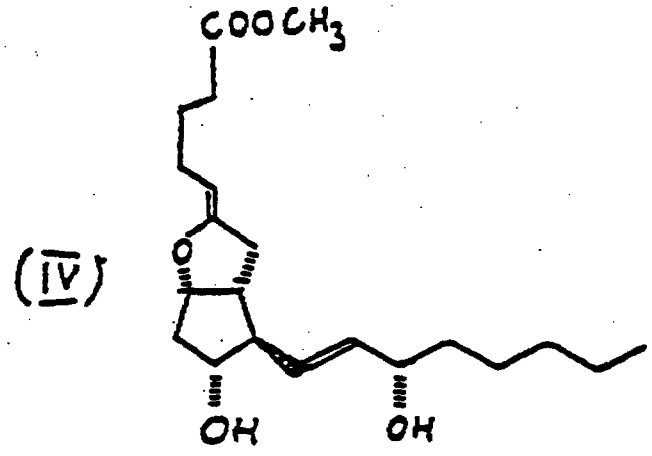
Medicaments having antithrombotic and antiaggregatory actions have already been disclosed. Thus, O-acetylsalicylic acid shows clinically detectable effects on prophylactic treatment of thromboses and strokes.

It is known that 1-(5-oxohexyl)-3,7-dimethylxanthine (pentoxifylline) is used as a pharmaceutical agent for improving the flow properties of the blood.

It has already been disclosed that the physiological arachidonic acid metabolite prostacyclin, of the formula IV



(IV)

is an exceedingly effective antiaggregatory substance. The mechanism of action which has been described is that prostacyclin stimulates cyclic adenosine 3',5'-monophosphate (cyclic AMP) in the platelets (Nature (London) 292 (1981) 364).

Unfortunately, the medical use of prostacyclin is greatly restricted because of its short half-life at physiological pH. The molecule is even less stable at acid pH, so that successful oral therapeutic use is also impossible (Prostaglandins, 15 (1978) 943). However, stable analogs of prostacyclin have been described, such as carbacyclins (J. Org. Chem. 46 (1981), 1954) and heteroiminoprostacyclins (see European Patent 34,778), in which the enol ether structure in the prostacyclin molecule, which is sensitive to hydrolysis, has been replaced by

structural elements which are insensitive to hydrolysis. The heteroiminoprostacyclin 2-aza-3-(4-carboxymethyl-1-thia-butyl)-6-β-(3-α-hydroxy-1-octenyl)-7-α-hydroxy-bicyclo(3.3.0)oct-2-ene of the formula II is known under the name tilsuprost.

It is known that the heteroiminoprostacyclins have high biological activity. Inter alia, they have vasodilating and antithrombotic actions, inhibit platelet aggregation and prevent bronchospasm. By reason of these valuable medical properties, representatives of this class of substances can be used, inter alia, as medicaments to reduce blood pressure, as substances having antiaggregatory and antithrombotic efficacy, to improve the flow properties of the blood and as bronchospasmolytics, as well as cytostatics.

It has been possible in our own experiments to confirm that the strengths of the antiaggregatory action of tilsuprost in vitro are of the same order of magnitude as for prostacyclin. However, in a number of our own biological investigations it has also been found that prostacyclin and heteroiminoprostacyclins often behave very differently. Thus, for example, it has surprisingly emerged that tilsuprost has no significant stimulant action on the cyclic AMP level in human platelets, in contrast to prostacyclin. In other words, the biochemical and pharmacological actions exerted by heteroiminoprostacyclins, such as tilsuprost, and the natural prostacyclin differ utterly from one another (see Tab. 2).

Combination products of heteroiminoprostacyclins and certain xanthines (see below) show superadditive effects.

Thus the invention relates to heteroiminoprostacyclins of the formula I (see formula sheet). In the text which follows these are to be understood to be those in which:
X denotes an oxygen or sulfur atom or an NH group,
Y denotes a straight-chain aliphatic hydrocarbon radical

having 2 - 6 carbon atoms or a cycloaliphatic hydrocarbon radical having 3 - 6 carbon atoms in the ring, which radicals can contain not more than one multiple bond,

Z denotes a radical of the formula $-CO_2R^1$ or $-CH_2OH$, R^1 denoting hydrogen, a straight-chain or branched alkyl radical having up to 8 carbon atoms, a straight-chain or branched singly olefinically unsaturated aliphatic hydrocarbon radical having 3 - 8 carbon atoms, a cycloaliphatic hydrocarbon radical which has 3 - 7 carbon atoms in the ring and not more than one multiple bond, or an araliphatic hydrocarbon radical having 6 - 9 carbon atoms or a suitable pharmaceutically tolerated metal or ammonium cation,

R^2 denotes a straight-chain or branched aliphatic hydrocarbon radical which has 4 to 6 carbon atoms and which can contain not more than one multiple bond, and

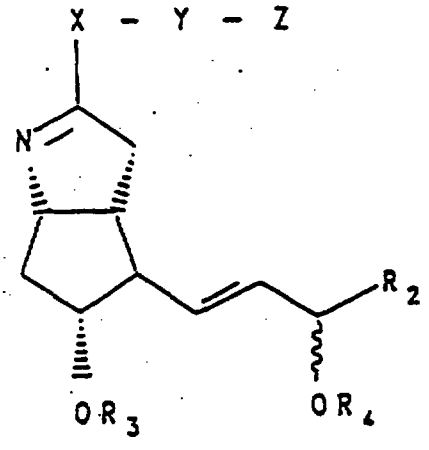
R^3 and R^4 either denote hydrogen or denote identical or different protective groups which can readily be eliminated under neutral or basic conditions.

The term "multiple bond" comprises both acetylenic and olefinic bonds; the latter are preferred. Examples of possible metal cations R^1 are those of the alkali metals, such as lithium, sodium and potassium, and of the alkaline earth metals, such as magnesium and calcium, as well as cationic forms of other metals, such as aluminum, zinc and iron. Pharmacologically tolerated ammonium cations are those which are derived from ammonia or primary, secondary or tertiary amines, such as the alkylamines, for example mono-, di- and trimethyl- or -ethyl-, -propyl-, -isopropyl-, -butyl-, -isobutyl-, -t-butyl- and N-(methylhexyl)-, N-methyl-N-hexyl-, benzyl- and β-phenylethylamine, ethylenediamine, diethylenetriamine, pyrrolidine, piperidine, morpholine, piperazine, mono-, di- and triethanolamine, ethyldiethanolamine, N-butylethanolamine, tris(hydroxymethyl)aminomethane and the like. Examples of suitable ammonium salts are the basic amine salts of lysine and of arginine. Examples of

suitable pharmacologically tolerated quaternary ammonium cations are tetramethylammonium, tetraethylammonium and benzyltrimethylammonium.

The invention relates to a combination product containing

A) a heteroiminoprostacyclin of the formula I



(I)

in which

X denotes an oxygen or sulfur atom or an NH group,

Y denotes a straight-chain aliphatic hydrocarbonradical having 2-6 carbon atoms or a cycloaliphatic hydrocarbon radical having 3-6 carbon atoms in the ring, which radicals can contain not more than one multiple bond,

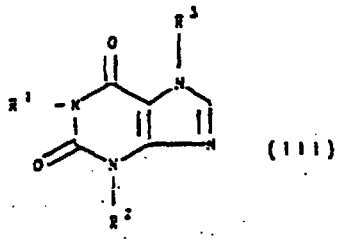
Z denotes a radical of the formula $-CO_2R^1$ or $-CH_2OH$, R^1 denoting hydrogen, an alkyl radical having up to 8 carbon atoms, a singly olefinically unsaturated aliphatic hydrocarbon radical having 3-8 carbon atoms, a cycloaliphatic hydrocarbon radical which has 3-7 carbon atoms in the ring and not more than one multiple bond, or an araliphatic hydrocarbon radical having 6-9 carbon atoms or a pharmaceutically tolerated metal or ammonium cation,

R^2 denotes an aliphatic hydrocarbon radical which has 4 to 6 carbon atoms and which can

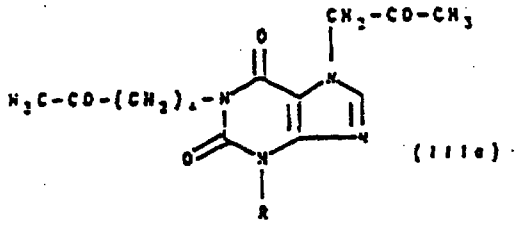
contain not more than one multiple bond, and R^3 and R^4 denote hydrogen or identical or different protective groups which can readily be eliminated under neutral or basic conditions,

and

B) at least one xanthine of the formula (III) or (IIIa)



(III)

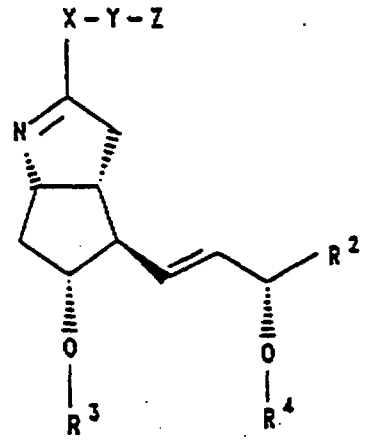


(IIIa)

in which one of the radicals R^1 and R^3 represents a straight-chain alkyl, (ω-1)-oxoalkyl or (ω-1)-hydroxyalkyl group - which can contain another hydroxyl group in the ω or (ω-2) position - having 3 to 8 carbon atoms, and the two other radicals R^2 and R^3 or R^1 and R^2 represent alkyl groups having 1 to 8 carbon atoms in the position of R^1 or R^3 and 1 to 4 carbon atoms in the position of R^2, and R in formula (IIIa) represents an alkyl radical having 1 to 4 carbon atoms, or a prodrug form of the oxoalkylxanthines of the formulae (III) or (IIIa) or of the hydroxyalkylxanthines of the formula (III), or a metabolite of a xanthine of the formula (III) or (IIIa), and the ratio by weight of the component A to the component B being between 1:8,000 and 1:10, with or without a pharmaceutical vehicle, for the treatment of diseases which are caused or characterized by defects in blood functions or blood constituents, in particular platelets or erythrocytes, or by defects in the physiological interactions between the blood constituents and the blood vessel wall.

The invention also relates to a combination product which contains as component A the heteroiminoprostacyclin which

has formula V



(V)

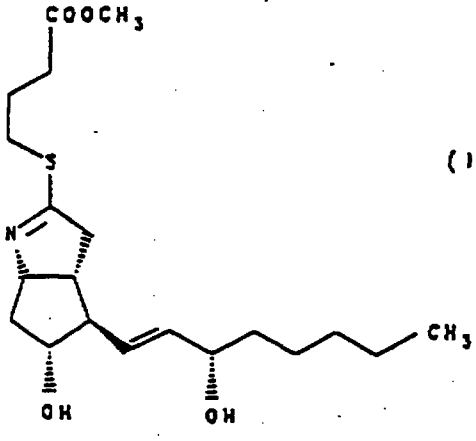
where X, Y, Z, R^2, R^3 or R^4 have the definitions specified in formula I, and as component B the xanthine derivative of the formula III,

where a) the total of the carbon atoms in all the substituents is 3 to 10,

b) R^1 or R^3 is a radical having 6 carbon atoms, or

c) R^1 or R^3 is a radical which has 6 carbon atoms and is substituted by a hydroxyl or oxo group in the (ω-1) position.

The invention also relates to a combination product which contains as component A tilsuprost of the formula II



(II)

The invention also relates to a combination product wherein the ratio by weight of component A to component B is between 1:2,000 and 1:20, in particular between 1:500 and 1:50

The invention also relates to the use of combinations of the components A) and B) for the treatment of the said diseases, and to a process for the preparation of pharmaceutical compositions.

Thus, according to the invention, the pharmacological actions of, in particular, the heteroiminoprostacyclins can be stimulated in a superadditive manner by addition of the xanthines (see Table 3) to an extent far above the calculated sum of the actions of the individual substances.

The preferred xanthine derivatives of the formula (III) are those in which the sum of the carbon atoms of all the substituents is not less than 3 and not more than 10. Exceptionally potent increases in the action are obtained, as is shown in more detail below, with those xanthine derivatives in which there is in the position of R^1 or R^3 a group which has 6 carbon atoms and which can contain up to one hydroxyl or oxo group in the (ω-1)-position, that is to say a hexyl, 5-oxohexyl or 5-hydroxyhexyl group, i.e. in particular 1-hexyl-3,7-dimethylxanthine (pentifylline), 1-(5-hydroxyhexyl)-3,7-dimethylxanthine, 1-(5-oxohexyl)-3,7-dimethylxanthine, 1,3-dimethyl-7-(5-hydroxyhexyl)xanthine, 1,3-dimethyl-7-(5-oxohexyl)-xanthine, 1-(5-hydroxyhexyl)-3-methyl-7-propylxanthine or 1-(5-oxohexyl)-3-methyl-7-propylxanthine (propentofylline) are particularly suitable for medical use and are thus preferred.

Surprisingly, the combination products to which the present invention relates are very especially suited for the clinical therapy of the abovementioned diseases because, by reason of the superadditive actions, the amounts of the combination constituents which are to be used in the form of the combination products according to the invention can be reduced to those amounts which show only a minimal pharmacological action when they are used alone, so that, at the same time, side effects which are

caused by these medicaments no longer occur or are diminished. This is of great importance because the prostacyclin analogs which do not have an enol ether structural moiety may cause serious side effects, such as arrhythmic effects and tachycardia; however, headaches, vomiting and flushing have also been described. In particular, the heteroiminoprostacyclins also exhibit not only advantageous medical actions but also undesired side effects. Undesired clinical symptoms have also been described for the xanthines.

In order to achieve the superadditive antiaggregatory and antithrombotic action, the combinations according to the invention can be in the form of dose units as solid presentations, such as capsules (including microcapsules which, in general, do not contain a pharmaceutical vehicle), tablets (including coated tablets and pills), or suppositories, it being the case that when capsules are used the capsule material can assume the function of the vehicle, and the contents can be in the form of, for example, a powder, gel, emulsion, dispersion or solution. However, it is especially advantageous and straightforward to prepare oral (peroral) formulations with the two active components A) and B), which contain the calculated amounts of the active compounds together with each desired pharmaceutical vehicle. It is also possible to use an appropriate formulation (suppository) for rectal therapy. Likewise, transdermal and parenteral (intraperitoneal, intravenous, subcutaneous, intramuscular) injection of solutions which contain the combinations according to the invention is possible.

The tablets, pills or granules can be prepared by customary processes, such as compression, immersion or fluidized bed processes, or by tank coating, and they contain vehicles and other customary auxiliaries, such as gelatin, agarose, starch, for example potato, corn or wheat starch, cellulose, such as ethylcellulose, silica, various sugars, such as lactose, magnesium carbonate

and/or calcium phosphates. The coating solution is usually composed of sugar and/or starch syrup and mostly also contains gelatin, gum arabic, polyvinylpyrrolidone, synthetic cellulose esters, surface-active substances, plasticizers, pigments and similar additives corresponding to the state of the art. All customary flow-regulating agents and lubricants such as magnesium stearate and release agents can be used for the preparation of the presentations.

The compositions preferably have the form of coating/core tablets or multilayer tablets, with O-acetylsalicylic acid and/or the xanthine being in the coating or in the core or in one layer, while the heteroiminoprostacyclin is in the core or in the coating or in another layer. The active components can also be present in a controlled-release form so that constant release over time is achieved. Thus, for example, the active compounds can be bound to ion exchangers or to metal cations (for example aluminum) or adsorbed onto material to control release or entrapped in material to control release (for example that based on cellulose or polystyrene resin, for example hydroxyethylcellulose). The particularly suitable xanthine component takes the form of commercially available pharmaceutical compositions which are released after a time lag, for example not until the intestinal tract is reached. A delayed release of the active compounds can also be achieved by providing the relevant layer or the compartment with customary enteric coatings.

It is self-evident that the dose which is to be used depends on a variety of factors, such as the organism which is to be treated (i.e. human or animal, age, weight, general state of health), the severity of the symptoms, the disease which is to be treated, (where appropriate) the nature of the concurrent treatment with other medicaments, the frequency of the treatment etc. In general, the doses are administered up to five times a day, and preferably once to three times a day. The

weights of the individual active compounds should be within the range indicated below or within the dose range which is effective and is tolerated by the organism which is to be treated.

Thus suitable therapy with the combinations according to the invention comprises, for example, the administration of one, two or more, preferably 3 to 8, single doses of the combination products, according to the invention, of A) 0.05 to 50, preferably 0.1 to 25, and in particular up to 10, mg, of heteroiminoprostacyclin in each, and B) 100 to 1200, preferably 100 to 400 or 600, mg of xanthine component, the amount of course depending on the number of single doses and on the disease which is to be treated, and it also being possible that a single dose can be composed of, for example, several dosage units administered at the same time. In general, the daily dose does not exceed 30 to 50 mg of component A and does not exceed 2,000 mg of xanthine, in particular on oral or rectal administration. The upper daily dose of these active compounds for i.v. or i.p. administration is generally 40% to 50% lower. Where possible, the dose of continuous infusions or intermittent infusions, for example for up to 14 days, should not exceed 0.005 mg to 0.01 mg of heteroiminoprostacyclin per minute and 0.1 - 1 mg of xanthine per minute, even though this may nevertheless be indicated temporarily for particularly severe disease symptoms.

The agents according to the invention can be used in the same manner as known antithrombotic agents and agents inhibiting the aggregation of blood platelets and the formation of metastases. In vivo uses embrace administration to humans and animals in order to prevent the formation of blood clots, such as to prevent transient ischemic attacks and for long-term prophylaxis following myocardial infarcts and strokes, and for arteriosclerosis and disturbances of peripheral blood flow (intermittent claudication, gangrene), as well as for treatment after

surgery to prevent postoperative thromboses and for the aftertreatment of cancer to prevent or diminish the formation of metastases. The use for patients who are connected to heart-lung machines and for renal dialysis is also possible, likewise for patients with artificial heart valves, vessel prostheses etc. Of course, use for the alleviation of pain and the inhibition of inflammation is also possible.

Examples of pharmaceutical compositions according to the invention

Examples of compositions of this type for use in humans (see Tab. 1) contain y mg of pentoxifylline or other xanthine derivatives as the pure substance and/or as a commercially available finished composition (Trental(R), supplied by Albert Roussel Pharma GmbH, Wiesbaden, or Rentylin(R), supplied by Dr. Rentschler Arzneimittel GmbH & Co., Laupheim (abbreviated to T and R respectively), or portions of these finished compositions, combined with z mg of tilsuprost. The pharmaceutical vehicles for these combinations are gels which have been solidified by heating: (a) 20 per cent by weight of gelatin/1 per cent by weight of glycerol in water and b) 1 per cent by weight of agarose in water and c) 10 per cent by weight of ethylcellulose T50 (Hercules GmbH, Hamburg) in acetone/water (80 : 20% by weight), in each case with and without 8 per cent by weight, which have been stirred in, of pentoxifylline or another xanthine derivative or commercially available gelatin capsules (size 0 for use in humans and large animals (supplied by Kapsugel, Basel)). For use in small animals (mice), the constituents of the compositions are reduced in accordance with the amounts of active compounds stated in Tab. 3, or smaller gelatin capsules (size 4) are used.

Methods

Method 1 - Induced aggregation of human platelets in vitro

Blood is taken by careful cannulization of the antecubital vein, and is immediately stabilized with sodium citrate (ad 0.38%), from apparently healthy male and female volunteers who have taken no medicaments in the preceding 10-day period. Platelet-rich plasma (PRP) is obtained as the supernatant after centrifugation at 140 x g for 15 minutes, and its platelet content should be in the range 2.5 - 3.5 x 10^{+8}/ml (Coulter counter). The platelet aggregation is followed optically by measurement of the transmission of light in a Born aggregometer. The total volume of the test mixture is 0.25 ml. The pre-incubation time with the trial product is 10 min at 37°C, and then aggregation is induced with 2 x 10^{-4} mol/l arachidonic acid or 1.7 µg/ml collagen. The trial product is tested on five different donors. Dose-effect curves are produced from the maximum aggregation amplitudes in each case, and the arithmetic mean of the ED_{50} (mol/l) is determined graphically. The measurements are carried out in the period 1-6 hours after blood sampling.

Method 2 - Induced aggregation of mouse platelets in vivo

Female mice (NMRI - Naval Medical Research Institute strain), weighing about 20-25 g, are treated orally with the active compounds or combinations of active compounds. After 1 hour, the blood sample is taken from the aorta under pentobarbital anesthesia. The preparation of PRP and the induction of aggregation with 6.8 µg/ml collagen or 3.66 x 10^{-3} mol/l arachidonic acid are carried out as described above (cf. also Thromb. Haemostasis 45 (1981) 1).

Method 3 - Determination of cyclic AMP in human platelets

The method follows in every detail the procedure in Nature (London) 292 (1981) 364: however, in place of

rabbit platelets the incubation was carried out with human platelet concentrate and ^{3}H-adenine at 20°C for 90 min. The excess adenine is removed as described in Nature, the active compounds (see Tab. 2) are added, and renewed incubation is carried out for 5 min (37°C). The cyclic ^{3}H-AMP formed is removed in the known manner and is quantified by measurement of the radioactivity.

Tab. 1

Example	Pharmaceutical vehicle	Xanthine content (mg)	Heteroiminoprostacyclin content (mg)
1	capsule	300 (T, cylindrically pressed)	0.15 (tilsuprost)
2	capsule	100 (pentifylline)	0.5 (tilsuprost)
3	1st layer: agarose containing 470 mg pentoxifylline plus 0.8 mg tilsuprost 2nd layer: R	470 (pentoxifylline)	0.8 (tilsuprost)
4	1 ml aqueous infusion solution	0.015 (pentoxifylline)	0.0002 (tilsuprost)

It is shown in Tab. 2 that the pharmacological action of the component A (tilsuprost) used according to the invention is not comparable with that of prostacyclin.

Tab. 2

	Aggregation inhibition ED_{50} (mol/l) (Method 1)	Cyclic AMP level mol/test mixture (action at ...mol/l)
Tilsuprost	8×10^{-9}	8.9×10^{-13} (at 1×10^{-9}) 9.8×10^{-13} (at 1×10^{-8})
Prostacyclin	8×10^{-9}	1.71×10^{-12} (at 1×10^{-9}) 19.35×10^{-12} (at 1×10^{-8})
No active compound (no inhibition)		9.0×10^{-13}

The results show that tilsuprost and prostacyclin are equipotent inhibitors of the aggregation of human platelets. The experiment on stimulation of cyclic AMP in human platelets by prostacyclin confirms the findings already known from Nature 292 (1981) 364. Surprisingly, in this experiment tilsuprost shows no significant stimulation.

The superadditive action of the combinations according to the invention in human platelets is demonstrated by the results listed in Tab. 3. The results show that the inhibitory action of tilsuprost on the aggregation of human platelets (method 1) can be superadditively increased by addition of xanthines. The table also shows that combinations of xanthines of the formula I, with R^3 = hydrogen, and tilsuprost have less pronounced effects.

Tab. 3

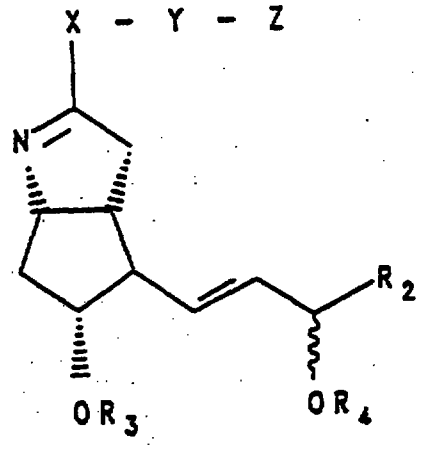
	Single substances (comparison) (Concentrations in mol/l)			% inhibition of aggregation
I	1.9×10^{-9}	tilsuprost		5
II	3.8×10^{-9}	tilsuprost		19
III	1.6×10^{-6}	carbacyclin		36
V	2.7×10^{-5}	pentoxifylline		0
VI	1.1×10^{-5}	pentifylline		0
VII	2.9×10^{-5}	propentofylline		0
VIII	3×10^{-5}	theophylline		4
IX	1.4×10^{-5}	1-methyl-3-isobutyl-xanthine		5

Combinations	% inhibition of aggregation
A) According to the invention	
II + V	93
II + VI	84
II + VII	95
B) Comparison	
II + VIII	45
II + IX	58

Patent Claims for the Contracting States BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A combination product containing

A) a heteroiminoprostacyclin of the formula I



(I)

in which

X denotes an oxygen or sulfur atom or an NH group,

Y denotes a straight-chain aliphatic hydrocarbon radical having 2-6 carbon atoms or a cycloaliphatic hydrocarbon radical having 3-6 carbon atoms in the ring, which radicals can contain not more than one multiple bond,

Z denotes a radical of the formula $-CO_2R^1$ or $-CH_2OH$, R^1 denoting hydrogen, an alkyl radical having up to 8 carbon atoms, a singly olefinically unsaturated aliphatic hydrocarbon radical having 3-8 carbon atoms, a cycloaliphatic hydrocarbon radical which has 3-7 carbon atoms in the ring and not more than one multiple bond, or an araliphatic hydrocarbon radical having 6-9 carbon atoms or a pharmaceutically tolerated metal or ammonium cation,

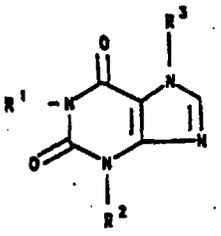
R^2 denotes an aliphatic hydrocarbon radical which has 4 to 6 carbon atoms and which can contain not more than one multiple bond, and

R^3 and R^4 denote hydrogen or identical or

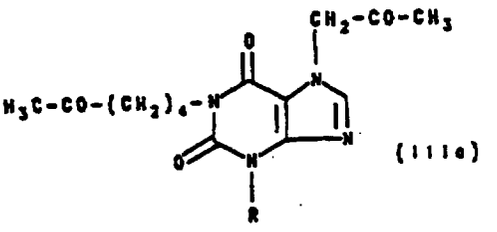
different protective groups which can readily be eliminated under neutral or basic conditions,

and

B) at least one xanthine of the formula (III) or (IIIa)



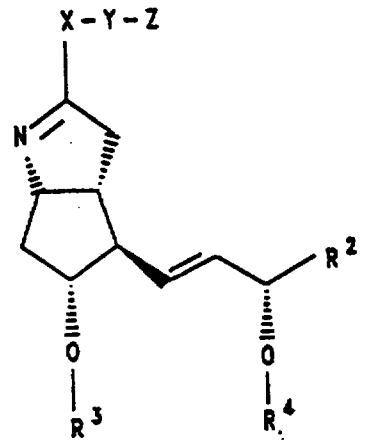
(III)



(IIIa)

in which one of the radicals R^1 and R^3 represents a straight-chain alkyl, (ω-1)-oxoalkyl or (ω-1)-hydroxyalkyl group - which can contain another hydroxyl group in the ω or (ω-2) position - having 3 to 8 carbon atoms, and the two other radicals R^2 and R^3 or R^1 and R^2 represent alkyl groups having 1 to 8 carbon atoms in the position of R^1 or R^3 and 1 to 4 carbon atoms in the position of R^2, and R in formula (IIIa) represents an alkyl radical having 1 to 4 carbon atoms, or a prodrug form of the oxoalkylxanthines of the formulae (III) or (IIIa) or of the hydroxyalkylxanthines of the formula (III), or a metabolite of a xanthine of the formula (III) or (IIIa), and the ratio by weight of the component A to the component B being between 1:8,000 and 1:10, with or without a pharmaceutical vehicle, for the treatment of diseases which are caused or characterized by defects in blood functions or blood constituents, in particular platelets or erythrocytes, or by defects in the physiological interactions between the blood constituents and the blood vessel wall.

2. A combination product as claimed in claim 1, which contains as component A the heteroiminoprostacyclin which has formula V



(V)

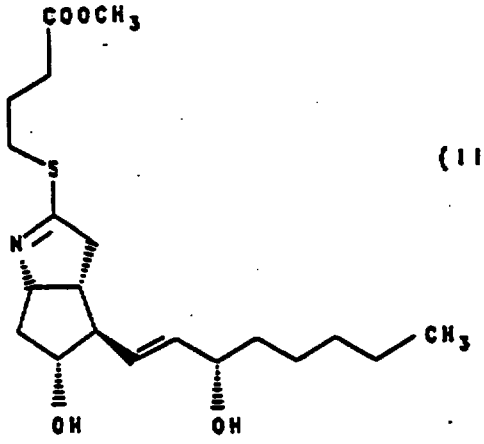
where X, Y, Z, R^2, R^3 or R^4 have the definitions specified in formula I, and as component B the xanthine derivative of the formula III,

where a) the total of the carbon atoms in all the substituents is 3 to 10,

b) R^1 or R^3 is a radical having 6 carbon atoms, or

c) R^1 or R^3 is a radical which has 6 carbon atoms and is substituted by a hydroxyl or oxo group in the (ω-1) position.

3. A combination product as claimed in claim 1 or 2, which contains as component A tilsuprost of the formula II



(II)

4. A combination product as claimed in one or more of claims 1 to 3, which contains as component B 1-hexyl-3,7-diemthylxanthine, 1-(5-oxohexyl)-3,7-di-

* C L M S *

methylxanthine or 1-(5-oxohexyl)-3-methyl-7-propylxanthine.

5. A combination product as claimed in one or more of claims 1 to 4, wherein the ratio by weight of component A to component B is between 1:2,000 and 1:20.

6. A combination product as claimed in claim 5, wherein the ratio by weight is between 1:500 and 1:50.

7. A combination product as claimed in one or more of claims 1 to 6, wherein at least one of components A and B is present in controlled-release form or in the form of a coating/core tablet or multilayer tablet.

8. A combination product as claimed in one or more of claims 1 to 7, wherein the combination product is in the form of a dosage unit which is to be administered orally or rectally and contains 0.1 mg to 25 mg of component A or 100 mg to 1,200 mg of component B.

9. A combination product as claimed in claim 8 containing 0.1 mg to 10 mg of component A or 100 mg to 600 mg of component B.

10. The use of components A and B as claimed in one or more of claims 1 to 9, components A, B and C, where C represents O-acetylsalicylic acid or pharmaceutically tolerated salts of O-acetylsalicylic acid, or of components A and C, where the ratio by weight of component A and to component B or A to component C or A to components B and C is between 1:8,000 and 1:10, with or without pharmaceutical vehicles, for the preparation of a pharmaceutical for the treatment of diseases which are caused or characterized by defects in blood functions or blood constituents, in particular platelets or erythrocytes, or by

defects in the physiological interactions between the blood constituents and the blood vessel wall.

11. The use as claimed in claim 10, wherein it contains a combination product as claimed in one or more of claims 1 to 9.

12. A process for the preparation of a combination product as claimed in one or more of claims 1 to 9, which comprises processing A) a heteroiminoprostacyclin of the formula (I) as claimed in claim 1 and B) xanthines of the formula (III) or (IIIa) as claimed in claim 1 or prodrug forms of the oxoalkylxanthines of the formulae (III) or (IIIa) or of the hydroxyalkylxanthines of the formula (III), or their metabolites, with or without pharmaceutical vehicles, in a conventional way to a pharmaceutical presentation, with the proviso that the ratio by weight of component A) to component B) is between 1:8,000 and 1:10.