urinary elimination of mesna.

4.6 Fertility, pregnancy and lactation

There are no adequate data from the use of mesna in pregnant or lactating women. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing mesna.

Pregnancy and lactation are contraindications for cytostatic treatment, and consequently Uromitexan is not likely to be used under these circumstances.

Should an individual patient be undergoing oxazaphosphorine therapy during pregnancy then Uromitexan should be administered to this patient. Mothers should not breast-feed whilst being treated with these drugs.

Animal studies have shown no evidence of embryotoxic or teratogenic effects of mesna.

4.7 Effects on ability to drive and use machines

Patients undergoing treatment with mesna may experience undesirable effects (including, e.g., syncope, light-headedness, 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

The most frequently occurring adverse reactions (> 10%) associated with use of mesna: headache, infusion site reactions, abdominal pain/colic, lightheadedness, lethargy/drowsiness, pyrexia, rash, diarrhoea, nausea, flushing, and influenza-like illness. 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).

Because mesna is used in combination with oxazaphosphorines or oxazaphosphorine-containing combination chemotherapy, it is often difficult to distinguish adverse reactions that may be due to mesna from those caused by concomitantly administered cytotoxic agents.

ADR frequency is based upon the following scale: Very common ($\geq 1/10$); Common ($\geq 1/100 - < 1/10$), Uncommon ($\geq 1/1,000 - < 1/100$), Rare ($\geq 1/10,000 - < 1/1,000$), Very rare ($< 1/10,000$), Unknown (adverse reactions reported in the post-marketing experience)

Health Products Regulatory Authority

System Organ Class (SOC)	Adverse Reaction	Frequency
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Lymphadenopathy Pancytopenia Leukopenia Lymphopenia Thrombocytopenia Eosinophilia	Common Unknown Unknown Unknown Unknown Unknown
IMMUNE SYSTEM DISORDERS	Anaphylaxis Hypersensitivity	Unknown Unknown
METABOLISM AND NUTRITION DISORDERS	Decreased appetite Feeling of dehydration	Common Common
PSYCHIATRIC DISORDERS	Insomnia Nightmare	Common Common
NERVOUS SYSTEM DISORDERS	Headache Light-headedness Lethargy/Drowsiness Dizziness Paresthesia Hyperesthesia Syncope Hypoesthesia Disturbance in attention Convulsion	Very common Very common Very common Common Common Common Common Common Common Common Unknown
EYE DISORDERS	Conjunctivitis Photophobia Vision blurred Periorbital oedema	Common Common Common Unknown
CARDIAC DISORDERS	Palpitations Electrocardiogram abnormal Tachycardia	Common Unknown Unknown
VASCULAR DISORDERS	Flushing Hypotension Hypertension	Very common Unknown Unknown
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	Nasal congestion Cough Pleuritic pain Dry mouth Bronchospasm Dyspnea Laryngeal discomfort Epistaxis Respiratory distress Hypoxia Oxygen saturation decreased Tachypnea Hemoptysis	Common Common Common Common Common Common Common Common Common Unknown Unknown Unknown Unknown Unknown

System Organ Class (SOC)	Adverse Reaction	Frequency
GASTROINTESTINAL DISORDERS	Abdominal pain/colic Nausea Diarrhoea Mucosal irritation ¹ Flatulence Vomiting Burning pain (substernal / epigastric) Constipation Gingival bleeding Stomatitis Bad taste	Very common Very common Very common Common Common Common Common Common Common Common Unknown Unknown
HEPATOBIILIARY DISORDERS	Transaminases increased Hepatitis Gamma-glutamyl transferase increased Blood alkaline phosphatase increased	Common Unknown Unknown Unknown
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Rash ² Pruritus Hyperhidrosis Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Drug rash ³ Ulcerations and/or bullae/blistering ⁴ Angioedema Fixed drug eruption Photodistributed rash Urticaria (localised or generalised) Burning sensation Erythema	Very common Common Common Unknown Unknown Unknown Unknown Unknown Unknown Unknown Unknown Unknown Unknown Unknown
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia Back pain Myalgia Pain in extremity Pain in jaw	Common Common Common Common Common
RENAL AND URINARY DISORDERS	Dysuria Acute renal failure	Common Unknown

System Organ Class (SOC)	Adverse Reaction	Frequency
GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS	Infusion site reactions - Infusion site pruritus - Infusion site rash - Infusion site pain - Infusion site erythema - Infusion site urticaria - Infusion site swelling Pyrexia Influenza-like illness Rigors Fatigue Chest pain Malaise Face edema Edema peripheral Asthenia Infusion site reactions ⁵	Very common Very common Very common Common Common Common Common Very common Very common Common Common Common Common Unknown Unknown Unknown Unknown
INVESTIGATIONS	Laboratory signs of disseminated intravascular coagulation Prothrombin time prolonged Activated partial thromboplastin time prolonged	Unknown Unknown Unknown

¹Oral, rectal

²Including nonpruritic, pruritic, erythema/erythematous, eczematous, papular, and/or macular rashes.

³ with eosinophilia and systemic symptoms.

⁴ mucocutaneous, mucosal, oral, vulvovaginal, anorectal.

⁵ thrombophlebitis, irritation

- Time to onset and experience with re-exposure

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.

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

- Infusion site reactions

In some subjects experiencing local cutaneous infusion site reactions, subsequent exposure to mesna resulted in a cutaneous event in other areas.

- 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, dyspnea, fever, headache, gastrointestinal symptoms, drowsiness, malaise, myalgia, and influenza-like symptoms.

- Gastrointestinal reactions

Gastrointestinal reactions reported in healthy subjects included nausea, vomiting, diarrhea, 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRC Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Reports of inadvertent overdose and observations from a high-dose tolerability study in healthy volunteers showed that, in adults, single doses in the range of approximately 4g to 7g of mesna can cause symptoms such as nausea, vomiting, abdominal pain/colic, diarrhoea, headache, fatigue, limb and joint pains, rash, flushing, hypotension, bradycardia, tachycardia, paresthesia, fever, and bronchospasm.

A markedly increased rate of nausea, vomiting and diarrhoea has also been found in oxazaphosphorine-treated patients receiving ≥ 80 mg mesna per kg per day intravenously compared with patients receiving lower doses or hydration treatment only.

A specific antidote to mesna is not known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: detoxifying agent for antineoplastic treatment

ATC Code: VO3AF01.

Mesna is an antidote, and offers the possibility of reliably preventing urotoxic side-effects associated with aggressive cancer chemotherapy using oxazaphosphorine cytostatics. Extensive and wide-ranging pharmacological and toxicological investigations have shown that mesna has no intrinsic pharmacodynamics and low toxicity. The pharmacological and toxicological inertness of mesna administered systemically and its excellent detoxifying effect in the efferent urinary tract and bladder, are due to the nature of its pharmacokinetics.

5.2 Pharmacokinetic properties

Mesna, a free thiol, is easily and rapidly transformed by auto-oxidation into its only metabolite mesna-disulphide (dimesna). Dimesna remains in the intravascular compartment and is quickly transported to the kidneys.

In the epithelium of renal tubuli, dimesna is again reduced to the free thiol compound, which is then able to react chemically in the urine with toxic oxazaphosphorine metabolites.

Elimination (being almost exclusively renal) starts immediately after administration. Excretion is as the free thiol (mesna) in the first 4 hours after a single dose, and almost exclusively as the disulphide (dimesna) thereafter.

Renal elimination is almost complete after approximately 8 hours.

Approximately 30% of an intravenous dose is bioavailable as free thiol (mesna) in the urine.

5.3 Preclinical safety data

Nothing relevant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Sodium Hydrochloride
Water for Injections

6.2 Incompatibilities

Mesna is incompatible with platinum derivatives (e.g. Cisplatin Carboplatin and nitrogen mustard) and must not be mixed in the same infusion solution.

Mixing mesna and epirubicin leads to inactivation of epirubicin and should be avoided.

6.3 Shelf life

Unopened: 5 years

Once opened, vials should be used immediately.

Chemical and physical in use stability have been demonstrated as follows:

Uromitexan is chemically compatible with 0.9% saline or 5.0% dextrose for 36 hours and in dextrose/saline for 24 hours at room temperature.

Uromitexan and ifosfamide are chemically compatible with:

- (i) 0.9% saline and dextrose/saline solution for one week at room temperature
- (ii) Water for Injections for one week under refrigeration
- (iii) 5% dextrose solution for 24 hours at room temperature
- (iv) 0.9% saline solution for 28 days at room temperature

Uromitexan and cyclophosphamide are chemically compatible with:

- (i) 10% dextrose solution for 2 hours at room temperature

Uromitexan does not contain a preservative.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. Any solutions which are discoloured, hazy, or contain visible particulate matter should not be used.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours (less when combined with cyclophosphamide in dextrose, see above) at 2 to 8°C unless dilution has taken place in controlled and validated aseptic conditions.

Uromitexan can also be stored in cola drinks or orange juice. Once opened and mixed for drinking, the mixture should be kept in the fridge in a sealed container for not more than 24 hours.

6.4 Special precautions for storage

Do not store above 30°C.

Keep the container in the outer carton.

6.5 Nature and contents of container

15ml clear, type 1 glass ampoules in a folded cardboard box. Ampoules contain 4ml or 10ml of solution.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

See section 6.3, Shelf life

7 MARKETING AUTHORISATION HOLDER

Baxter Holding B.V.
Kobaltweg 49
3542CE Utrecht
Netherlands

8 MARKETING AUTHORISATION NUMBER

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