The chemical name for the active substance mesna is sodium 2-mercaptoethanesulphonate.

Mesna protects, for example, the urinary organs during ifosamide treatment of tumours. In addition, mesna has long been used as a mucolytic agent.

Mesna is a white, hygroscopic powder with a characteristic odour. The substance is very sensitive to oxidation and rapidly reacts on contact with oxygen, especially in a moist atmosphere, to give dimesna.

Mesna has hitherto been applied orally, parentally and as an inhalant. All the forms of presentation used have been liquid preparations. For oral application, only an aqueous solution is supplied. Since mesna is very sensitive to oxidation and reacts to give barely absorbable dimesna in the presence of oxygen, the aqueous solution must be protected from oxygen. The solution is sealed in glass ampoules for this purpose. The ampoules have to be opened by the patients just before use. This is an awkward procedure for oral application. Moreover, the solution is relatively heavy and demands a lot of storage space.

The main disadvantage of the drinking solution is the very unpleasant taste, so that patients are very reluctant to take it, even when it is flavoured. Since patients being treated with cytostatic substances often suffer from nausea and loss of appetite in any case, the unpleasant taste further impairs cooperation. For the reasons given above, there has long been a need for a pleasantly flavoured, stable and individually dosed oral form of presentation.

Although mesna is a crystalline powder, all attempts to prepare tablets, coated tablets or soft gelatine capsules have hitherto failed. In the case of soft gelatine

capsules, good protection from oxygen and decomposition was achieved by embedding in a lipid matrix. Due to interaction of the mesna with the capsule coverings, however, cracks were continually produced in the capsules during storage. The capsules were physically unstable. Direct formation of tablets of the active substance was also unsuccessful due to the high bulk volume of up to 500 ml/100 g.

Aqueous granulation of the active substance as preparation for forming tablets could not be achieved either by making into a conventional paste or by fluidised bed granulation, because mesna liquefies immediately on contact with water.

Surprisingly, it has now been found that mesna can be readily granulated using ispropanol or a mixture of water and isopropanol and that the granulate obtained can be readily further processed, using further auxiliary substances, to produce tablets and coated tablets. These tablets have high chemical stability, are easy to take and have virtually no taste if they are swallowed immediately.

Therefore, the invention relates to a tablet which contains, with reference to one part by weight of mesna,

0.01 - 1 parts by weight of a binder,
0.03 - 0.4 parts by weight of a disintegrant,
0.01 - 0.2 parts by weight of a lubricant and
0.1 - 1 parts by weight of a filler and, in the case of an effervescent tablet, an additional 0.05 - 30 parts by weight of a conventional physiologically acceptable effervescent mixture. In addition, this type of tablet may optionally also contain conventional physiologically acceptable flavouring, sweetening and/or aromatic substances.

Furthermore, the invention relates to a granulate which can be used for this type of tablet.

The amount by weight of mesna in this type of tablet is generally between 10 and 80 percent by weight, the remainder being the previously cited auxiliary substances, wherein the amount of each is with reference to one part by weight of mesna. For example, the preparations according to the invention contain 100 to 800 mg of mesna, preferably 300 to 500 mg of mesna.

Furthermore, the invention relates to a process for preparing this type of stable mesna tablet, which contains mesna as active substance (for example 10 - 80 wt.%), optionally conventional flavouring, sweetening and aromatic substances and, with reference to one part by weight of mesna
0.01 - 1 parts by weight of a binder,
0,03 - 0,4 parts by weight of a disintegrant,
0.01 - 0.2 parts by weight of a lubricant,
0.1 - 1 parts by weight of a filler and, in the case of an effervescent tablet, an additional 0.05 - 30 parts by weight of a conventional physiologically acceptable effervescent mixture and the preparation of a corresponding granulate, wherein preparation takes place in that mesna is first granulated with a C_1-C_4 alcohol or acetone or a mixture of the organic substances mentioned with water and a filler and binders, optionally also a disintegrant, in a manner which is known per se, wherein the auxiliary substances mentioned are used in the amounts specified with respect to one part by weight of mesna, or else only part of these amounts are added and the remainder is added after granulation, the granulate obtained is dried and then the lubricant and optionally the remainder of the binder, filler and disintegrant is added, the whole is homogenised and then compressed to form tablets and optionally the

tablets thus obtained are provided with a film coating using a known method. In the case of an effervescent tablet, the organic acid from the effervescent mixture or else the whole effervescent mixture is also added after drying the granulate.

Further specific forms of the invention are given in the Patent Claims.

Examples of auxiliary substances and carriers according to the invention which are in accordance with the Claims are:

Fillers: for example starch, cellulose, lactose, saccharose, fructose, sorbitol, mannitol, calcium phosphate, calcium hydrogen phosphate.
The total amount of filler in the tablet is 0.1 - 1 parts by weight, with reference to one part by weight of mesna.

Binders: for example gelatine, cellulose ether, pectins, alginates (sodium alginate), polyvinylpyrrolidone, lactose, microcrystalline cellulose (Avicel).
The total amount of binder in the tablet is 0.01 - 1 parts by weight, with reference to one part by weight of mesna.

Disintegrant: for example alginates, starch (corn starch), pectins, carboxymethyl cellulose, ultramylopectin, bentonite, polyvinyl-polypyrrolidone (in polyvinylpoly-pyrrolidone, the thread-like macromolecules of the polyvinylpyrrolidone are cross-linked; the product is insoluble in all conventional solvents; it has a porous

structure and is capable of swelling up a great deal;

particle size distribution: ca. 50% > 50 μm,
a maximum of 1% > 250 μm;
Bulk density: 280 - 380 g/litre)
The total amount of disintegrant in the tablet may be 1 - 10 wt.%.

Lubricants: for example stearic acid, stearates, polyglycols, talc, highly dispersed silicon dioxide.
The amount of lubricant per 1 part by weight of mesna is, in the case of a conventional tablet for swallowing, preferably 0.01 - 0.1, in particular 0.01 - 0.05 parts by weight.
In the case of an effervescent tablet 0.05 - 0.15 parts by weight of lubricant are preferably used to 1 part by weight of mesna.
The total amount of lubricant in the tablet may be 0.2 - 10 wt.%.

Lactose (for example coarse-grained) and/or calcium hydrogen phosphate are preferably used as fillers, polyvinylpyrrolidone and/or microcrystalline cellulose (Avicel) are preferably used as binders, starch, preferably corn starch, is preferably used as a disintegrant and stearates (for example magnesium stearate) are preferably used as lubricants.

The following are used, for example, to 1 part by weight of mesna:
Lactose; 0.06 - 0.4 parts by weight, preferably 0.13 - 0.33, in particular 0.2 - 0.25 parts by weight.

Calcium hydrogen phosphate; 0.1 - 0.3 parts by weight, preferably 0.1 - 0.23, in particular 0.1 - 0.12 parts by weight.
Corn starch (for the granulate phase); 0.03 - 0.3 parts by weight, preferably 0.13 - 0.33, in particular 0.2 - 0.25 parts by weight.
Polyvinylpyrrolidone; 0.02 - 0.1 parts by weight, preferably 0.03 - 0.06, in particular 0.04 - 0.06 parts by weight.
Microcrystalline cellulose (Avicel); 0.03 - 0.3 parts by weight, preferably 0.05 - 0.25, in particular 0.08 - 0.1 parts by weight.
Corn starch (for the exterior phase, that is after granulation); 0.02 - 0.25 parts by weight, preferably 0.03 - 0.1, in particular 0.06 - 0.07 parts by weight.
Magnesium stearate; 0.01 - 0.03 parts by weight, preferably 0.01 - 0.02, in particular 0.015 - 0.018 parts by weight.
The ratio of the auxiliary substances to each other is for example in the range
lactose : calcium hydrogen phosphate : corn starch : polyvinypyrrolidone (granulate phase) : Avicel : corn starch : magnesium stearate (exterior phase) of say
1 : 0.4 : 0.4 : 0.2 : 0.4 : 0.3 : 0.07.

If a different binder from polyvinylpyrrolidone is used, the following amounts are used, for example, to 1 part by weight of mesna:

gelatine:	0.01 - 0.06 parts per one part by weight of mesna
cellulose ether:	0.01 - 0.04 parts per one part by weight of mesna
pectin:	0.01 - 0.04 parts per one part by weight of mesna
sodium alginate:	0.01 - 0.1 parts per 1 part by weight of mesna

In addition to the active substance mesna, the granulate preferably contains lactose, calcium hydrogen phosphate, corn starch and polyvinylpyrrolidone (as binder). Calcium hydrogen phosphate acts, for example, as a filler and the corn starch preferably acts as a tablet disintegrant. In the exterior tablet phase corn starch is preferably used, again as a disintegrant, and microcrystalline cellulose (Avicel) is used as a dry binder.

A lactose with the following particle size fractions is preferably used as lactose:

Particle size distribution	100 %	< 800 µm
	12-35 %	< 400 µm
*	Max. of 7%	< 200 µm

In addition, it is favourable if the lactose used satisfies the following conditions:

Bulk density:	560 g/litre
Tamped down weight:	620 g/litre
Angle of rest (flowability):	35°

Types K 25, K 30 and K 90 may be used, for example, as polyvinylpyrrolidone.
Polyvinylpyrrolidones are characterised by a K value which is calculated from the relative viscosity. It is a measure of the degree of polymerisation and molecular weight. The previously mentioned polyvinylpyrrolidones are characterised by the following parameters:

Molecular weight:

PVP K 25 =	29 000
PVP K 30 =	45 000
PVP K 90 =	1 100 000

Particle size distribution as a percentage:

	> 50 µm	> 100 µm	> 200 µm	> 250 µm
PVP K 25	90 %	50 %	5 %	max. 1 %
PVP K 30	90 %	50 %	5 %	max. 1 %
PVP K 90			95 %	90 %

Bulk density:

PVP K 25 = 400 - 600 g/litre
PVP K 30 = 400 - 600 g/litre
PVP K 90 = 110 - 250 g/litre.

For granulating the active substance mesna, a mixture of isopropanol and water is preferably used, which contains, for example, 10 % to 50 %, preferably 20 % to 40 % and in particular 30 % to 35 % of water. With reference to the active substance mesna, for example 0.3 to 3 parts, preferably 0.5 to 2 parts and in particular 0.7 to 1 part of this granulating liquid is preferably used. Instead of isopropanol, other C_1 - C_4 alcohols (for example methanol, ethanol) or acetone may also be used. This agent may also be used as a mixture with water, wherein the same mixing ratio as used for the ispropanol/water mixtures is appropriate. In addition, it is advantageous to add a binder such as polyvinylpyrrolidone to the granulating solution, wherein the amount of polyvinylpyrrolidone is for example 0.1 % to 10 %, preferably 1 % to 5 % and in particular 3 % to 5 %.

In addition, it may be advantageous to add other conventional pharmaceutical auxiliary substances and carriers to the granulate or during granulation.

Furthermore, the tablets may also contain: anti-adhesion substances, absorption accelerators, hydrophilising

substances, moisturisers and substances equivalent thereto, as well as conventional flavouring, sweetening and aromatic substances.

If the tablet according to the invention is an effervescent tablet, then this tablet also contains a conventional physiologically acceptable effervescent mixture. The amount of this effervescent mixture, with reference to one part by weight of mesna, is 0.05 - 30 parts by weight. An effervescent mixture of this type consists of a substance which releases carbon dioxide (CO_2 provider) in the presence of an acid in aqueous or alcoholic medium and a physiologically acceptable organic acid. Suitable CO_2-providing substances are, for example, sodium, potassium, magnesium or calcium carbonates or hydrogen carbonates, preferably the neutral carbonates in the case of magnesium and calcium. Mixtures of these carbonates are also possible. Suitable organic acids which release carbon dioxide from this type of carbonate are, for example, organic saturated or unsaturated di- and tricarboxylic acids with 2 to 8, preferably 2 to 6 carbon atoms, which may also contain one, two, three or four, preferably one or two hydroxyl groups. Examples of these are citric acid, tartaric acid, adipic acid, maleic acid, fumaric acid. Alginic acid can also be used. Mixtures of the acids mentioned are also possible.

0.02 - 18 parts by weight, for example, of the CO_2-providing component in the effervescent mixture and 0.03 - 12 parts by weight of the relevant acid component are used to one part by weight of mesna. When preparing the effervescent tablet, the entire effervescent mixture may be added as such, for example, after the granulating stage. However it is also possible or preferred to add the component in the effervescent mixture which provides the carbon dioxide before granulating and to admix the

corresponding relevant acid component later, to the dry granulate, together with, for example, the lubricant, flavouring, sweetening and aromatic substances as well as optionally the remainder of the filler, binder and disintegrant.

To shield the unpleasant taste more effectively, it has proven worthwhile to provide the mesna tablets for swallowing with a suitable coating. This coating may be a conventional sugar dragee coating or else it may be a polymer-containing film coating. Suitable examples of these are copolymers based on dimethylaminoethyl methacrylate and neutral methacrylates (for example Eudragit E), hydroxypropyl methylcellulose, molecular weight 11 000 (for example Pharmacoat 606), ethyl cellulose (for example Aquacoat).

The tablets are prepared (all stages except for drying) at temperatures, for example, between 10°C and 80°C, preferably 18°C to 50°C, in particular 20°C to 30°C.

The granulates are dried at, for example, between 40°C and 80°C, preferably 50°C to 70°C.

If the granulate is used as such as a pharmaceutical preparation, for example as a drinking granulate, this preferably contains only a binder in addition to the active substance mesna. The binder may be one of the binders cited, but a mixture of such binders may also be used. 0.1 - 1 parts by weight of binder is preferably used to one part by weight of mesna. The upper particle size in a granulate of this type is 3 mm.

The granulate contains, for example, 100 mg to a maximum of 2 g of mesna. Mesna is generally present in the granulate in an amount such that it makes up 10 - 80 percent by

weight of the mass of the granulate. Binder, filler and optionally lubricant vary by the same order of magnitude as in the tablets.

In order to conceal the taste, it is recommended that granulate which is taken directly is provided with a coating. These may be known and conventional coatings which only dissolve, for instance, in acid gastric juice or else they may be resistant to gastric juice and only go into solution in the intestinal tract.

In addition, it is recommended that flavouring, sweetening and/or aromatic substances be added to the granulate.

Suitable aromatic substances are the following: pineapple, apple, apricot, raspberry, cherry, cola, orange, passion fruit, lemon, grapefruit. The granulate should contain 0.05 - 0.2 parts by weight of aromatic substance, with reference to one part by weight of mesna.

The following substances may be used as sweeteners: saccharine and its sodium salt, cyclamic acid and its sodium salt, ammoniumglyclyl rhizinate, fructose, saccharose, xylitol, glucose, sorbitol, mannitol. The granulate should contain 0.003 - 12 parts by weight of sweetener, with reference to 1 part by weight of mesna. The granulate may be covered with a lacquer which is insoluble in water, to improve the taste. The following substances are used, for example, for this purpose: copolymers of dimethylaminomethacrylic acid and neutral methacrylates which are insoluble in water and saliva but dissolve in acids (such as, for example, Eudragit® E). Lacquers which are resistant to gastric juice, however, may also be used, such as, for example, shellac, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate and methacrylates (for example Eudragit® L and S). Organic acids may be added

to stabilise these granulates which are resistant to gastric juice, in order to make the suspension being applied weakly acid. 0.0125 - 2 parts by weight of dry lacquering substance should be applied per 1 part by weight of mesna.

The flavouring, sweetening and aromatic substances cited are used in the amounts also given for the mesna tablets according to the invention. The same applies to the coatings.

Example 1

To prepare a granulate for 4000 tablets with 300 mg of mesna per tablet, 1200 mg of mesna, 280 g of lactose, 120 g of calcium hydrogen phosphate and 120 g of corn starch are passed through a 0.8 mm mesh sieve and then homogenised for 15 minutes in a suitable mixer. This is then moistened with a mixture of 616 g of isopropanol and 284 g of water which contains 60 g of polyvinylpyrrolidone and the moist material passed though a 2 mm mesh sieve. The granulate is dried, for instance, in a fluidised bed with an incoming air temperature of 70°C for a period of 8 minutes,

The dried granulate is then, for example, passed through a 0.8 mm sieve together with 80 g of corn starch and 120 g of microcrystalline cellulose and homogenised for 20 minutes in a suitable mixer.

20 g of magnesium stearate are then added and mixing is continued for a further 2 minutes. The pressing dust thus obtained is compressed in a suitable tablet press to give, for example, tablets with the following technical data:

nominal mass	500.0 mg
diameter	11.0 mm
radius of raised portion	8.5 mm
thickness	5.4 - 5.6 mm

The tablets may then be continuously sprayed in a suitable apparatus with 225 g of a film suspension (containing a conventional polymer-containing coating material or a conventional sugar-containing coating material), so that an individual tablet is given a film of 15 mg weight.

Example 2

To prepare a mesna granulate, 4 kg of pure mesna is moistened with 1.9 kg of a solution of 114 g of polyvinylpyrrolidone with a K value of 25 in a mixture of 1126 g of isopropanol and 660 g of water and granulated through a 2 mm sieve. This moist material is dried in a fluidised bed to a residual moisture content of less than 30% relative humidity and screened to a maximum particle size of 1 mm. To conceal the taste, this granulate is coated in a fluidised bed spray apparatus with a suspension having the following composition:

Eudragit® E (12.2% strength solution in isopropanol/acetone)	4.80 kg
Magnesium stearate	0.48 kg
Isopropanol	6.72 kg
	12.00 kg

Eudragit E is a commercially available cationic polymer, based on methacrylate, for coating pharmaceutical preparations.

It is recommended that, after the application of 6 kg of suspension, intermediate drying is performed and the granulate is passed through a 1.5 mm sieve. After application of all the suspension, sieving is repeated to give a particle size of 1.8 mm.

To improve the taste, a flavoured sugar granulate with the following composition is added to this active substance granulate:

sugar powder	14.400 kg
flavouring (pulvis)	0.406 kg

mixed well and moistened with 0.9 kg of water, granulated through a 2 mm sieve and dried to a residual moisture content of less than 30% relative humidity in a suitable dryer.

Finally both granulates are homogeneously mixed and weighed into sachets in 5 g doses. One sachet contains 1 g of mesna.

When administered, the contents of one sachet is suspended in 100 ml of water.



Patent Claims:

1. A tablet containing mesna as active substance, optional conventional flavouring, sweetening and aromatic substances, as well as
0.01 - 1 parts by weight of a binder
0.03 - 0.4 parts by weight of a disintegrating agent
0.01 - 0.2 parts by weight of a lubricant
0.1 - 1 parts by weight of a filler as well as, in the case of an effervescent tablet, an additional
0.05 - 30 parts by weight of a conventional physiologically acceptable effervescent mixture, each being with respect to one part by weight of mesna.

2. A tablet according to Claim 1, characterised in that the tablet contains 10 - 80 parts by weight of mesna and the substances cited in Claim 1, each being with respect to one part by weight of mesna.

3. A tablet according to one or more of the preceding Claims, characterised in that the tablet is coated with a conventional film.

4. A process for the preparation of a stable tablet containing mesna as active substance, optional conventional flavouring, sweetening and aromatic substances, as well as
0.01 - 1 parts by weight of a binder
0.03 - 0.4 parts by weight of a disintegrating agent
0.01 - 0.2 parts by weight of a lubricant
0.1 - 1 parts by weight of a filler as well as, in the case of an effervescent tablet, an additional
0.05 - 30 parts by weight of a conventional physiologically acceptable effervescent mixture, each being with respect to one part by weight of mesna,

characterised in that mesna is first granulated in a way which is known per se with a C_1-C_4-alcohol or acetone or a mixture of the organic substances mentioned with water and a filler and binders, optionally also a disintegrating agent and optionally, in the case of an effervescent tablet, with the CO_2 supplier from the effervescent mixture, wherein the auxiliary substances mentioned are used in the amounts relating to one part by weight of mesna or else only a part of these amounts is used and the remainder is added after granulation, the granulate obtained is dried and then the lubricant and, in the case of an effervescent tablet, the organic acid from the effervescent mixture or else the whole effervescent mixture and optionally the remainder of the binder, filler and disintegrating agent as well as optional flavouring, sweetening and aromatic substances, are added, the entire mixture is homogenised and then compressed to form tablets and optionally the tablets obtained in this way are provided with a film coating in a known manner.

5. A granulate containing mesna as active substance, optional conventional flavouring, sweetening and aromatic substances as well as
0.01 - 1 parts by weight of a binder and optionally
0.01 - 0.2 parts by weight of a lubricant
0.1 - 1 part by weight of a filler,
each being with respect to one part by weight of mesna.

6. A granulate according to one or more of the preceding Claims, characterised in that the granulate is coated with a conventional film.

7. A process for preparing a mesna granulate containing mesna as active substance, optional conventional flavouring, sweetening and aromatic substances, as well as
0.01 - 1 parts by weight of a binder and optionally
0.01 - 0.2 parts by weight of a lubricant
0.1 - 1 part by weight of a filler,
each being with respect to one part by weight of mesna, characterised in that one part by weight of mesna is granulated with a C_1-C_4-alcohol or acetone or a mixture of the organic substances mentioned with water and
0.01 - 1 parts by weight of a binder and optionally
0.1 - 1 parts by weight of a filler and/or
0.01 - 0.2 parts by weight of a lubricant, the granulate obtained is dried, the dry granulate is optionally provided with a film coating and optionally conventional flavouring, sweetening and aromatic substances are added, the whole mixture is homogenised and the product obtained in this way is optionally provided with a film coating in a known manner.