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Injectable Mesna Solutions

Description

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The chemical name of the active substance mesna is sodium-2-mercaptoethane sulfonate. (Formula I)

$HS-CH_2-CH_2-SO_3Na$ Formula I

Mesna for example protects the urinary organs in the treatment of tumour diseases with ifosfamide. In addition, mesna has already been used for a long time as a mucolytic agent.

Mesna is a white hygroscopic powder with a characteristic odour. The substance is highly sensitive to oxidation and rapidly decomposes on contact with oxygen to form dimesna, particularly in a humid atmosphere. (Formula II)

$NaSO_3-CH_2-CH_2-S-S-CH_2-CH_2-SO_3Na$ Formula II

Mesna has hitherto been applied orally, parenterally and by means of inhalation. All the dosage forms used are liquid formulations that are given in the form of ampoules or drinkable ampoules. Since mesna is very sensitive to oxidation and reacts in the presence of oxygen to form dimesna, which is poorly absorbed, the aqueous solution has to be protected against oxygen. For this purpose the solution is sealed into glass ampoules.
The solution for parenteral application is offered in 2 ml, 4 ml and 10 ml ampoules containing 10 % mesna.
Mesna is used to prevent urotoxic symptoms during ifosfamide therapy.

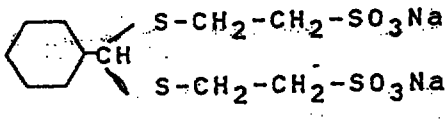
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Mesna is generally given simultaneously with ifosfamide as well as after 4 and after 8 hours, in each case in a dose that corresponds to 20 % of the ifosfamide dose, applied intravenously. The ifosfamide dose can be between 1g/m^2 to 8 g/m^2 body surface. The corresponding mesna doses consequently lie within a very broad spectrum. There was therefore a desire for multi-dose containers from which any quantity of injectable solution could be withdrawn and no wastage, such as incurred with opened ampoules, occurred. These injection bottles were also intended to contain a larger volume of solution.

DAB 9 requires that multi-dose containers be preserved to provide protection against microbial contamination. The injectable solution filled into ampoules is very stable. This formulation was therefore used and only one preservative, namely benzyl alcohol, used throughout the world for parenterally applied aqueous systems, was added thereto. The pH value of this solution is adjusted to 6.5 - 8.5 with sodium hydroxide solution. The solution also contains a complexing agent since mesna forms coloured complexes with heavy metal ions.

Stability storage tests showed, however, that these solutions were partially unstable.
The degradation product was identified as mesna acetal with benzaldehyde (Formula III)



Formula III

Benzaldehyde occurs in the formulation through oxidation of the benzyl alcohol used as preservative.

It has now surprisingly been found that this degradation product is only formed at pH values < 7.5 and is not formed at an pH value of 7.5 - 8.5.

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The invention thus relates to an injectable solution which contains, to 1 part of mesna

for example 0.00002 - 2.0 parts by weight
preferably 0.0001 - 1.0 parts by weight
in particular 0.0002 - 0.7 parts by weight of NaEDTA
as complexing agent and
for example 0.0002 - 2.0 parts by weight
preferably 0.0003 - 1.7 parts by weight
in particular 0.0004 - 1.4 parts by weight
of sodium hydroxide for pH adjustment and
for example 0.001 - 30.0 parts by weight
preferably 0.01 - 20.0 parts by weight
in particular 0.018 - 12.0 parts by weight
of benzyl alcohol as preservative.

The amount by weight of mesna in an injectable solution of this type is generally 1 mg per ml to 540 mg/ml. The solutions can be applied directly i.v. or designed as infusion solutions or concentrates as supplements to infusions.
The appropriate volumes are between 0.5 ml and 100 ml. Water for injection purposes is used as solvent.

In addition to the above listed auxiliary substances it is also possible to use:
complexing agents: for example the
calcium disodium salt of
edetic acid, citric acid,
tartaric acid or salts of
orthophosphoric acid.

The following are for example suitable to adjust the pH:
sodium hydroxide, potassium hydroxide,
tromethamine, sodium acetate,
trisodium citrate,
sodium monohydrogen phosphate,
potassium monohydrogen phosphate.

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Preservatives: for example
p-hydroxybenzoic acid ester,
m-cresol,
organomercuric compounds,
chlorobutanol, quaternary
ammonium compounds.

The preservatives may also be used in combination with benzyl alcohol.

To prepare the solution 80-90%, preferably 85% of the requisite amount of water (lacking in oxygen) are prepared and sodium edetate, benzyl alcohol and mesna dissolved with stirring and constant nitrogen gassing. When dissolution is complete the pH is adjusted to 8.0 by adding 10N sodium hydroxide solution. This solution is made up to the final volume with water (lacking in oxygen).

The solution obtained in this manner is sterilised by filtration through conventional pathogen-proof filters and then filled into appropriate containers for injectable preparations. The solution is covered with nitrogen during and after filtration. The storage time until filling into the injection containers, including the time to prepare the solution, should not exceed 5 hours.

For sterilisation purposes, conventional pathogen-proof filters, for example conventional bacteria filters with a pore size of 0.2 um are used. The glass vessels used are previously sterilised in conventional manner. The injection water used must be sterile and pyrogen-free and meet the requirements of the Deutsches Arzneibuch 10, 1991 edition. The injection vessels used are appropriately those made of tubular glass or blow-moulded glass of hydrolytic class II (for example 10R, 30R, 50H), see in this connection Deutsches Arzneibuch 10, 1991 edition, VI.2.1. and DIN standards 58366 part 1 and part 5). In addition, the injection vessels as well as additional

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auxiliary substances, such as rubber stoppers and crimped caps, should meet the requirements of DIN standards 58366, part 2 and part 3, as well as 58367, part 1.

The volume of solution in the appropriate containers amounts per container to between 4 ml and 100 ml, preferably between 10 ml and 75 ml, in particular between 40 ml and 60 ml. The amount of mesna per glass vessel is for example 4 mg to 50 g, preferably 1 g to 7.5 g, in particular 4 g - 6 g.
After filling the solution under aseptic conditions, the bottles are gassed with nitrogen to expel the oxygen and closed with injection stoppers. The filled injection bottles are sterilised in a steam steriliser.

The following examples illustrate the invention:

Example 1

Injection bottle with 50 ml of a 10 % injectable mesna solution

Composition

mesna (INN)	5000.0 mg
benzyl alcohol	520.0 mg
sodium edetate	12.5 mg
sodium hydroxide	10.0 - 70.0 mg[1) 2)]

Water for injection purposes 50.0 ml approx. ≙ 52.5 g

1) Used to adjust the pH value and is therefore variable
2) Used as 10N sodium hydroxide solution 25-175 x 10^{-3} ml [3)]
3) The use of more or less is balanced by water for injection purposes

The density of the solution is 1.05 g/ml.

Preparation of the solution

85 % of the amount of water for injection purposes (lacking in oxygen)

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are filled into a suitable vessel and the appropriate amounts of sodium edetate, benzyl alcohol and mesna dissolved therein with stirring and constant nitrogen gassing. The solution is adjusted to a pH value of 8.0 by addition of 10N sodium hydroxide solution and the result made up to the final volume with water for injection purposes (lacking in oxygen).
The water for injection purposes may contain a maximum of 1.5 ppm oxygen at 20°C. pH value, density and refractive index (n^{20} 1.34-1.36) are determined as in-process controls.
The solution is sterilised by filtration using a 0.2 um membrane filter. The solution is covered with nitrogen during and after filtration. A Sartorius SM 11107 or SM 11307 or Pall Filter NRP is, for example, used as a conventional pathogen-proof filter. Particular and bacterial contamination is avoided during storage of the solution before filling. Storage at room temperature (20° - 22°C) should not exceed 4 hours. Additional conventional prefilters may also be used for purposes of sterile filtration (for example Sartorius SM 13400 or Pall LPA) to protect the sterile filter.

Cleaning the injection bottles

DIN 50H/II, colourless 50 ml injection bottles are used as containers. They are flushed with hot and cold demineralised water and with air. All cleaning media are filtered to free them of suspended matter. To prevent recontamination due to particles from the air, the bottles are dried and sterilised using hot air (discontinuously at 180°C, 2 hours, continuous at 350°C for 10 minutes).

The rubber stoppers (for example Helvoet FM 157/1 grey) used to close the injection bottles are cleaned using demineralised water and, for example, a cleaning agent consisting of non-ionogenic surfactants and phosphoric acid esters in aqueous solution (for example MB 70, Huber, Freiburg).
The cleaned stoppers are rinsed free of fibres and fluff using water for injection purposes or filtered demineralised water.

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The stoppers cleaned in this manner are then sterilised using steam.
The injection bottles cleaned and sterilised in this manner are then gassed aseptically with nitrogen to displace the oxygen in the air, filled with 52 ml mesna solution and gassed again. Finally, the stoppers are positioned and secured with crimped caps. The filling volume is statistically monitored by then weighing the contents. The nominal filling amount is 52 ml = 54.6 g. The residual oxygen content in the headspace of the injection bottle is also monitored.
The filled injection bottles are sterilised in a steam steriliser (at least 120° / 20 minutes).
The injection bottles are checked for incorrect closure, outer faults, clarity and particulate impurities.

Example 2

Injection bottle with 50 ml of a 50 % concentrate (W/V) for addition to infusion solutions:
Composition:

mesna	25,000 g
benzyl alcohol	0.520 g
Na EDTA	0.0125 g
sodium hydroxide	0.05 - 0.35 g

water for injection purposes ad 50,000 ml = 61.0 g

The density of the concentrate is 1.22 g/ml 20°C. The preparation and sterile filtration of the solution, cleaning and sterilisation of the bottles and rubber stoppers, filling, closing of the bottles and final sterilisation are carried out according to Example 1.

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Injectable Mesna Solutions

Claims

1. An injectable mesna solution characterised in that the pH value is adjusted to a value above 7.5.

2. A process for the preparation of an injectable mesna solution, characterised in that a mesna solution is adjusted to a pH value of over 7.5 by addition of alkaline substances.

3. The use of the injectable mesna solution according to Claim 1 for the preparation of a medicament for preventing urotoxic side effects of oxazaphosphorin treatment.

4. A medicament for preventing the side effect of oxazaphosphorin consisting of an injectable mesna solution with a pH value greater than 7.5.

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Injectable Mesna Solutions

Abstract

Storage-stable injectable mesna solutions with a pH value higher than 7.5 are described together with a method of manufacture.

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INJECTABLE MESNA SOLUTIONS

The chemical name for the active substance mesna is sodium 2-mercaptoethanesulphonate. (Formula I)

$HS-CH_2-CH_2-SO_3Na$ formula I

Mesna protects, for example, the urea-excreting organs during tumour treatment with ifosfamide. Mesna has also long been used as a mucolytic.

Mesna is a white, hygroscopic powder having a characteristic odour. The substance is highly sensitive to oxidation and is rapidly converted to dimesna on contact with oxygen, in particular in a moist atmosphere. (Formula II)

$NaSO_3-CH_2-CH_2-S-S-CH_2-CH_2-SO_3Na$ formula II

Mesna has hitherto been administered orally, parenterally and by inhalation. All dosage forms which have been used are liquid preparations which are supplied as ampoules or drinking ampoules. As mesna is highly sensitive to oxidation and reacts in the presence of oxygen to yield the poorly resorbed dimesna, the aqueous solution must be protected from oxygen. To this end, the solution is sealed in glass ampoules.
The solution for parenteral administration is supplied in ampoules of 2 ml, 4 ml and 10 ml, which contain 10% mesna. Mesna is used to prevent the urotoxic effects of treatment with ifosfamide.

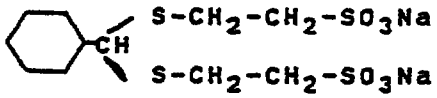
Mesna is generally administered intravenously simultaneously with ifosfamide and after 4 and 8 hours, in each case in a dose amounting to 20% of the dose of ifosfamide. The dose of ifosfamide may be between 1 g/m^2 and 8 g/m^2 of body surface. The corresponding doses of mesna are accordingly spread over a very wide range. A desire was thus expressed for multi-dose containers, from which any desired quantity of injection solution may be withdrawn without having to accept the losses which occur

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in the case of opened ampoules. These injection bottles should moreover contain a larger volume of solution.

According to DAB 9 [German pharmacopoeia], multi-dose containers must be preserved in order to prevent microbial contamination. The injection solution filled in ampoules is very stable. This formulation was thus used and a preservative merely added, namely benzyl alcohol, which is used worldwide for aqueous systems which are administered parenterally. The pH value of this solution is adjusted to 6.5-8.5 with sodium hydroxide solution. The solution moreover contains a complexing agent, as mesna forms coloured complexes with heavy metal ions.

Stability testing revealed, however, that these solutions were sometimes unstable.
The decomposition product was identified as the acetal of mesna with benzaldehyde (formula III)



formula III

Benzaldehyde occurs in the formulation due to the oxidation of the benzyl alcohol used as preservative.

It has surprisingly now been found that this decomposition product occurs only at pH values of < 7.5 and is not formed if the pH is adjusted to 7.5-8.5.

The invention thus relates to an injection solution which contains, relative to 1 part of mesna,

for example 0.00002 - 2.0 parts by weight
preferably 0.0001 - 1.0 parts by weight
in particular 0.0002 - 0.7 parts by weight
of NaEDTA as complexing agent and

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for example 0.0002 - 2.0 parts by weight
preferably 0.0003 - 1.7 parts by weight
in particular 0.0004 - 1.4 parts by weight
of sodium hydroxide to adjust pH and
for example 0.001 - 30.0 parts by weight
preferably 0.01 - 20.0 parts by weight
in particular 0.018 - 12.0 parts by weight
of benzyl alcohol as preservative.

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The weight of mesna in such an injection solution is generally 1 mg per ml to 540 mg/ml. The solutions may be administered directly intravenously or be designed as infusion solutions or concentrates as an additive to infusions.
The corresponding volumes are between 0.5 ml and 100 ml. Water suitable for injection is used as the solvent.

The following may also be used in addition to the above-stated auxiliary substances:

complexing agents: for example the calcium-disodium salt of edetic acid, citric acid, tartaric acid or salts of orthophosphoric acid.

The following are, for example, suitable for adjusting pH sodium hydroxide, potassium hydroxide, trometamol, sodium acetate, trisodium citrate, sodium monohydrogen phosphate, potassium monohydrogen phosphate.

Preservatives: for example p-hydroxybenzoic acid esters, m-cresol, organomercury compounds, chlorobutanol, quaternary ammonium compounds.

The preservatives may also be used in combination with benzyl alcohol.

The solution is produced by initially introducing 80-90%, preferably 85% of the necessary quantity of (low-oxygen)

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water into a vessel and dissolving sodium edetate, benzyl alcohol and mesna with stirring and constant passage of nitrogen. Once dissolution is complete, a pH value of 8.0 is established by adding 10N sodium hydroxide solution. This solution is made up to the final volume with (low-oxygen) water.

The resultant solution is sterilised by filtration through microbe-retaining filters conventional for this purpose and then filled in appropriate containers for injection preparations. This solution is provided with a blanket of nitrogen during and after filtration. The storage time until filling in the injection containers should not exceed 5 hours, including the time for preparation of the solution.

Conventional microbe-retaining filters, for example conventional bacterial filters with a pore size of 0.2 μm are used for sterilisation. The glass vials used are previously sterilised in the conventional manner. The water for injection used must be sterile and contain no pyrogens and comply with the requirements of the German pharmacopoeia, 10th edition, 1991. The injection vials used are conveniently made from glass piping or furnace glass of hydrolysis class II (for example 10R, 30R, 50H), *c.f.* in this connection German pharmacopoeia, 10th edition, 1991, VI.2.1 and DIN standards 58366 parts 1 and part 5. The injection vials and the other auxiliary materials, such as rubber bungs and crimped caps, should moreover comply with the requirements of DIN standards 58366, part 2 and part 3 and 58367, part 1.

The quantity of solution in the particular containers are between 4 ml and 100 ml, preferably between 10 ml and 75 ml, in particular between 40 ml and 60 ml per container. The quantity of mesna per glass vial is, for example 4 mg to 50 g, preferably 1 g to 7.5 g, in particular 4 g - 6 g.

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Once the solution has been filled under aseptic conditions, the bottles are flushed with nitrogen to expel any oxygen and sealed with injection bungs. The filled injection bottles are sterilised in a steam steriliser.

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The following examples illustrate the invention:

Example 1

Injection bottle with 50 ml of a 10% mesna injection solution

Composition		
Mesna (INN)	5000.0	mg
Benzyl alcohol	520.0	mg
Sodium edetate	12.5	mg
Sodium hydroxide	10.0-70.0	mg[1) 2)]
Water suitable for injection	50.0	ml ≙ 52.5 g

1) Used to adjust pH value and thus variable.
2) Used as 10N sodium hydroxide 25-175 × 10^{-3}ml [3)]
3) Excess or shortfall offset by water suitable for injection.

The density of the solution is 1.05 g/ml.

Production of solution

85% of the quantity of (low-oxygen) water for injection are introduced into a suitable vessel and the appropriate quantities of sodium edetate, benzyl alcohol and mesna are dissolved with stirring and constant passage of nitrogen. A pH value of 8.0 is established by adding 10N sodium hydroxide solution and the solution is made up to the final volume with water suitable for injection (low-oxygen). The water suitable for injection may contain at most 1.5 ppm of oxygen at 20°C. pH value, density and refractive index (n^{20}_D 1.34-1.36) are determined as process control parameters.
The solution is sterilised by filtration through a 0.2 µm membrane filter. The solution is provided with a nitrogen blanket during and after filtration. Conventional microbe-

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retaining filters which are used are, for example Sartorius SM 11107 or SM 11307 or Pall Filter NRP. The solution is stored until filled with protection from particulate and bacterial contamination. Storage at room temperature (20°-22°C) should not exceed 4 hours. Conventional prefilters (for example Sartorius SM 13400 or Pall LPA) may additionally be used for sterile filtration in order to protect the sterile filter.

Cleaning of injection bottles

The containers used are colourless, 50 ml DIN 50H/II injection bottles. They are rinsed with hot and cold demineralised water and air. Suspended materials are removed from all cleaning media by filtration.
While avoiding recontamination with air-borne particulates, the bottles are dried with hot air and sterilised (batchwise at 180°C, 2 hours, continuously at 350°C, 10 minutes).
The rubber bungs (for example Helvoet FM 157/1 grey rubber bungs), with which the injection bottles are sealed, are cleaned using demineralised water and, for example, a detergent consisting of an aqueous solution of non-ionic surfactants and phosphoric acid esters (for example MB 70, Huber, Freiburg).
The cleaned bungs are rinsed free of fibres and lint using water suitable for injection or filtered demineralised water. The bungs cleaned in this manner are then sterilised with steam.
The injection bottles cleaned and sterilised in this manner are then flushed with nitrogen to expel atmospheric oxygen, filled with 52 ml of mesna solution and again flushed with gas. Bungs are then inserted and the crimped caps fastened. Filling volume is randomly monitored by reweighing the contents. The required filling quantity of 52 ml = 54.6 g. The residual oxygen content in the headspace of the injection bottle is also monitored.

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The filled injection bottles are sterilised in a steam steriliser (at least 120°/20 minutes).
The injection bottles are inspected for sealing defects, external defects, clarity and particulate contamination.

Example 2

Injection bottle with 50 ml of a 50% concentrate (wt./vol.) as additive for infusion solutions.
Composition:

Mesna	25.000	g
Benzyl alcohol	0.520	g
Na EDTA	0.0125	g
Sodium hydroxide	0.05-0.35	g
Water suitable for injection to make up to	50.000	ml = 61.0 g

The density of the concentrate is 1.22 g/ml 20°C.
Production and sterile filtration of the solution, cleaning and sterilisation of the bottles and rubber bungs, filling, sealing of bottles and final sterilisation proceed in accordance with example 1.

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Patent Claims

1. Mesna injection solution,
characterised in that
the pH value is adjusted to a value of above 7.5.

2. Process for the production of a mesna injection solution,
characterised in that
a mesna solution is adjusted to a pH value of above 7.5 by the addition of alkaline substances.

3. Use of the mesna injection solution according to claim 1 for the production of a pharmaceutical preparation to prevent the urotoxic side effects of treatment with oxazaphosphorines.

4. Pharmaceutical preparation to prevent the side effect of oxazaphosphorine,
characterised in that
it consists of a mesna injection solution with a pH value which is greater than 7.5.

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Injectable Mesna Solutions

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Abstract

Storage-stable injectable mesna solutions with a pH value higher than 7.5 are described together with a method of manufacture.

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