Ifosfamide is the INN for 3-(2-chloroethyl)-2-(chloroethylamino)-tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide. Ifosfamide is an important cytostatic medicinal active ingredient of the oxazaphosphorine type.

Ifosfamide is a white crystalline powder with a melting point of 48°C to 51°C and strongly hygroscopic properties. Ifosfamide already starts to sinter below the melting point, so it has to be stored at the lowest possible temperatures. Contact with atmospheric moisture should also be avoided as far as possible. Ifosfamide has a solubility in water of about 10 percent by weight, but is of only limited stability in aqueous solution.

As yet, ifosfamide has only been registered in formulations for parenteral use. Ifosfamide is available in the form of sterile crystals filled into injection vials in dosages of 200 mg to 2000 mg. Prior to administration, the sterile crystals must be dissolved in water for injectable preparations so as not to exceed a concentration of 4%. This solution is suitable for intravenous injection. For short intravenous infusion, the ifosfamide solution is dissolved in 500 ml of Ringer's solution or similar infusion fluids. The infusion time is *ca.* 30 minutes or may be 1 to 2 hours. For 24-hour infusion, the ifosfamide solution is dissolved for example in a total of 3 litres of 5% dextrose saline solution.

The preparation and processing of ifosfamide gives rise to a variety of problems. The preparation of ifosfamide crystallized under sterile conditions yields a product of changeable physical characteristics. The variation in flowability has a particularly adverse effect on the dosage accuracy during filling.

The processing of ifosfamide is further complicated by its hygroscopicity and low melting point. On prolonged storage,

the sterile crystals sinter and the rate of dissolution decreases. When ifosfamide begins to sinter, the clarity of solution and the pH of the solution also decrease with simultaneous yellowing; the solution is then generally no longer suitable for therapeutic use.

The difficulties of preparing the sterile crystals are compounded above all by serious disadvantages in their use. They can only be used parenterally by specialized medical staff. The patient has to be admitted to hospital as an inpatient or attend at least once a day for treatment. This is very time-consuming for both staff and patient.

The potential danger of the substance is such that preparation of the sterile injectable solution from the dry substance requires expensive protective measures for the staff. Parenteral therapy is unpleasant for a patient because he has to suffer a painful puncture in the administration and is connected to an infusion apparatus for the duration of the infusion.

On account of all these disadvantages, there has long been a need for an oral form of administration which no longer has the disadvantages listed. With oral administration, it would be possible to treat the patient as an outpatient. Taking ifosfamide orally would be pleasant for the patient and would no longer constitute a risk for the medical staff.

However, all attempts to develop a solid oral form have so far failed because of the described physicochemical properties of ifosfamide. Soft gelatin capsules could not be produced as a medicinal form. The active ingredient appeared to react with the shell in this case, the shell became tanned and the capsule no longer dissolved in the gastric juice. Many attempts to develop a tablet have likewise failed so far. The substance stuck to the dies of the tableting machine, the tablets were too soft and some of the active

ingredient splashed out of the mould in liquefied form during compression.

It has now been found, surprisingly, that a mixture of ifosfamide with microcrystalline cellulose can be filled into hard gelatin capsules. Surprisingly, there is no disadvantageous interaction of ifosfamide with the shell in this case. Although the shell contains 12% to 15% of water (weight/weight) and ifosfamide is both hygroscopic and moisture-sensitive, the filled hard gelatin capsule proves to be stable on storage over several years. Even after several years of storage, the shell dissolves in the gastric juice within a few minutes.

For example, the ifosfamide capsules according to the invention contain between 100 mg and 800 mg, preferably between 200 mg and 500 mg of ifosfamide.

The composition of the capsules consists essentially of ifosfamide and microcrystalline cellulose; it optionally also contains small amounts of conventional flow regulators and antiadhesion agents. These flow regulators and antiadhesion agents can be used individually or in a mixture. The total amount of such additional flow regulators and antiadhesion agents is for example 0.001 to 0.1 part by weight, preferably 0.01 to 0.04 part by weight, based on 1 part by weight of ifosfamide. Examples of suitable flow regulators and antiadhesion agents are those mentioned for example in the following textbooks:

W.A. Ritschel, DIE TABLETTE (THE TABLET), Editio Cantor Verlag, page 125, 1st edition 1966

Sucker, Fuchs, Speiser, PHARMAZEUTISCHE TECHNOLOGIE (PHARMACEUTICAL TECHNOLOGY), G. Thieme Verlag, Stuttgart, pages 334 to 336, 1st edition 1978

Münzel, Büchi, Schultz, GALENISCHES PRAKTIKUM (LABORATORY MANUAL OF GALENICS), Wissenschaftliche Verlagsgesellschaft, Stuttgart, page 731, 1st edition 1959

R. Voigt, LEHRBUCH DER PHARMAZEUTISCHEN TECHNOLOGIE (TEXTBOOK OF PHARMACEUTICAL TECHNOLOGY), 4th edition, Verlag Chemie, Weinheim, page 195, 1st edition 1982
P.H. List, ARZNEIMITTELLEHRE (TEXTBOOK OF DRUGS), Wissenschaftliche Verlagsanstalt, Stuttgart, page 86, 1st edition 1976

Particularly suitable examples are magnesium stearate and other stearates, highly disperse silicon dioxide, stearic acid, talc and polyglycols (for example with molecular weights of 4000 to 6000).

Preferably, 0.002 to 0.02 part by weight, especially 0.005 to 0.008 part by weight of flow regulator was used per 1 part by weight of ifosfamide, and 0.004 to 0.08 part by weight, especially 0.016 to 0.032 part by weight of antiadhesion agent was used per 1 part by weight of ifosfamide.

The capsules can optionally also contain fillers such as starch, cellulose, lactose, fructose, sucrose, mannitol, sorbitol or calcium phosphate, binders such as gelatin, cellulose, pectins, alginates or polyvinylpyrrolidone, and disintegrating agents such as alginates, carboxymethyl celluloses, polyvinylpyrrolidones and ultraamylopectin.

Particularly suitable flow regulators are highly disperse silicon dioxide (for example Aerosil® such as Aerosil® V 200) and magnesium stearate.

The amount of microcrystalline cellulose in the capsule according to the invention is generally 0.2 to 4 parts by weight, preferably 0.25 to 1 part by weight and especially 0.3 to 0.35 part by weight, based on 1 part by weight of ifosfamide.

As regards crystallinity, the microcrystalline cellulose used should have a crystalline index* of between 0.5 and 0.9, for example 0.7. The degree of polymerization of the microcrystalline cellulose is preferably in the range 200 to 300. Furthermore, the microcrystalline cellulose used according to the invention should have for example a mean particle size of *ca.* 50 µm or less than 50 µm. For example, the mean particle size is less than 40 µm, especially 20 µm. The microcrystalline cellulose used is preferably Avicel®, *e.g.* Avicel® with a particle size spectrum of less than 38 µm (Avicel® PH 105) (*i.e.* at least 90% of the microcrystalline cellulose has a mean particle size of less than 38 µm, especially 20 µm).

Surprisingly, it was now also possible to produce tablets with ifosfamide as the active ingredient, the combination of tricalcium phosphate and polyethylene glycol being particularly important. These measures now make it possible for the first time to compress on a conventional tableting press.

Because of its physical properties, the substance ifosfamide cannot be compressed to tablets in conventional manner directly on tableting machines. All attempts to compress the active ingredient using the known adjuncts, for example microcrystalline cellulose, lactose, starch, talc, highly disperse silicon dioxide and calcium hydrogen phosphate, resulted in failure. Attempts using granulation in conventional manner or in a fluidized bed also failed to produce tablet compositions which could be processed without difficulty. In all cases, the composition was found to adhere strongly to the die or mould during the compression process.

* Crystalline index is understood as meaning the quotient of the crystalline part and the sum of the crystalline and amorphous parts. The index has a value of 0.71, for example, for crystalline cellulose with a particle size of *ca.* 50 µm.

The tablets according to the invention contain, based on one part by weight of ifosfamide,
0.1 - 1.0 part by weight of tricalcium phosphate and
0.04 - 0.4 part by weight of polyethylene glycol (for example with a molecular weight of 4000 to 6000),
and additionally contain, based on the tablet weight,
5 - 60% by weight of a filler and flow regulator,
1 - 10% by weight of a disintegrating agent,
0.1 - 10% by weight of an antiadhesion agent and
0.1 - 80% by weight of a binder.

By way of example, the following is used according to the invention per 1 part by weight of ifosfamide:
0.1 - 1.0 part by weight, preferably 0.2 - 0.5 and especially 0.25 - 0.30 part by weight of tricalcium phosphate. Based on the tablet mixture, the amount of tricalcium phosphate is for example 3.5 to 35% by weight, preferably 7 to 17.8% by weight and especially 9 to 11% by weight.

The amount of polyethylene glycol is for example 0.04 - 0.4 part by weight, preferably 0.1 - 0.2 and especially 0.13 - 0.15 part by weight per 1 part by weight of ifosfamide. Polyethylene glycol with molecular weights of 4000 to 6000 is particularly suitable, polyethylene glycol 6000 being preferred. Based on the tablet mixture, the amount of polyethylene glycol is for example 1 to 14.0% by weight, preferably 3.5 to 7.5% by weight and especially 4.5 to 7 or else 4.5 to 6% by weight. The weight ratio of tricalcium phosphate to polyethylene glycol is for example 1:0.5.

The tablet according to the invention also contains the following:

Fillers and flow regulators in an amount of 5 to 60% by weight, based on the tablet weight. Examples of suitable fillers are starches, celluloses, lactose, sucrose, fructose,

sorbitol, mannitol, calcium phosphate, calcium carbonate, calcium sulphate and magnesium carbonate or oxide. 5 - 60% by weight, based on the tablet weight, is used.

Examples of suitable flow regulators are microcrystalline cellulose, lactose, polyglycols, starches, celluloses, talc, talcum siliconisatum, calcium arachidate or stearate, cetyl alcohol, stearyl alcohol, myristyl alcohol, stearic acid and lauric acid. If the flow regulator is not also acting as a filler at the same time, 0.5 - 10% by weight thereof, based on the tablet weight, is used.

Disintegrating agents, for example alginates, starches (corn starch), pectins, carboxymethyl celluloses, polyvinylpyrrolidone, ultraamylopectin and bentonites. 1 - 10% by weight, based on the tablet weight, is used.

Antiadhesion agents, for example glycols, talc, talcum siliconisatum, talcum stearinicum, calcium stearate, aluminium stearate and stearic acid. 0.1 - 10% by weight, based on the tablet weight, is used.

Binders, for example gelatin, cellulose ethers, amylose, pectins, cellulose, dextrose, polyglycols and tragacanth. 0.1 - 80% by weight, based on the tablet weight, is used.

Apart from ifosfamide, tricalcium phosphate and polyethylene glycol, the tablet according to the invention contains the following substances in particular:
0.2 - 1.2 parts by weight, preferably 0.4 - 1.0 and especially 0.70 - 0.90 part by weight of microcrystalline cellulose, based on one part by weight of ifosfamide, or 7 to 43, preferably 15 to 35% by weight, based on the tablet weight;
0.15 - 1.0 part by weight, preferably 0.24 - 0.68 and especially 0.30 - 0.40 part by weight of lactose, based on

one part by weight of ifosfamide, or 5.0 to 36, preferably 8.5 to 25% by weight, based on the tablet weight;
0.02 - 0.24 part by weight, preferably 0.05 - 0.20 and especially 0.1 - 0.15 part by weight of corn starch, based on one part by weight of ifosfamide, or 0.7 to 8.5, preferably 2.0 to 6.5% by weight, based on the tablet weight;
0.02 - 0.30 part by weight, preferably 0.06 - 0.20 and especially 0.07 - 0.09 part by weight of talc, based on one part by weight of ifosfamide, or 0.70 to 10, preferably 2 to 6.5% by weight, based on the tablet weight; and
0.004 - 0.2 part by weight, preferably 0.02 - 0.12 and especially 0.035 - 0.05 part by weight of magnesium stearate, based on one part by weight of ifosfamide, or 0.1 to 7.2, preferably 0.7 to 4.5% by weight, based on the tablet weight.

Both tablets and capsules can be provided with a coating in conventional manner. Said coatings can be water-soluble, swellable, water-insoluble or gastric juice-resistant coatings applied to the tablets or capsules from an aqueous dispersion or solution or else from a solution or dispersion in an organic solvent such as, for example, ethanol, isopropanol, acetone, ether, dichloromethane or methanol.

The capsules and tablets are produced at between 15°C and 26°C, for example, preferably at between 18°C and 22°C. The relative humidity in the production areas should not exceed 40%.

The solid ifosfamide formulations according to the invention for oral administration are prepared by a process in which, between 15°C and 30°C, either one part by weight of ifosfamide is homogeneously mixed with 0.1 - 4 parts by weight, preferably 0.2 - 4 and especially 0.25 - 1 part by weight of microcrystalline cellulose and optionally small amounts of a conventional flow regulator and antiadhesion agent and filled into capsules, or one part by weight of ifosfamide is homogeneously mixed with

0.01 - 1.0 part by weight of tricalcium phosphate,
0.04 - 0.4 part by weight of polyethylene glycol,
0.15 - 2, preferably 0.5 - 1.5 and especially 1 - 1.3 parts by weight of a filler and flow regulator,
0.03 - 0.5, preferably 0.05 - 0.4 and especially 0.08 - 0.2 part by weight of a disintegrating agent,
0.003 - 0.5, preferably 0.01 - 0.4 and especially 0.05 - 0.2 part by weight of an antiadhesion agent and
0.003 - 3, preferably 0.01 - 2 and especially 0.1 - 1 part by weight of a binder

and then compressed to tablets and, optionally, the capsules or tablets obtained are provided with a conventional coating.

Example 1:

Ifosfamide capsule composition

According to the invention, the capsule composition is prepared for example by the following method:

For 12,000 capsules of 250 mg, 3.0 kg of ifosfamide, 1.002 kg of microcrystalline cellulose and 0.018 kg of highly disperse silicon dioxide, for example, are passed through a 0.8 mm sieve and then mixed for 4 minutes in a suitable mixer. 0.06 kg of magnesium stearate (passed through a 0.8 mm sieve) is then added to this mixture and mixing is continued for 1 minute. The finished capsule composition is filled into size 1 hard gelatin capsules on a capsule machine equipped with size 1 moulds, so that each capsule contains *ca.* 340 mg of capsule composition.

For 20,000 capsules of 500 mg, 10.0 kg of ifosfamide, 3.34 kg of microcrystalline cellulose and 0.06 kg of highly disperse silicon dioxide, for example, are passed through a 0.8 mm sieve and then mixed for 4 minutes in a suitable mixer. 0.2 kg of magnesium stearate (passed through a 0.8 mm sieve) is then added to this mixture and mixing is continued for 1 minute. The finished capsule composition is filled into size 00 hard gelatin capsules on a capsule machine equipped with size 00 moulds, so that each capsule contains *ca.* 680 mg of capsule composition. The microcrystalline cellulose is used for example in the form of Avicel PH 105, which has a special particle size spectrum and is a filler with a good binding capacity and flowability.

To produce gastric juice-resistant capsules, 3000 g of a coating suspension in an organic solvent (isopropanol) are applied for example to 2500 size 1 capsules with an active ingredient content of 250 mg of ifosfamide. The 3000 g of suspension contain:

1440 g of an anionic polymer of methacrylic acid and methacrylic acid esters with an average molecular weight of 150,000, for example, to which a conventional plasticizer is added, 18 g of propane-1,2-diol, 36 g of magnesium stearate and 1506 g of isopropanol.

An example of a suitable methacrylic acid/ methyl methacrylate copolymer is Eudragit L®, especially in the form of a 12.5% solution in isopropanol (Eudragit L®/12.5%). Such copolymers are soluble in a neutral to weakly alkaline medium by salification with alkalies.

Example 2:

Ifosfamide tablet

The formulation of a tablet with an active ingredient content of 250 mg has for example the following composition:

One 700 g tablet contains:

Ifosfamide	250 mg
Tricalcium phosphate, fine	70 mg
Microcrystalline cellulose	200 mg
Lactose	85 mg
Polyglycol 6000	35 mg
Corn starch	30 mg
Talc	20 mg
Magnesium stearate	10 mg

To prepare the tablet composition for 1500 tablets, 375 g of ifosfamide, 105 g of fine tricalcium phosphate, 300 g of microcrystalline cellulose, 127.5 g of lactose, 52.5 g of polyglycol 6000, 45 g of corn starch and 30 g of talc are passed through a sieve of 0.8 mm mesh and mixed for 15 minutes in a suitable mixer. 15 g of magnesium stearate, also passed through a sieve, are then added and mixing is

continued for 2 minutes. The tablet composition is then compressed to tablets on a suitable tableting press.

To produce tablets with a gastric juice-resistant coating, 500 g of the aqueous dispersion described below, for example, are applied to 1050 g of tablets:

100 g of the aqueous dispersion contain:

Polyglycol 6000	1.600 g
Titanium dioxide	1.100 g
Iron oxide, yellow	0.156 g
Talc	4.000 g
Dimethylpolysiloxane	0.100 g
Eudragit L® 30 D*	55.000 g
Water	38.044 g
	100.000 g

The film solution is sprayed on for example in apparatuses conventionally used for this purpose, the solvent or dispersant being removed continuously by drying.

* Eudragit L® 30 D is an aqueous dispersion of an anionic copolymer based on methacrylic acid and ethyl acrylate. The ratio of free carboxyl groups to ester groups is about 1:1. The average molecular weight is 250,000.

CLAIMS:

1. A solid oral ifosfamide formulation, characterized in that it takes the form of ifosfamide capsules, the weight of the capsule consisting essentially of the active ingredient, ifosfamide, and microcrystalline cellulose, optionally with additional smaller amounts of a conventional flow regulator and antiadhesion agent, or in that it takes the form of tablets containing, based on one part by weight of ifosfamide,
0.1 - 1.0 part by weight of tricalcium phosphate and
0.04 - 0.4 part by weight of polyethylene glycol,
and additionally containing, based on the weight of the tablet,
5 - 60% by weight of a filler and flow regulator,
1 - 10% by weight of a disintegrating agent,
0.1 - 10% by weight of an antiadhesion agent and
0.1 - 80% by weight of a binder.

2. A process for the preparation of solid ifosfamide formulations for oral administration, characterized in that, between 15°C and 30°C, either one part by weight of ifosfamide is homogeneously mixed with 0.1 - 4 parts by weight of microcrystalline cellulose and optionally small amounts of a conventional flow regulator and antiadhesion agent and filled into capsules, or one part by weight of ifosfamide is homogeneously mixed with
0.1 - 1.0 part by weight of tricalcium phosphate,
0.04 - 0.4 part by weight of polyethylene glycol,
0.15 - 2 parts by weight of a filler and flow regulator,
0.03 - 0.5 part by weight of a disintegrating agent,
0.003 - 0.5 part by weight of an antiadhesion agent and
0.003 - 3 parts by weight of a binder
and then compressed to tablets and, optionally, the capsules or tablets obtained are provided with a conventional coating.