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(54) Title: PHARMACEUTICAL COMBINATION PREPARATIONS CONTAINING ERYTHROPOIETIN AND MODIFIED HAEMOGLOBINS			
(54) Bezeichnung: PHARMAZEUTISCHE KOMBINATIONSPRÄPARATE ENTHALTEND ERYTHROPOIETIN UND MODIFIZIERTE HÄMOGLOBINE			
(57) Abstract The invention relates to pharmaceutical combination preparations containing erythropoietin and one or several modified haemoglobins. The inventive combination preparations are used especially for treating manifest anaemia. The inventive pharmaceutical combination preparation comprises a) individual forms of administration of an erythropoietin preparation suitable for an individual dose of a quantity of 3,000 - 7,000 U of the active agent and b) 50 - 100 ml of one or several modified haemoglobins. The erythropoietin preparation and the modified haemoglobin can be provided in separate or single forms of administration.			
(57) Zusammenfassung Die Erfindung betrifft pharmazeutische Kombinationspräparate enthaltend Erythropoietin-Präparate und ein oder mehrere modifizierte Hämoglobine. Die Kombinations-Präparate werden insbesondere zur Behandlung manifester Anämien eingesetzt. Gegenstand der vorliegenden Erfindung ist ein pharmazeutisches Kombinationspräparat, das a) einzelne Darreichungsformen eines Erythropoietin-Präparates geeignet für die Einzeldosierung des Wirkstoffes in einer Menge von 3.000-7.000 U und b) 50-100 ml eines oder mehrerer modifizierter Hämoglobine umfaßt, wobei Erythropoietin-Präparat und modifiziertes Hämoglobin in getrennten Darreichungsformen oder in einer einheitlichen Darreichungsform vorliegen können.			

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Pharmaceutical combination preparations containing erythropoietin and modified haemoglobins

Description

The invention is concerned with pharmaceutical combination preparations containing erythropoietin preparations and one or more modified haemoglobins. The combination preparations are especially useful for the treatment of manifest anaemias.

The macromolecule ferritin (molecular weight at least 440 kD depending on the iron content) plays a significant rôle in the diagnosis of anaemias. An estimation of the fullness level of the iron reservoir is possible by determining the ferritin and the transferrin saturation (M. Wick, W. Pingerra, P. Lehmann "Ferritin in iron metabolism and diagnosis of anaemias", pages 5-22, 38-50, 65-77, 94-97, 2nd expanded edition 1994, published by Springer Vienna, New York), with the totality of the iron stored as basic ferritin in the depot organs liver, spleen and bone marrow amounting to about 800-1200 mg. A lower ferritin concentration is the definitive characteristic for detecting iron deficiency states and their difference from other causes of hypochromic anaemia, such as e.g. chronic inflammations and tumours.

It is known to treat transfusion-mediated anaemias in haemodialysis patients with recombinant erythropoietin (rhEPO), with it being necessary as a rule to carry out an iron substitution in parallel to the EPO therapy. This iron substitution is effected by the intravenous administration of iron(III) salts, with two intravenously administerable iron preparations being available on the German medicament market at present. These are the medicaments "Ferlecit" and "Ferrum Vites". "Ferlecit" is an iron(III) gluconate complex, while "Ferrum Vites" is an iron(III) oxide saccharate complex.

It has, however, become evident that in the case of manifest anaemias with manifest iron deficiency and iron utilization disorders (< 30 mg/dl ferritin) iron substitution with the mentioned preparations has disadvantages, since for the treatment of manifest anaemias relatively large amounts of a pharmacologically harmless iron salt have to be infused. The use of the aforementioned iron preparations holds the possibility of unexpected circulatory reactions up to collapse, especially when large amounts have to be injected relatively rapidly.

In WO 96/15805 there is described a haemoglobin therapy for haemodialysis according to which very low doses of stroma-free haemoglobin are administered over a period of 10 to 45 minutes in order to achieve a haemostabilization and to avoid a lowering of blood pressure in sensitive patients. However, this described therapy is not successful in the case of manifest iron deficiency anaemias.

Also, WO 95/24213 describes the use of natural or recombinant haemoglobin or their chemically modified derivatives for anaemia treatment. Furthermore, this document discloses the combined administration of one of the aforementioned haemoglobins with one or more haematopoietic growth factors, inter alia with EPO. Examples 4 and 5 as well as some of the Figures show that a combined administration of EPO and rh haemoglobin lead to an increased haematopoiesis.



However, this document does not disclose a practical therapeutic regime for an optimal regulation and treatment of patients with manifest anaemias. Also, it is not evident therefrom, as in the case of patients treated with EPO, that it is possible to produce an optimal EPO effect without avoiding an EPO resistance.

It has now been found that the use of relatively high infusions amounts of 50-100 ml of modified haemoglobin (about 100-200 mg Fe^{2+}) together with 3,000-7,000 U of EPO is surprisingly advantageous for the treatment of manifest anaemias (the abbreviation "IU" can also be used in place of the abbreviation "U" for International Units).

Accordingly, in one aspect the present invention provides a pharmaceutical combination preparation comprising (a) individual administration forms of an erythropoietin preparation suitable for the individual dosing of the active substance in an amount of 3,000-7,000 U, and b) 50-100 ml of one or more modified haemoglobins, containing 100-200 mg Fe^{2+} .

In a further aspect, the present invention provides process for the production of pharmaceutical combination preparations of the invention characterized by formulating 3,000-7,000 U of an erythropoietin preparation in the form of individual administration forms and 50-100 ml of modified haemoglobin containing 100-200 mg Fe^{2+} together or separately from each other with pharmaceutically usual carriers or adjuvants and making the respective preparations available in the form of combination preparations.

In other aspects the present invention provides the use of erythropoietin preparations with 3,000-7,000 U of EPO and 50-100 ml of one or more modified haemoglobins containing 100-200 mg Fe^{2+} for the production of a pharmaceutical combination preparation for the treatment of manifest anaemias; use of erythropoietin preparations with 5,000-7,000 U of EPO and 80-100 ml of one or more modified haemoglobins containing 160-200 mg Fe^{2+} for the production of a pharmaceutical combination preparation for the treatment of manifest anaemias with iron utilization disorders; use of erythropoietin preparations with 3,000-5,000 U of EPO and 80-100 ml of one or more modified haemoglobins containing 160-200 mg Fe^{2+} for the production of a pharmaceutical combination preparation for the treatment of manifest anaemias with iron utilization disorders.

In a further aspect, the present invention provides pharmaceutical unit pack comprising 3,000-7,000 U of an erythropoietin preparation in individual administration forms and 50-100 ml of one or more modified haemoglobins containing 100-200 mg Fe^{2+} as a single administration form in one container or as separate administration forms in separate containers.

In further aspects, the invention provides method of treatment of manifest anaemias comprising the step of administering to a patient, in combination, or separately, 3,000-7,000 U erythropoietin, and 50-100 ml of one or more modified haemoglobins containing 100-200 mg Fe^{2+} ; method of treatment of manifest anaemias with iron utilization disorders comprising the step of administering to a patient, in combination, or separately, 3,000-7,000 U erythropoietin, and 50-100 ml of one or more modified haemoglobins containing 100-200 mg Fe^{2+} ; and method of treatment of manifest anaemias without iron utilization disorders comprising the step of administering to a patient, in combination, or separately, 3,000-7,000 U erythropoietin, and 50-100 ml of one or more modified haemoglobins containing 100-200 mg Fe^{2+} .

In the combination preparations of the invention which contain 3,000-7,000 U of erythropoietin and 50-100 ml of one or more modified haemoglobins, the EPO and the modified haemoglobin may be present in separate administration forms or in a single administration form.



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In accordance with the invention 3,000-7,000 U of an erythropoietin preparation and 50-100 ml of one or more modified haemoglobins are used as the optimal dose depending on the clinical picture of the anaemia. Thus, in the case of manifest anaemias without iron distribution disorders, a high dose of Fe^{2+} , about 80-100 ml (about 160-200 mg Fe^{2+}), preferably 85-95 ml, in the form of a modified haemoglobin and a lower dose of EPO between 3,000 and 5,000 U is administered in accordance with the invention.

When there are iron distribution disorders in the case of manifest anaemias, a higher EPO dose of about 5,000-7,000 U of EPO, preferably 6,000-7,000 U, especially about 7,000 U of EPO, and a high Fe^{2+} dose, about 80-100 ml, preferably about 100 ml, in the form of one or more modified haemoglobins is preferably administered.

For the treatment of iron utilization disorders in the case of manifest anaemias the combination preparation in accordance with the invention preferably contains 3,000-7,000 U of EPO and 80-100 ml of a modified haemoglobin, preferably about 5,000 U of EPO, and about 100 ml of one or more modified haemoglobins. For the treatment of manifest iron deficiency anaemias the combination preparation likewise preferably contains 3,000-7,000 U of EPO and 80-100 ml of a modified haemoglobin.

As modified haemoglobins in the meaning of the invention there are suitable in principle all haemoglobins described in WO 95/24213 page 20, line 15 to page 27, line 2. In particular, these are also cross-linked haemoglobins or cross-linked haemoglobin polymerizates, such as e.g. diacetylsalicylic acid (diaspirin), cross-linked haemoglobin (DCL-Hb) or other blood substitutes based on modified haemoglobins. For example, the following preparations come into consideration as modified haemoglobins: Hem Assist® (Baxter; DCL human Hb); PolyHeme® (Northfield, Upjohn, human Hb, cross-linked and polymerized); Hemopure® (Biopure, Upjohn; bovine Hb, polymerized); Optro® (Somatogen, Eli Lilly; recombinant human Hb); HemOlink® (Hemosol, Fresenius; human Hb, cross-linked and polymerized); PEG-modified bovine Hb (manufactured by Enzon; polyethylene glycol-modified Hb); polyoxyethylene-modified human Hb (manufactures Apex and Ajinimoto). The haemoglobins can also be used in accordance with the invention in the form of haemoglobin preparations which contain pharmaceutically compatible adjuvants known per se. Such preparations are described, for example, in WO 95/24213.

As suitable erythropoietin preparations in the meaning of the present invention there come into consideration those active substances which are comparable with respect to the physiological effect of human EPOs. Suitable EPO preparations are, for example, recombinant human EPO (rhEPO; see European Patent EP 0,205,564 or EP 0,411,678) or also corresponding modifications of these proteins. As modifications there come into consideration, for example, such proteins with molecular weights higher or lower than 34,000 Da (molecular



weight of urinary EPO), likewise isoforms of the enzyme or proteins with different glycosylation. In particular, proteins chemically modified by PEG (polyethylene glycol) can also be used. Further, there basically also come into consideration such proteins which are derived by deletions, substitutions or additions from the amino acid sequence of the natural EPO with a length of 166 amino acids. These proteins have essentially comparable physiological properties to rhEPO. In particular, these proteins have biological properties which cause bone marrow cells to increase the production of reticulocytes and red blood corpuscles and/or to increase haemoglobin synthesis or iron uptake. In place of these proteins there can also be used low molecular substances, which are denoted as EPO mimetics, and which bind to the same biological receptor. These mimetics can preferably also be administered orally. The amount of such proteins or mimetics to be administered is determined by comparing the biological activity between EPO and these active substances.

The concentrations in accordance with the invention of EPO and haemoglobin-Fe²⁺ permit in their combination an optimal anaemia treatment, especially the treatment of manifest anaemias. The treatment with the combination preparation is preferably effected once weekly, whereby the amount of haemoglobin of 300 ml per week should not be exceeded (e.g. 3 x 100 ml infusions).

In the meaning of the present invention there should be understood under the term "combination preparation" not only those medicament packs in which the EPO preparation and the haemoglobin are presented in juxtaposition in a finished marketable unit pack (so-called combination pack), but also those medicament packs which either contain a suitable amount of an EPO preparation or a suitable amount of a haemoglobin in the form of the respective individual preparations, with the individual preparations with respect to the amount of contents being presented such that they can be administered in the meaning of the invention for the combined dose with the respective other preparation. In these cases there is usually enclosed with the preparations from the pharmaceutical manufacturer or the medicament importer a medicament package insert which is required by law in many countries and in which are contained directions or information concerning the combined dose of the individual preparations.

The combination preparations can preferably be present in a single administration form in which the respective amounts of the EPO preparation and the haemoglobin are present in juxtaposition in one container.

This can be e.g. an injection solution or infusion solution or its lyophilizate, which, for example, is filled into ampoules. This administration form has the advantage that the EPO is stabilized by the modified haemoglobin during the production and storage of the administration form. In the case of a lyophilizate, the EPO, after its dissolution, is activated by the modified haemoglobin. The fixed combination of the two active substances in the form of a lyophilizate has the further advantage that it can be handled simply and safely. The lyophilizate is dissolved in the ampoule by the addition of pharmaceutically usual injection media and is administered intravenously.

It is also possible to administer the EPO preparation and the modified haemoglobin in the form of separate pharmaceutical formulations (free combination) simultaneously or, however, also in succession. This free combination, which can be made available in a unit pack, has the advantage of greater flexibility. Thus, these administration forms also enable the modified haemoglobins to be administered 1-3 days prior to the EPO administration.

This free combination, which can be made available in a single unit pack (medicament pack) also has the advantage that each patient to be treated can be prescribed a particular individual amount of an EPO preparation and of a haemoglobin. Furthermore, these combination preparations offer the advantage of greater safety when performing the therapy, since in each case the optimal synchronized amount of the individual preparation is fixed. A safe therapy



and simple handling by the personnel performing the treatment or in the area of self medication performed by patients is guaranteed by the combination preparation in accordance with the invention.

Where the EPO preparation is made available as a lyophilizate, the medicament packs (combination packs) contain the corresponding amount of the EPO preparation in glass ampoules or in cartridges. The haemoglobin can be present in solid form (lyophilizate) or also in liquid form in a separate container. Further, the combination pack preferably contains a reconstitution solution in order to dissolve either the EPO lyophilizate alone or also together with the haemoglobin. If the haemoglobin is present as a ready-for-use solution, the solution can be mixed together with the EPO solution when the combined administration of EPO and haemoglobin has to be effected. Basically, the haemoglobin can also be made available as a concentrate for addition to conventional infusion solutions, by which means a longer administration over several hours can be effected.

Combination preparations in the meaning of the present invention are also those unit packs which in each case make available individual administration forms of the erythropoietin preparation or of the haemoglobin as independent medicaments, with the individual preparations being provided such that they contain the requisite amounts of the individual substances for the combination in accordance with the invention of the EPO preparation and the haemoglobin. As a rule, the medicament packs contain the previously described package insert containing corresponding instructions for the combined administration with EPO or with haemoglobin in the required amount. A corresponding instruction can also be present as a pack imprint on the medicament pack (secondary packaging) or on the primary packaging (ampoule, blister strips, etc.). Thus, in the case of the EPO-containing medicament with 3,000-7,000 U of EPO it is, for example, indicated thereon that this preparation should especially be administered together with a haemoglobin preparation containing 50-100 ml of one or more modified haemoglobins. In the case of the haemoglobin preparation there is a reverse indication to the combined administration with 3,000-7,000 U of an erythropoietin preparation.

A further possibility for providing the EPO preparation comprises making available corresponding multi-dose preparations which contain the EPO preparation in higher amounts compared with individual doses. These preparations are especially suitable for use in clinics in which a large number of patients are treated daily. These multi-dose preparations contain the EPO preparation in dosages of up to 500,000 U, especially up to 100,000 or 50,000 U. The multi-dose preparations have the advantage that they permit the skilled medical personnel to withdraw any dosage of the EPO preparation, for example by withdrawing corresponding amounts by volume of the finished injection solution. This is especially advantageous in the treatment of patients with different dosage requirements of the active substance or in the treatment of children in which a lower dosage of the EPO preparation is required. From an injection solution of, for example, 100,000 U of EPO, preferably freshly prepared at the beginning of the day, there can be performed, circumstances permitting, all patient treatments required during this day without the need to prepare separate injection solutions for each of the individual patients. This can lead to a significant time saving or to an easing of the burden of work for skilled medical personnel. Preferably, the individual EPO dosages are withdrawn in the range of 3,000 U, 5,000 U and 7,000 U.

The multi-dose preparations can also be present in the form of solutions, which are filled into cartridges. These cartridges are suitable for use in so-called pens, which permit administration by patients themselves and an individual dosage withdrawal. For example, these cartridges contain the EPO preparation in an amount of 10,000 or 20,000 U, whereby different dosing intervals can be realized by appropriate adjustment of the withdrawal volume.



The production of the pharmaceutical administration forms of the invention is effected according usual processes known in galenical technology with pharmaceutically usual adjuvants. The process for the production of the pharmaceutical combination preparation in accordance with the invention and the pharmaceutical unit pack, which contains the combination of preparations in accordance with the invention, are likewise objects of the invention.

In carrying out the therapy, the diagnostic parameters ferritin and transferrin saturation have to be controlled. The ferritin value is in the normal range when it amounts to $400 \mu\text{g/l} \pm 50\%$. The transferrin saturation should amount to 20-40%.

The invention will be illustrated hereinafter in more detail on the basis of working Examples.

Example 1:

Patients with manifest iron deficiency (ferritin $< 12 \text{ ng/ml}$, transferrin saturation $< 15\%$ and haemoglobin $< 12 \text{ g/dl}$) are given by infusion 5,000 U of rhEPO once per week and 100 ml of a modified haemoglobin preparation, preferably DCL-Hb, three times per week. This treatment is repeated for a further five weeks until the values for ferritin, transferrin saturation and haemoglobin or haemocrit lie in the normal range.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgement or any form of suggestion that the prior art forms part of the common general knowledge in Australia.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers or steps but not the exclusion of any other integer or group of integers or steps.



The claims defining the invention are as follows:

1. Pharmaceutical combination preparation comprising
 - a) individual administration forms of an erythropoietin preparation suitable for the individual dosing of the active substance in an amount of 3,000-7,000 U, and
 - b) 50-100 ml of one or more modified haemoglobins, containing 100-200 mg Fe^{2+} .
2. Combination preparation according to claim 1, characterized in that it contains 3,000-7,000 U of an erythropoietin preparation and 80-100 ml of modified haemoglobin, containing 160-200 mg Fe^{2+} .
3. Combination preparation according to claim 1 or 2, characterized in that it contains 5,000-7,000 U of an erythropoietin preparation and 80-100 ml of modified haemoglobin, containing 160-200 mg Fe^{2+} .
4. Combination preparation according to any one of claims 1-3, characterized in that it contains 6,000-7,000 U of an erythropoietin preparation and about 100 ml of modified haemoglobin.
5. Combination preparation according to claim 1, characterized in that it contains 3,000-5,000 U of an erythropoietin preparation and 80-100 ml, preferably 85-95 ml, of modified haemoglobin, containing 160-200 mg Fe^{2+} .
6. Combination preparation as claimed in any one of claims 1 to 6 wherein the erythropoietin preparation and modified haemoglobins are present in separate administration forms.
7. Combination preparation as claimed in any one of claims 1 to 6 wherein the erythropoietin preparation and modified haemoglobins are present in a single administration form.



8. Process for the production of pharmaceutical combination preparations according to claims 1 to 7, characterized by
formulating 3,000-7,000 U of an erythropoietin preparation in the form of individual administration forms and 50-100 ml of modified haemoglobin containing 100-200 mg Fe^{2+} together or separately from each other with pharmaceutically usual carriers or adjuvants and making the respective preparations available in the form of combination preparations.
9. Use of erythropoietin preparations with 3,000-7,000 U of EPO and 50-100 ml of one or more modified haemoglobins containing 100-200 mg Fe^{2+} for the production of a pharmaceutical combination preparation for the treatment of manifest anaemias.
10. Use of erythropoietin preparations with 5,000-7,000 U of EPO and 80-100 ml of one or more modified haemoglobins containing 160-200 mg Fe^{2+} for the production of a pharmaceutical combination preparation for the treatment of manifest anaemias with iron utilization disorders.
11. Use of erythropoietin preparations with 3,000-5,000 U of EPO and 80-100 ml of one or more modified haemoglobins containing 160-200 mg Fe^{2+} for the production of a pharmaceutical combination preparation for the treatment of manifest anaemias without iron utilization disorders.
12. Pharmaceutical unit pack comprising 3,000-7,000 U of an erythropoietin preparation in individual administration forms and 50-100 ml of one or more modified haemoglobins containing 100-200 mg Fe^{2+} as a single administration form in one container or as separate administration forms in separate containers.
13. Unit pack according to claim 12, characterized in that
in each case the erythropoietin preparation and the modified haemoglobin are present in separate administration forms in the form of solutions for injection or infusion purposes.



14. Method of treatment of manifest anaemias comprising the step of administering to a patient, in combination, or separately, 3,000-7,000 U erythropoietin, and 50-100 ml of one or more modified haemoglobins containing 100-200 mg Fe²⁺.
- 5 15. Method of treatment of manifest anaemias with iron utilization disorders comprising the step of administering to a patient, in combination, or separately, 3000-7000 U erythropoietin, and 50-100 ml of one or more modified haemoglobins containing 100-200 mg Fe²⁺.
- 10 16. Method of treatment of manifest anaemias without iron utilization disorders comprising the step of administering to a patient, in combination, or separately, 3,000-7,000 U erythropoietin, and 50-100 ml of one or more modified haemoglobins containing 100-200 mg Fe²⁺.
- 15 17. Method of treatment of manifest anaemias, with or without iron utilization disorders, comprising administering to a patient, a combination preparation in accordance with any one of claims 1 to 7.
- 20 18. Pharmaceutical combination preparations, processes for production thereof, uses of erythropoietin preparations, pharmaceutical unit packs or methods of treatment substantially as herein described with reference to the Examples.

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