I/We, the Applicant(s)/Nominated Person(s) specified below, request I/We be granted a patent for the invention disclosed in the accompanying standard complete specification.

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By: [Signature]

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I, John David O'Connor, of 31 Market Street, Sydney, New South Wales, 2000, Australia, Patent Attorney for the Applicant/Nominated Person in respect of an invention entitled:

**An Intravenous Form of Thalidomide for the Therapy of Immunological Diseases**

state the following:-

The Applicant/Nominated Person has entitlement from the actual inventors as follows:

The Applicant/Nominated Person is the assignee of the actual inventors.

The Applicant/Nominated Person is the applicant of the basic application listed on the Patent Request.

The basic application listed on the Patent Request is the first application made in a Convention country in respect of the invention.

DATED 3 September 1998

John David O'Connor
An aqueous thalidomide solution is described which is suitable as a parenteral form of application of thalidomide, particularly as an intravenous form of application, for the therapy of immunological diseases, and a method of producing the corresponding thalidomide solution is also described.

Claim

1. An aqueous thalidomide solution with a pH less than or equal to 5.5, in which one of the two enantiomers of thalidomide, (+)-(R)-thalidomide or (-)-(S)-thalidomide, is dissolved in pure form in isotonic glucose solution.
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Invention Title: An Intravenous Form of Thalidomide for the Therapy of Immunological Diseases  

The following statement is a full description of this invention, including the best method of performing it known to me/us:-
An intravenous form of thalidomide for the therapy of immunological diseases

This invention relates to a parenteral form of application of thalidomide and to a method of producing it.

The excessive formation of the cytokinin TNF-α (tumour necrosis factor α) plays a central part in the pathogenesis of graft-versus-host syndrome, aphthous stomatitis, erythema nodosum leprosum, morbus Boeck, morbus Crohn, rheumatoid arthritis and a series of other diseases which are associated with inflammatory symptoms. One basis for the therapy of these diseases consists of the targeted suppression of
the release of TNF-α, by administering immunomodulating active ingredients, such as dexamethasone or thalidomide for example. Whereas injectable forms of corticoids such as dexamethasone exist, this has hitherto not been the situation for thalidomide.

In the treatment of aphthous stomatitis, thalidomide has been shown to be superior to classical immunosuppressants. Other examples of diseases in which thalidomide has exhibited good efficacy without resulting in a general immunosuppression include cutaneous lupus erythematosus, pyoderma gangrenosum and orogenital ulcers with morbus Behçet, as well as ulcerations in HIV-infected patients, which do not differ histologically from aphthous ulcers and in which - in contrast to the majority of HIV-associated mucocutaneous lesions - no microbial instigators can be detected. As distinct from stomatitis aphthosa, these lesions, which can be characterised as major aphthae, can occur in the entire digestive tract, and when located in the pharyngeal space or the oesophagus make the absorption of food difficult, and also make the taking of oral medication difficult, due to the pain which they cause. The pathogenetic factors are endogenous mediators which have effects on the endothelium and on circulating leukocytes. Under the influence of locally-formed TNF-α and other cytokinins, there is a marked increase in the adhesiveness of the endothelium in relation to leukocytes, which makes a definitive contribution to the development of venous vasculitis. Substances which, like thalidomide, suppress this alteration of the endothelium without at the same time blocking the specific cellular immune defence, can constitute an important advance in therapy.

In severe cases of pharyngeal or oesophageal ulcers, in which the taking of oral medication is made difficult, or in which this may even be impossible, and in cases of HIV-associated pathology in which severe symptoms of diarrhoea make the use of oral medication unpredictable, the parental administration of active ingredients is appropriate. However, the low solubility of thalidomide in water (0.012 mg/ml; Arch. Pharm. 321, 371 (1988)) constitutes an obstacle to the parenteral application of this active ingredient. There has therefore been no lack of attempts to develop water-soluble forms of application.
Water-soluble thalidomide derivatives are known from DE 42 11 812. These thalidomide derivatives have a considerably higher solubility in water than that of thalidomide and are suitable for parenteral application.

In addition, thalidomide prodrugs have been proposed for parenteral application which can be applied in water-soluble form in the physiological pH range and which are toxicologically harmless (DE 196 13 976). A disadvantage here is that both types of the aforementioned compounds involve higher production costs than those for the production of thalidomide.

The underlying object of the present invention consisted of developing a water-soluble form of application of thalidomide. The object was also that the form of application to be developed should be stable in a form dissolved in water and that its non-physiological physicochemical properties should not give rise to toxicological effects.

It has been found that under certain conditions the requirements imposed on the form of application to be developed can be fulfilled by the use of pure enantiomers of thalidomide. Pure enantiomers in the sense of this invention contain less than 1% of their optical antipodes.

The enantiomers of thalidomide have a solubility in water which is higher by a factor of 6 than that of the racemate. The production of aqueous solutions is not practicable, however, due to the tendency of thalidomide to undergo spontaneous hydrolysis. However, if the pH of aqueous solutions falls within a pH range which is less than or equal to 5.5, hydrolysis does not occur.

According to the current state of knowledge, it is not possible to associate a defined isomer with the mode of action of thalidomide against immunological diseases. Pure enantiomers of thalidomide are converted into the racemate again in vitro and in vivo. Therefore, the antipode is also formed immediately after the parenteral administration of one of the isomers of thalidomide in vivo. An equilibrium is established after about 4 hours.

The present invention accordingly relates to a solution, which is suitable for parenteral application, of one of the two thalidomide enantiomers.
wherein this solution is an aqueous solution with a pH less than or equal to 5.5 and contains glucose as a constituent. According to the invention, one of the two thalidomide enantiomers is dissolved in isotonic glucose solution.

The definition of the invention comprises both solutions of (+)-(R)-thalidomide and solutions of (-)-(S)-thalidomide, which can be used individually or alternatively for parenteral application, particularly for intravenous application.

Suitable injectable forms of application of thalidomide are those which have a content of active ingredient of at least 0.2 mg/ml.

The present invention further relates to a method of producing the aqueous thalidomide solution. According to this feature of the invention, (+)-(R)-thalidomide or (-)-(S)-thalidomide is added in pure form to an isotonic glucose solution with a pH of 4 to 5 and this mixture is shaken until complete dissolution of the respective thalidomide enantiomer has occurred, is subsequently treated with ultrasound and is filtered under aseptic conditions.

The form of application according to the invention is toxicologically harmless for both rapid and slow infusion (10 ml/min).

Drugs according to the invention contain glucose in addition to one of the enantiomers of thalidomide. Other adjuvant substances may optionally be added to the thalidomide solution. The choice of these further adjuvant substances and the amounts to be used depend on exactly how the drug is to be administered.

The amount of active ingredient to be administered to the patient, which depends on the weight of the patient, on the type of parenteral application, on the indication and on the degree of severity of the illness, is usually between 0.1 and 1 mg/kg.
Examples

Example 1
For the production of infusion solution in a concentration of 200 \( \mu g/ml \), 70 mg (\( + \))-\((R)\)-thalidomide in 350 ml of a 5% glucose solution for infusions (pH 4 to 5) were introduced into a glass infusion bottle. The mixture was thoroughly shaken and treated for 15 minutes with ultrasound. Since the dissolved thalidomide concentration depends on the intensity of shaking and of the ultrasound treatment, both steps were repeated until complete dissolution was achieved. The water temperature in the ultrasonic bath reached a maximum of 33°C. The solution was filtered under aseptic conditions through a Millex GS sterile filter with a pore size of 0.22 \( \mu m \) (Millipore S.A., Molsheim, France) into a sterile glass infusion bottle. The solution was stored at room temperature.

The pH of the final solution was 5.5.

The duration of the ultrasound treatment can be reduced by using a solution of the pure enantiomer in ethanol. This has an initial concentration which is higher by a factor of 5 to 10.

Example 2
For the production of infusion solution in a concentration of 200 \( \mu g/ml \), 70 mg (\( - \))-\((S)\)-thalidomide in 350 ml glucose solution for infusions (pH 4 to 5) were introduced into a glass infusion bottle. The procedure employed was as in Example 1.

The pH of the final solution was 5.5.

Testing of stability
Portions for analysis were removed daily from the solutions on 10 successive days.

After 10 days, the respective thalidomide enantiomers were still completely intact, without hydrolysis having occurred.
After this period of time, the thalidomide enantiomers contained less than 1 % of their optical antipodes.
The claims defining the invention are as follows:

1. An aqueous thalidomide solution with a pH less than or equal to 5.5, in which one of the two enantiomers of thalidomide, (+)-(R)-thalidomide or (-)-(S)-thalidomide, is dissolved in pure form in isotonic glucose solution.

2. An aqueous thalidomide solution according to claim 1, characterised in that it has a content of active ingredient of at least 0.2mg/ml.

3. An aqueous thalidomide solution, substantially as hereinbefore described with reference to any one of the Examples.

4. A method of producing the aqueous thalidomide solution according to any one of claims 1 to 3, characterised in that (+)-(R)-thalidomide or (-)-(S)-thalidomide is added in pure form to an isotonic glucose solution with a pH of 4 to 5 and this mixture is shaken until complete dissolution of the respective thalidomide enantiomer has occurred, is subsequently treated with ultrasound and is filtered under aseptic conditions.

5. A method of producing an aqueous thalidomide solution, substantially as hereinbefore described with reference to any one of the Examples.

6. A method for the suppression of release of TNF-α in a mammal which method includes or consists of administering to said mammal an effective amount of a solution according to any one of claims 1 to 3.

7. A solution according to any one of claims 1 to 3 when used for the suppression of release of TNF-α.

8. Use of a solution according to any one of claims 1 to 3 for the preparation of a medicament for the suppression of release of TNF-α.

Dated 10 September, 1998
Grunenthal GmbH

Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON
An Intravenous Form of Thalidomide for the Therapy of Immunological Diseases

ABSTRACT
An aqueous thalidomide solution is described which is suitable as a parenteral form of application of thalidomide, particularly as an intravenous form of application, for the therapy of immunological diseases, and a method of producing the corresponding thalidomide solution is also described.