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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Referencia: Expediente No. 07.078.103

Act. 538 PETICION Folios: 2

Solicitud de Patente de InvenciOn titulada: "Preparaciones inyectables de diclofenaco y sus sales farmacØuticamente aceptables"

Solicitante: Troikaa Pharmaceuticals, Inc.

S0LIcITIJD DE EXAMEN DE PATENTABILIDAD SEGCJN EL ARTICULO 44 DE LA DECISION
486. GAcErA No. 591

ALVARO CORREA ORD61ZEZ, mayor de edad y vecino de Bogota D.C., identificado segün aparece al pie de mi firma, en mi condición de apoderado de la sociedad arriba mencionada, solicito que se examine la invenciOn de la referenda segtn los requisitos de patentabilidad previstos en la Decision 486 de la Comisión de la Comunidad Andina de Naciones. Adjunto recibo de caja por valor de $420.000 para cubrir la tasa correspondiente segØn la Resolución

44372 del 26 de diciembre de 2007.

Atentamente,

.T,XARO CORREK51D
’C.No.79.143.366 de UsaquØn
.P.20.281

Anexo: Recibo de caja No. 08-40484 por valor de $420.000
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Industria y Comercio
SUPERINTENDENCIA

DIVISION DE NUEVAS CREACIONES

RADICACION EXPEDIENTE No. 07-78103

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 591 DE

FECHA 30 DE ABRIL DE 2008 EL TERMINO HABIL SE1JALADO POR LA LEY

EXPIRA EL 30 DE JULIO DE 2008

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicaciôn 40 en la gaceta de Propiedad Industrial, deberÆ solicitar y cancelar el examen de

patentabilidad so pena de que (a solicitud caiga en abandono, de acuerdo COfl (0
establecido en el ArtIculo 44 de (a Decision 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.
SI NO X

United States Patent [19]
HoD et al.

[541 ANTIPHLOGISTIC, ANALGESIC,
ANTIPYRETIC INJECTION PREPARATION

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Birmingham, Ala.

[21] AppI. No.: 281,579

[22] Filed: Jul. 28, 1994

[51] mt. C1.6... A61K 311135
[52) U.S. Cl... 514/567
[58] Field of Search...5 14/567

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[11] Patent Number: 595549650

[45] Date of Patent: Sep. 10, 1996

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[57] ABSTRACT

An antiphiogistic, analgesic, antipyretic parenteral prepara-

tion is disclosed comprising diclofenac, its salt, or both, a surfactant, cosurfactant, water, having a pH of 3-10, and
optionally comprising an oily component, that can exhibit sustained therapeutic levels of diclofenac in plasma.

38 Claims, I Drawing Sheet

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ANTIPHLOGISTIC, ANALGESIC,
ANTIPYRETIC INJECTION PREPARATION

TECHNICAL FIELD

The present invention relates to an antiphlogistic, anal-
gesic, antipyretic parenteral preparation, and, in particular, to an antiphlogistic, analgesic, antipyretic parenteral prepa-ration comprising diclofenac, its salt, or both, as effective components. The parenteral preparation of the present 10 invention provides a sustain release of the drug, along with substantial reduction of side effects upon and after admin-istration.

BACKGROUND ART

G)IDiclo and its salts possess excellent antiphlogistic, an gesic, antipyretic activities, and are widely used for treating various inflammatory diseases, such as acute and chronic rheumatoid arthritis, osteoarthritis, and the like. They are typically formulated for oral administration, as a suppository, in an ointment, or the like.
For these preparations, however, i.e., oral dosage forms, suppositories, and ointments, the pharmaceutical effects fluctuate due to differences between the amount of drug administered and the amount of drug absorbed by the body. In addition, these preparations require a certain period of time for the active components to exhibit their effects because of a time-lag between the administration and absorption. Therefore, intravenous or intramuscular admin-istration is desirable to obtain immediate antiphlogistic, analgesic, or antipyretic effects in the case of serious symp-toms requiring an urgent treatment, e.g., for effecting an anti-inflammatory or analgesic action after an operation or injury, or visceral pain associated with an attack, cancer, or the like.

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For these reasons parenteral preparations comprising diclofenac and/or its salt have been developed. These com-

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ons comprise diclofenac, its salt, or both, and an
such as propylene glycol, benzyl alcohol, 2F

eparenteralpreparationsntainingdiclofenac and/or its salt have the following side
effects. First, theyp4ce pain at the injection site during
inj they indu iidØffects,such as prócôi 45 dial anxiety, iiie, cold sweÆt,breithizigdiffidulty,niftbfiess ofexliØthffie, and the like, due to the rapid increase in drug cdhefitration in the plasma immediately after the injection. In addition, the therapeutic effect of these conventional

injectable preparations lasts for a short period of time 50 because the drug is eliminated from the plasma quickly.
The present inventors, therefore, have developed antiphlogistic, analgesic, antipyretic parenteral preparations comprising diclofenac, its salt, or both, which gives reduced side effects upon parenteral administration. Moreover, these 55 new parenteral preparations sustain the release ofthe drug to achieve long-lasting therapeutic effects.

SUMMARY OF THE INVENTION

Diclofenac parenteral compositions have been developed
by the present inventors that comprise a therapeutically effective amount of diclofenac, and/or pharmaceutically

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Other objectives, features, and advantages of the inven-tion will hereinafter become more readily apparent from the following description.

BRIEF DESCRIPTION OF THE DRAWING

FIG. Iis a figure showing the plasma profile of diclofenac after intramuscular injection.

DETAILED DESCRIPTION OF THE
INVENTION AND PREFERRED
EMBODIMENTS

Diclofenac used in the parenteral preparation of the present invention as an active component is a compound exhibiting antiphlogistic, analgesic, and antipyretic activi-ties. Its chemical name is 2-(2,6-dichloro-anilino)phenyl acetate. The salts of diclofenac are not specifically limited so long as such salts are pharmaceutically acceptable, and include, for example, alkali metal salts, e.g., sodium salts, potassium salts, etc., ammonium salts, diisopropanol amine salts, and the like. Among these salts, sodium salt is par-ticularly preferred.
The amount of diclofenac and/or its salt to be incorpo-rated in the parentgrgi preparation is preferablyabout 2-200 an more preferably about 5-50 mg/
Nonionic surfactants are preferable for use as the surfac-tant in the present invention. Preferable nonionic surfactants include polyoxyethylene castor oil, polyoxyethylene hydro-genated castor oil, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene alkyl esters, polyoxyethylene alkyl ethers, and sorbitan fatty acid esters. These surfactants can be used either alone or in combination with one more other surfactants. More preferable examples of nonionic surfac-tants are polyoxyethylene castor oil or polyoxyethylene hydrogenated castor oil with 30-70 moles of ethylene oxide, polyoxyethylene alkyl esters or polyoxyethylene alkyl ethers with 2-40 moles of ethylene oxide, and polyoxyeth-ylene sorbitan fatty acid esters with 5-40 moles of ethylene oxide. Included in particularly preferable nonionic surfac-tants are polyoxyethylene (40 E.O.) hydrogenated castor oil, polyoxyethylene (60 E.O.) hydrogenated castor oil, poly-oxyethylene (20 E.O.) sorbitan monooleate, polyoxyethyl-ene (20 E.O.) sorbitan monopalmitate, and polyoxyethylene (20 E.O.) sorbitan monostearate.
The amount of surfactant(s) in the parenteral preparation of the present invention vanes depending on the type(s) of surfactants used. In general, a preferable range is about 2-60 wt %, with the particularly preferable range being about 5-45 wt %.

In the parenteral preparation of the present invention, compounds that function as solubilizers or cosolvents as well as surfactants are preferred. Such compounds can be referred to as cosurfactants.Mno)yærh or plyhyAca].. may be used as such cosurfactant either alone or in combination with one or more of the like. Given as examples ArA,fiophvdric alcohol 5 are JMUZXLWaohW,jyL alcohQl, "cnd the like; and as examples of I h dric are .rotvjne g1yl,jicj..l,3-buty ene g yco, poyiyl-.jjcols with molecular weights of G0-4000 dalton. Specific examples of such polyethylene glycols include polyethylene glycol 300; polyethylene glycol 400, polyeth-ylene glycol 600, and polyethylene glycol 4,000.
65 Such a cosurfactant may be incorporated in the parenteral preparation of the present invention in an amount of about 0.5-30 wt %, and preferably 2-15 wt %.

- ceeptable salt thereof, a surfactant, a cosurfactant, water At and having aIjfj).In addition, according to preferred aspects of the present invention, the composition also con-tains an oily component.

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According to preferred aspects of the present invention,
such a consurfactant includes benzyl alcohol. The amount of benzyl alcohol % and referably less
an 5 wt %. When benzyl alcohol is employed the cosurfactant component, the amount of cosurfactant com-ponent is about 0.5 wt % to about 25 wt %, preferably about 1 wt % to about 20 wt %, and most preferably about 2 wt % to about 15 wt % of the total composition. When a second cosurfactant is employed with the benzyl alcohol as the cosurfactant component, ethyl alcohol is preferable. The amount of the ethyl alcohol is preferably about 0.5 wt % to about 15 wt % of the total composition. The ethyl alcohol reduces the viscosity ofthe preparation which makes admin-istration easier.

In addition, benzyl alcohol should be less than about 25 wt %, and preferably about 20 wt % or lower, to prevent undesired reactions with body tissue upon administration. In addition, according to a further preferred aspect of the present invention, an oily component is employed in the composition. Incorporation of an oily component in the parenteral preparation of the present invention decreases the peak plasma concentration of diclofenac or its salt after administration, increases the time to achieve peak plasma concentration of diclofenac or its salt after administration, and prolongs the period of time for which diclofenac or its salt remains active.

One or more oily components selected from the group consisting of glycerin fatty acid esters, fatty acid esters, and hydrocarbons can be used as the oily component in the present invention. Pharmaceutically acceptable monoglyc-erides, diglycerides, or triglycerides or their mixtures can be used as the glycerin fatly acid ester, irrespective of their sources or origins, whether they are naturally occurring or synthetic compounds, or semi-synthetic compounds. Given as preferable glycerin fatty acid esters are almond oil, olive oil, sesame oil, peanut oil, fennel oil, camellia oil, corn oil, castor oil, cotton seed oil, and soybean oil, either crude or refined, and medium chain fatty acid triglycerides. They may be used either alone or in combination of one or more oily components. Particularly preferred are cotton seed oil, castor oil, soybean oil, and medium chain fatty acid triglyc-erides. Isopropyl myristate is preferably used as the fatty acid ester; and light or heavy liquid paraffin as the hydro-carbon. These oily components may be incorporated in the parenteral preparation of the present invention in an amount of about 0.5-30 wt %, preferably 1-15 wt %.
Another essential component ofthe parenteral preparation
of the present invention is water. However, other compo-nents, such as preservatives, stabilizers, coloring preven-tives, soothing agents, isotonic agents, and the like, may be

§invention

added as needed. The parenteral preparation of the present has a pHof 3-10, preferablä.0, arid more preferably 4.5-7.5. The adjustment of the pH to the above-mentioned range can be accomplished preferably by the addition of a buffering agent. Acetic acid, citric acid, phos-phoric acid, and/or their salts are given as examples of preferred buffering agents.
The parenteral preparation of the present invention can be prepared according to a conventional method, for example, dissolving the diclofenac, its salt, or both in a surfactant or in a surfactant/cosurfactant mixture. To aid in the dispersion and dissolution of diclofenac, its salt, or both, surfactants that are paste-like at room temperature can be heated to form a liquid. To this mixture is added, as required, the oily component. Purified water containing a buffering agent, isotonic agents, and the like is added and the mixture is

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thoroughly stirred. The resulting mixture can then be ster-ilized, for example, by passing the mixture through a 0,22 pm filter.
The preferred preparations of the present invention are in
5 the form of microemulsions, and most preferably micro-
emulsions of the oil-in-water type. However, microemul-sions of the water-in-oil type can also be employed, if desired.

An oil-in-water microemulsion is one in which oil drop-
lets (disperse phase) of 10 to 200 nanometers are dispersed
in water (continuous phase). The oil droplets are stabilized
by a surfactant and a cosurfactant.
Injection pain is reduced with the preferred microemul-
sion formulation of diclofenac sodium by two mechanisms. V
15 First, the continuous phase of the microemulsion is an /
isotonic aqueous buffer. This aqueous buffer prevents hyper-
tonic or hypotonic conditions from occurring at the injection V site. Hypertonic or hypotonic condition can disrupt the 1/1

membranes of cells near the injection site and causepain20. V
When injected, solvents are known to produce a hypotonic, effect. For example, the conventional prior-art formulation
contains 20% propylene glycol. This propylene glycol may cause injection pain.
Second, the diclofenac is contained within the oil droplets
25 of the microemulsion. Because it takes time for the oil
droplets to destabilize and free-up the diclofenac, the diclofenac is released into the bloodstream at a much slower rate than conventional prior-art formulations. This slower release rate prevents diclofenac from precipitating at the
30 injection site. Because the solvent (propylene glycol) of the
prior-art conventional formulation disperses rapidly upon injection, diclofenac can precipitate at or near the injection site. The precipitation of the diclofenac can contribute to injection pain.
In addition to the reduction in pain, the microemulsion formulation of diclofenac has an additional benefit. Because
of the time it takes for the oil droplets to destabilize, the microemulsion formulation sustains the release of diclofenac and its salts, which maintains effective levels of
40 drug for a longer duration than prior-art preparations.
Another preferred aspect of the present invention is that
the preparations can be formulated without the oily compo-nent. These formulations are surfactant micelies. These

formulations can be filter sterilized and have relatively high
45 drug-loadings and good stability. The size of the droplets of
a surfactant micelle can be similar to that of the microemul-sion disperse phase, except that the surfactant micelle in many cases is somewhat smaller, such as less than 10
nanometers.

50 The present invention makes it possible to obtain antiphlogistic, analgesic, antipyretic parenteral preparations that cause no pain upon injection, can avoid occurrence of side effects such as shock which occurs with past diclofenac injectable preparations (due to rapid plasma diclofenac
55 concentration increase immediately after the injection), and
displays therapeutic action over an extended period of time. Other features of the invention will become apparent in
the course of the following description of the preferred

60 examples of the present invention, which are given for

illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

65 Example 1:
Polyoxyethylene (60 E.O.) hydrogenated castor oil was melted by heating (about 32 wt % of the final composition).

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Soybean oil (about 2 wt % of the final composition) and benzyl alcohol (about 10 wt % of the final composition)
were added and mixed. Dielofenac sodium (about 2.44 wt %
of the final composition) was added to the resulting solution
and dissolved. Then, 2.03 w/v % acetic acid buffer solution (about 53.56 wt % of the final composition) adjusted to p1-1 4.5 was added to the solution. The mixture was gently mixed, sterilized by filtering it through a membrane filter (0.22-pm filter; manufactured by Millipore Co.), and filled in vials which were sterilized in advance to obtain antiphlo-gistic, analgesic, antipyretic injection preparation of the present invention. This resultant microernulsion is thermo-dynamically stable, This microernulsion results from the physical chemistry of the formulation, not from processing it through high-shear equipment.

Example 2:

A parenteral preparation containing about 33 wt % of polyoxyethylene (60 E.O.) hydrogenated castor oil, about 7 wt % of soybean oil, abou.4.0j&%ofbenzyj.ajoho1, about 2.44 wt % of diclofenac sodium and 47.56 wt % of 2.03 w/v % ofsodium acetate aqueous buffer was prepared according to the general procedure set forth in Example 1.

Example 3:

A parenteral preparation containing about 19 wt % of polyoxyethylene (40 E.O.) hydrogenated castor oil, about 26 wt % of medium chain fatty acid triglyceride, about LQyt %fbeiiyl alcohol, about 2.44 wt % of diclofenac sodium and abóii423frwt of 2.03 w/v % ofsodium acetate aqueous buffer was prepared according to the general procedure set forth in Example 1.

Example 4:

About 35 wt % of polyoxyethylene (20 E.O.) sorbitan monooleate, abQu7 wt% qf.bgn,zd-aleelle,- out 2.44 wt % of diclofenac s urn and 55.56 3 w/v % of sodium acetate aqueous buffer was prepared according to the general procedure set forth in Example 1.

Example 5

A parenteral preparation containing about 35 wt %of polyoxyethylene (60 E.O.) hydrogenated castor oil, about 10 wt % of soybean oil,! f..b.4..alohoI, about 2.44 WI % of diclofenac sodium and 42.56 wt % of 2.03 w/v % of sodium acetate aqueous buffer was prepared according to the general procedure set forth in Example 1,

Example 6

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Example 8

A parenteral preparation containing about 26 wt % of polyoxyethylene (40 E.O.) hydrogenated castor oil, about 19 wt % of medium chain fatty acid triglyceride, abouX4.CL.wJ. 2.44 wt % of diclofenac sodium and
about 42.56 wt % of sodium acetate aqueous buffer was prepared according to the general procedure set forth in Example 1.

10 Example 9
A parenteral preparation containing about 32 wt % of polyoxyethylene (40 E.O.) hydrogenated castor oil, about 13

wt % of medium chain fatty acid triglyceride, about.Qwx 15 % of bcnzyl alcohol, about 2.44 wt % of diclofenac sodium

’dabo-426 wt % of 2.03 w/v % of sodium acetate aqueous buffer was prepared according to the general pro-cedure set forth in Example 1.

20 Example 10

A parenteral preparation containing about 30 wt % of polyoxyethylene (60 E.O.) hydrogenated castor oil, about 15 wt % of medium chain fatty acid triglyceride, about 10 wt 25 % of benzyl alcohol, about 2.44 wt % of diclofenac sodium and about 42.56 wt % of 2.03 w/v % of sodium acetate aqueous buffer was prepared according to the general pro-cedure set forth in Example 1.

30 Example 11

Polyoxyethylene (60 E.O.) hydrogenated castor oil (33 wt
% of the final composition) was heated and benzyl alcohol (about 10 wt %) was added and mixed. Diclofenac sodium

(about 1.46 wt %) was dissolved in the mixture and soybean 35 oil (about 7 wt %) was added and mixed. Sodium acetate
aqueous buffer (about 48.54 wt % of 2.03 w/v %) was added.
The mixture was processed using a homogenizer to obtain a parenteral preparation.

40 Example 12

A parenteral preparation having a pH of about 4.5 and
containing about 27.31 wt of polyoxyethylene (60 E.O.) o hydrogenated castor oil, about 1.02 wt oil
45 about 10,1Lwt _% of zyl
ethanol, about 2.44 wt of diclofenac sodium, and about
56.54 wt of a 0.69 wt ofsodium acetate aqueous buffer
composition was prepared according to the general proce-
dure set forth in Example I.
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A parenteral preparation containing about 34 wt % of polyoxyethylene (60 E.O.) hydrogenated castor oil, about 10 wt % of soybean oil, about 10 wt % ofbozyl alcohol, about 55
2.44 wt % of diclofenac s urn and about 43.56 wt % of 2.03 w/v % of sodium acetate aqueous buffer was prepared according to the general procedure set forth in Example 1.

Example 7 60

A parenteral preparation containing about 32 wt % of polyoxyethylene (60 E.O.) hydrogenated castor oil, about 2 wt % of soybean oil, IOwt % of henzyl alcohol, about 0.98 wt % of diclofenac sodium and about 55.02›wt of 2.03 wfv 65 % of sodium acetate aqueous buffer was prepared according to the general procedure set forth in Example 1.

Comparative Example I

To a heated mixture of 20 mL of propylene glycol and 4 mL of benzyl alcohol, 2.5 g of diclofenac sodium was added to dissolve. Purified water, with its osmotic pressure adjusted with mannitol, was added to the solution to make the total volume 100 mL. The preparation contained 25 mg/mL of diclofenac sodium.

Test Example I

The antiphiogistic, analgesic, antipyretic parenteral preparations of the present invention, prepared in Examples 1, 2, and 5, each containing about 25 mg/mL of diclofenac sodium, and the parenteral preparation containing 25 mg/mL of diclofenac sodium prepared in Comparative Example I were intramuscularly injected into hind-legs of SD rats (age: 8 weeks) at a dose of 10 mg/kg. A specified period of time

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thereafter, 0.2 mL of blood was collected from the eye-grounds to quantify the diclofenac concentration in the plasma by HPLC.
The results are shown in FIG. 1. It is clear that the Comparative Example 1 of diclofenac releases drug quickly in the blood, because of the high peak levels early on. Whereas the preparations of Examples 1, 2, and 5 did not show high peak levels early on. Furthermore, these prepa-rations maintained thereafter a suitable concentration of drug for an extended time, thus avoiding any shocks due to an initial high concentration. In addition to the changes in the diclofenac concentration in blood, the area-under-curve (AUC) of the diclofenac concentration was calculated. As shown in Table L, the antiphlogist{c, analgesic, antipyretic parenteral preparations of the present invention obtained in Examples 1, 2, and 5, which contain about 25 mg/mL diclofenac sodium, exhibited the same AUC as Comparative Example 1. These results show that diclofenac sodium is released from the injection preparations of the present invention in a sustained manner without lowering the AUC, reducing the risks of side effects due to a rapid increase in diclofenac concentration in ’plasma after injection, and extend the duration of drug in the blood.

TABLE 1

Preparation AUC. (pg. hrlziL)

Example 1 24.0
Example 2 26.7
Example 31.6
Comparative Example 1 27.6

Obviously, numerous modifications and variations of the present invention are possible, in light of the above teach-ings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced other-wise than as specifically described herein.
What is claimed is:

1. An antiphiogistic, analgesic and antipyretic parenteral preparation comprising a therapeutically effective amount of diclofenac, its pharmaceutically acceptable salt, or both, a surfactant, a cosurfactant, and water, and having a pH of
3-10.

2. The parenteral preparation according to claim 1,
wherein said surfactant is a nonionic surface active agent.
3. The parenteral preparation according to claim 1,
wherein said surfactant is one or more compounds selected
. from the group consisting of polyoxyethylene castor oil, polyoxyethylene hydrogenated castor oil, polyoxyethylene
sorbitan fatty acid esters, sorbitan fatty acid esters, poly-oxyethylene alkyl esters, and polyoxyethylene alkyl ethers.
(4. The parenteral preparation according to claim 1,
wherein said cosurfactant is one or more compounds
. .j selected from the group consisting of monohydric alcohols Landdfio1S.

LiiiŁralpreparation according to claim I, wherein said cosurfactant is one or more compounds selected from the group consisting of benzyl alcohol, ethyl alcohol, propylene glycol, glycerin, 1,3-butylene glycol, polyethylene glycols with a molecular weight of 300 to 4,000 dalton.
6. The parenteral preparation according to claim 1, wherein said cosurfactant is one or more compounds selected from the group consisting of benzyl alcohol, pro-pylene glycol, and ethyl alcohol.
7. The parenteral preparation according to claim 1, wherein the pH is adjusted by a buffering agent.

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8. The parenteral preparation according to claim 1, wherein the pH is adjusted by one or more compounds selected from the group consisting of acetic acid, citric acid, or phosphoric acid, or the salts thereof.
5 9. The parenteral preparation according to claim 1, com-
prising 2-200 mg/niL or diclofenac, its salt, or both, 2-60 wt % of a surfactant, and 0.5-30 wt % of a cosurfactant.
10. The parenteral preparation according to claim I, comprising 5-50 mg/niL of diclofenac, its salt, or both, 5-45
10 wt % of a surfactant, and 2-15 wt % of a cosurfactant.
11. An antiphiogistic, analgesic, antipyretic parenteral preparation comprising diclofenac, its salt, or both, a sur-factant, a cosurfactant, an oily components, and water, and having a pH of 3-10.
is 12. The parenteral preparation according to claim 11,
wherein said oily component is one or more compounds selected from the group consisting of glycerin fatty acid esters, fatty acid esters, and hydrocarbons selected from the group consisting of light liquid paran and heavy liquid
20 paraffin.
13. The parenteral preparation according to claim 11, wherein said oily component is one or more compounds selected from the group consisting of cotton seed oil, castor oil, soybean oil, medium chain fatty acid triglycerides,
25 isopropyl myristate, and liquid paraffin.
14. The parenteral preparation according to claim 11, wherein said surfactant is a nonionic surface active agent. IS. The parenteral preparation according to claim 11, wherein said surfactant is one or more compounds selected
30 from the group consisting of polyoxyethylene castor oil,
polyoxyethylene hydrogenated castor oil, polyoxyethylene sorbitan fatty acid esters, sorbitan fatty acid esters, poly-oxyethylene alkyl esters, and polyoxyethylene alkyl ethers.
16. The parenteral preparation according to claim 11,
35 wherein said cosurfactant is one or more compounds selected from the group consisting of monohydric alcohols and polyhydric alcohols.
17. The parenteral preparation according to claim 11, wherein said cosurfactant is one or more compounds
40 selected from the group consisting of benzyl alcohol, ethyl
alcohol, propylene glycol, glycerin, 1,3-butylene glycol, polyethylene glycols with a molecular weight of 300 to 4,000 dalton.
18. The parenteral preparation according to claim 11,
45 wherein said cosurfactant is one or more compounds selected from the group consisting of benzyl alcohol, pro-pylene glycol, and ethyl alcohol.
19. The preparation of claim 1$ wherein the benzyl alcohol is about 0.5 to about 25% by weight.
so 20. The preparation of claim 18 wherein the benzyl
alcohol is about 1 to about 20 wt %.
21. The preparation of claim 18 wherein the amount of said ethyl alcohol is about 0.5 to about 15 wt % of the preparation, and the amount of said benzyl alcohol is about
55 0.5 to about 20 wt %.
22. The parenteral preparation according to claim 11, wherein the pH is adjusted by a buffering agent.
23. The parenteral preparation according to claim 11, wherein the pH is adjusted by one or more compounds
60 selected from the group consisting of acetic acid, citric acid,
or phosphoric acid, or the salts thereof.
24. The parenteral preparation according to claim 11, comprising 2-200 mg/niL of diclofenac, its salt, or both, 2-60 wt % of a surfactant, 0.5-30 wt % of a cosurfactant,
65 and 0.5-30 wt % of an oily component.
25. The parenteral preparation according to claim 11, comprising 5-50 mg/niL of diclofenac, its salt, or both, 5-45

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wt % of a surfactant, 2-15 wt % of a cosurfactant, and 1-15
wt % of an oily component.
26. An aritiphiogistic, analgesic, antipyretic parenteral microemulsiori preparation comprising of diclofenac, its
salt, or both; a surfactant and a cosurfactant, wherein the amount of said cosurfactant is about 0.5 to 30 wt % of the preparation, an oily component, and water, and having a pH of 3-10.

27. The preparation of claim 26 wherein the amount of said cosurfactant is about I to about 20 wt %.
28. The preparation of claim 26 wherein the amount of said cosurfactant is about 2 to about 15% by weight.
29. The preparation of claim 26 wherein said cosurfactant also contains ethyl alcohol.
30. The parenteral preparation according to claim 26, wherein said oily component is one or more compounds selected from the group consisting of glycerin fatty acid esters, fatty acid esters, and hydrocarbons selected from the group consisting of light liquid paraffin and heavy liquid paraffin.
31. The parenteral preparation according to claim 26, wherein said oily component is one or more compounds selected from the group consisting of cotton seed oil, castor oil, soybean oil, medium chain fatty acid triglycerides, isopropyl myristate, and liquid paraffin.
32. The parenteral preparation according to claim 26, wherein said surfactant is a nonionic surface active agent.

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33. The parenteral preparation according to claim 26, wherein said surfactant is one or more compounds selected from the group consisting of polyoxyethylene castor oil, polyoxyethylene hydrogenated castor oil, polyoxyethylene sorbitan fatty acid esters, sorbitan fatty acid esters, poly-oxyethylene alkyl esters, and polyoxyethylene alkyl ethers.
34. The parenteral preparation according to claim 26, wherein the pH has been adjusted by buffering agent.
10 35. The parenteral preparation according to claim 26, wherein the pH has been adjusted by one or more com-pounds selected from the group consisting of acetic acid, citric acid, or phosphoric acid, or the salts thereof,
36. The parenteral preparation according to claim 26,
15 comprising 2-200 mg/xnL of diclofenac, its salt, or both,
2-60 wt % of a surfactant, and 0.5-30 wt % of an oily component.
37. The parenteral preparation according to claim 26,
20 comprising 5-50 mg/mL of diclofenac, its salt, or both, 5-45
wt % of a surfactant, 1-15 wt % of an oily component.
38. A method for treating a patient in need of an antiphlo-gistic agent, analgesic or antipyretic agent, which comprises administering to said patient a preparation according to
25 claim 1 by parenteral administration.

United States Patent [19]
Gaffi

[54] PARENTERAL SOLUTIONS FOR DICLOFENAC SALTS

[75] Inventor: Bruno Galli, Seltisberg, Switzerland
[73] Assignee: Ciba-Geigy Corporation, Ardsley,
N.Y.

[21) AppI. No.: 129,885
[22] Filed: Sep. 30, 1993
[30] Foreign Application Priority Data
Oct. 22, 1992 [CHI Switzerland.........................3275/92 [51) mt. C1.6..A61K 31/195 [52] U.S. CI... 514/567 [58] Field of Search...5 14/567
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[11] Patent Number: 513899681

(45] Date of Patent: Feb. 14, 1995

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A. F. Gunnison et al: Sulfite Hypersensitivity. A critical Review, CRC Critical Review in Toxicology, vol. 17 (1987), Issue 3, pp. 185-214.
Search Report, European Patent Application No. 93810720.8 Ciba-Geigy (1993).
Primary ExaminerRaymond J. Henley, III Attorney, Agent or FirmIrving M. Fishman; Karen G. Kaiser
[57] ABSTRACT
The invention relates to a pharmaceutical composition in the form of a sterilizable parenteral solution compris-ing a diclofenac salt and stabilizers, such as ethyl lactate combined with glutathione or N-acetylcysteine.

4 Claims, No Drawings

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PARENTERAL SOLUTIONS FOR DICLOFENAC SALTS

f The invention relates to a pharmaceutical composi- 5
/ tion in the form of a sterilisable parenteral solution

comprising a diclofenac salt and stabilisers, to a process for the preparation of that solution and to the use of
stabilisers in that preparation process.
Various medicaments having different structures are 10 available for the treatment ofinflammatory diseases, for example rheumatism. Since such diseases are often chronic, treatment with anti-inflammatory medica-

ments (anti-inflammatory drugs, antiphiogistics) gener- ally has to extend over a prolonged period, with a regu- 15 lar, uninterrupted supply of active ingredient. In partic- ular, when administered peroraily over long periods
many non-steroidal anti-inflammatory drugs (NSAIDs) may cause side-effects throughout the gastro-intestinal tract, for example nausea, vomiting, epigastric pain and 20 also gastric ulcers. In addition, the release of active ingredient from peroral dosage forms, such as tablets or dragØes, is slow, which can be disadvantageous in the

treatment of sudden acute rheumatic pain. 25 The preferred group ofNSAIDs includes the sodium
salt of diclofenac, which was introduced a considerable time ago in many countries and is obtainable in various

dosage forms, such as dragØes, suppositories orinjection solutions, under the trade mark fiVoltarol (Ciba- 30 Geigy).

It is known that small amounts of diclofenac salts in aqueous solution, especially at elevated temperature under heat-sterilisation conditions, can cyclise to form

1-(2,6-dichlorophenyl)-indolin-2..one with the splitting 35 off of hydroxide ions. Oxidation with oxygen present in

the solution may result in the formation offurther unde-sired secondary products.
In order to suppress oxidation reactions, antioxidants, inter alia from the group ofreducing sulfur compounds, 40 are added to injection solutions (see Pharmazeutische

Tecbnologie (Pharmaceutical Technology), published by Heinz Sucker et al., G. Thieme Verlag Stuttgart DE,
1978, page 313). For example, the commercially avail-able injection solution comprising the active ingredient 45 VOLTAROL (see Rote Liste (Red List) 1987, No. 03169, index of preformulated medicaments, Editlo

Cantor) comprises the excipient sodium disulfite (so- dium pyrosulfite) which is permitted as an antioxidant
for injectables. Reduction and/or decomposition reac so tions ofthose excipients can effect changes in the pH of the aqueous solution outside the physiologically accept-able range of from 7 to 8. After the addition of the antioxidant, the injection solution to be sterilised must therefore be neutralised or buffered in a subsequent step 55 in order to meet the requirement that the pH conditions of a solution for parenteral, especially Lm., administra-tion be physiologically acceptable.
Antioxidants from the group ofreducing sulfur com-pounds are known to have allergenic potential with the 60 risk of asthma attacks and anaphylactic shock; see the review article: Sulfite Hypersensitivity by A. F. Gunni-son and D. W. Jacobsen in CRC Critical Reviews in Toxicology, Vol. 17 (1987), Issue 3, pages 185-214, see especially Section C, pages 195-197. The addition of 65 sulfites to preformulated medicaments must therefore

be declared and the packaging must carry a warning (Proposal U.S. Fed. Reg. 19.11.1985).

The problem underlying the present invention is to prepare a novel, improved, sulfite-free dosage form for the parenteral administration of diclofenac salts that has the advantage over heat-sterilisable injection solutions known hitherto both of a stable pH value and of im-proved tolerability of the antioxidant used, combined with rapid onset of activity and long-lasting action of the active ingredient at a therapeutic level.
That problem is solved by the present invention, which relates to a pharmaceutical composition in the form of a parenterally administrable injection solution comprising the active ingredient diclofenac or a phar-

maceutically acceptable salt thereof. That injection solution comprises:
a) a pharmaceutically acceptable salt of diclofenac;

b) 1,2-propylene glycol or polyethylene glycol 300-400 as solubiliser;
c) a pharmaceutically acceptable stabiliser selected from the group consisting of glutathione, glutathione combined with a C2.3alkanecarboxylic acid C2alky1 ester, or with bydroxy-C24alkanecarboxylic acid C2. 4alkyI ester or with N-acetylcysteine and N-acetylcys-teine combined with a C2.3alkanecarboxylic acid C2al-kyl ester or with hydroxyCa1knecarboxylic acid Ca1kyl ester and
d) a carrier liquid acceptable for injection formula-tions and, where appropriate, further excipients that are acceptable therefor.
When the stabilisers of component c) are used, no formation of oxidation products of the indolin-2-one compound beyond the permitted limits is detected. Likewise, the undesired formation of oxidation prod-ucts of the diclofenac salt is effectively suppressed. In addition, the pH value of the solution remains con-stantly neutral over a long period of up to several months.

Within the context ofthe description ofthe invention, the terms and definitions mentioned hereinbefore and hereinafter have preferably the following meanings: The term pharmaceutical composition defines a solu-tion that is suitable for parenteral administration, espe-cially i.m., but also i.v., and that can be used in the treatment of inflammatory conditions accompanied by pain, especially rheumatism.
Component a) - A pharmaceutically acceptable salt of diclofenac, o-(2,6-dichlorophenylamino)-phenylacetjc acid, is especially an alkali metal salt, for example the sodium or the potassium salt, or the salt formed with an amine, for example a mono-, di- or tn- CI-C4alkyla-mine, for example diethyl- or triethyl-amine, hydroxy-C2-C4alkylamine, for example ethanol-mine, or hy-droxy-C2--C4alkyI-Cj-C4alkylamine, for example dime-thylethanolamine, or a quaternary ammonium salt, for example the tetramethylainmonium salt or the choline salt of diclofenac.
Special preference is given to the sodium salt and the potassium salt of diclofenac, see Merck Index, Eleventh Edition No. 3071. Those salts are presentip the jc-

tion solution in a dài fTrªm. approgCl ipty aproxlmately 150 m4 The preferred active ’5 to ç pcentrat1on in the iarniaceutica1 composition is

from approximately 10 mg/inl to -approximately. mg/mi.
Component b) - *J,2.pXgpyLene Merck Index Eleventh Edition

No. 7868) or polyethylene glycol having a molecular weight of approximately 300-400 (Merck Index Elev-enth inn-N.-5*5). osesolubilisers are present in

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the pharmaceutical composition in an amount of from aif5to ite1y-- approximately 0 % (weight-
/volu 20% to ap-proximat.hepreferredaæ,ountsof that corn-ponenfper formulation are from 500 to 2000 nlg, espe- 5 cially from 500 to 1000 mg.
Component c) - The pharmaceutically acceptable stabiliser C2.a1kanecarboxylic acid C2.alkyl ester is, for example, ethyl acetate or ethyl propionate. A by-droxy-C2.a1kanecathoxylic acid C24alkyl ester is espe- 10 daily ethyl lactate. Racemic mixtures or optically pure forms (enantiomers) oflactic acid may be used as stabi-lisers. In a preferred embodiment, ethyl lactate in com-bination with glutathione or with N-acetylcysteine is used as stabilizer for the injectable pharmaceutical corn- 15 position. It was also not known hitherto that under neutral or approximately neutral conditions that combi-nation of excipients effectively stabilizes the pH value of aqueous solutions comprising diclofenac salts.
Glutathione (see Merck Index Eleventh Edition No. 20 4369) is known as a pharmaceutical excipient; see R.

Voigt, Lehrbuch der Phaxrnazeutischen Chemie (lent- book ofPharmaceutical Chemistry), 6th edition, Verlag Chesnie Weinheim, Federal Republic of Germany, 25 pages 504-506, in which the use of that excipient as an
antioxidant for hydrophilic systems ifdescribed. N-Acetyl-L-cysteine (see Merck Index Eleventh Edi-tion No. 82) is known as a pharmaceutical excipient.

Glutathione or N-acetylcysteine is present in a pre- 30 ferred amount of approximately from 1.0 to 5.0 mg per
formulation. Combined with those stabilisers, ethyl lactate is added in a preferred amount of approximately from 0.02 to 3.0

The pharmaceutical composition comprises a total of 35 from approximately 0.1 mg/mI to approximately 3
mg/ml, preferably from approximately 1 mg/ml to approximately 2 mg/nil, of component c).
The pharmaceutically acceptable carrier liquid d) is water that has been rendered germ- and pyrogen-free in 40 accordance with the specifications of national phar-macopoeias for intravenous solutions.
The carrier liquid d) may comprise non-toxic excipi-ents that are acceptable for injection formulations, for example water-soluble excipients required for establish 45 ing isotonic conditions, for example ionic additives, such as sodium chloride, or non-ionic additives, such as sorbitol, xnannitol, glucose, lactose, fructose or sucrose. In particular, those additives, for example sodium chlo-ride or mnnitol, are present in the amounts prescribed 50 in national pbarinacopoeias that are required for estab-lishing isotonic conditions in the injection solutions. The volume ofthe carrier liquid d) in admixture with components a), b) and c) is, for example, approximately from 1 to 5 ml, preferably from 1 to 2 nil. In preferred forms, injection solutions comprising the customary doses of 50, 75 or 100 mg of diclofenac sodium have a total volume of approximately from 1 to 5 ml, prefera-bly 3 ml.
The pharmaceutical composition according to the 60 present invention can be used as an injection solution for parenteral administration, especially i.m. and i.v., in the treatment of pain, inflammation and/or rheumatic diseases in warm-blooded animals (humans). Daily doses of approximately from 25 to 200 mg of active 65 ingredient can be administered, the individual dosage form comprising the customary amount of active ingre-dient of, for example, 25, 50, 75, 100 or 150 mg.

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The invention relates also to a process for the prepa-ration ofthe pharmaceutical composition. That process comprises dissolving components a), b) and c) in the carrier liquid d) in any desired order and, where appro-priate, adding further excipients that are acceptable for injection formulations.
In a preferred form of the process, components a).active ingredientand b)solubiliser--are added to the carrier liquid d). Component c)stabilisersis then added to that solution.
The active ingredient a) is added to a portion of the carrier liquid d) preferably in comminuted form, espe-cially finely ground form. Finely ground diclofenac salt has a preferred average particle size ofless than 200 pm and can be used especially at a particle size ofless than 100 p.m. To produce particles of that size, customary comminution techniques are used, for example grinding in an air-jet, ball or vibrator mill or by processes known per se in an ultrasound disintegrator, for example ofthe Branson Sonifier type, for example as described in J. Pharrn. Sd. 53 (9), 1040-1045 (1965), or by means of high-speed stirring of a suspension, for example using a stirrer of the Homorex type from Brogli & Co., Basic. The portion of carrier liquid d) to be used is approxi-mately from I to 2 ml, to which are added all of the solubiliser b) as well as the finely ground active ingredi-ent a) and the stabilisers c).
The slightly acidic aqueous solution is, for example, rendered basic to a pH of approximately 8.0. That can be effected by the addition of a pharmaceutically ac-ceptable dilute aqueous base, for example dilute sodium hydroxide solution, preferably 0.IN NaOH solution. The addition is customarily carried out with simulta-neous pH monitoring. If necessary the solution is made up to the required injection volume with sterile, germ-free and pyrogen-free water. The injection solution can be introduced under aseptic conditions into ampoules or injection vials ofsuitable capacity and beat-sterilized in an autoclave (above 120°/at least 15 min.).
The invention relates also to the use of the stabiliser c) selected from the group consisting of glutathione, glutathione combined with a C23alkanecarboxylic acid C2.4alkyl ester, or with hydroxyC2-inlkrnecarboxylic acid C2.4alkyl ester or with N-acetylcysteune and N-acetylcysteine combined with a C2..3alkanecarboxylic acid Calkyl ester or with liydroxy-C2.4ailcanecar-boxylic acid Ca1kyl ester in the process described hereinbefore.
The present invention relates preferably to a pharma-ceutical composition in the form of a parenterally ad-ministrable injection solution comprising:
a) the sodium salt of diclofenac;
b) 1,2-propylene glycol or polyethylene glycol 300 as soIubiliser,
c) ethyl lactate combined with glutathione or with N-acetylcysteine as stabilizers and
d) a carrier liquid acceptable for injection formula-tions and, where appropriate, further excipients that are acceptable therefor.
The invention relates especially to the formulations described in the Examples.
The following Examples serve to illustrate the inven-tion described in full above; they are not intended to limit the scope of that invention in any way.

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EXAMPLE 1

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diclofenac sodium (fiVoItaXol) 75.0 mg
1,2-propylene glycol (dist.) 1000.0 ma 5
ethyl lactate 0.1 mg
glutathione or N-acetylcysteine 2.0 mg
IN NaOH solution to PH 8.3
water per injection ad 3.0 ml
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A portion ofthe water is introduced under a nitrogen protecting gas atmosphere. All of the glutathione or N-acetylcysteine is dissolved therein. All ofthe 1,2-pro-pylene glycol and the active ingredient, which has pre-viously been ground to an average particle size of ap 15 proximately 100 ian, are added thereto. The pH value of the solution is adjusted tcp}J.jwith 0.IN sodium hydroxide solution, and ethyl lactate is added. The

solution is made up to 3 ml (per formulation) with water 20 and then filtered using a sterile filter of 0.2 1km pore size
(consisting, for example, of NYLON, polypropylene or acrylic copolymer) and then sterilised for 15 minutes at 121 C. 3.3 ml portions of the solution from the total
batch are introduced into friable ampoules. 25

EXAMPLE 2

diclofenac sodium (fiVoltzrol) 75.0 tog
polyethylene glycol 300 1000.0 mg 30
glutathione or N-scezylcysteine 2.0 mg
ethyl lactate 0.1 tog
IN NaOH solution to PH 8.0
water per injection ad 3.0 ml

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A portion ofthe water is introduced under a nitrogen protecting gas atmosphere. All of the glutathione or N-acetylcysteine combined with ethyl lactate is dis-solved therein. All of the polyethylene glycol 300 and the active ingredient, which has previously been 40 ground to an average particle size of approximately 100 p.m, are added thereto. The pH value of the solution is adjusted to pH 8.0 with 0.1N sodium hydroxide solu-tion. The solution is made up to 3 ml (per formulation) with water and then filtered using a sterile filter of 0.2 ’ am pore size (consisting, for example, of NYLON, polypropylene or acrylic copolymer) and then sterilised for 15 minutes at 121 C. 3.3 ml portions ofthe solution

from the total batch are introduced into friable am 50 ponies.
EXAMPLE 3

(Analogous to Example I or 2)

diclofenac sodium (fiVoltarol) 75.0 tog
polyethylene glycol 300 780 mg

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-continued

benzyl alcohol 120 ms
macintol 8.6 mg
ethyl lactate 0.1 tog
glutathione or N-acetyicyszeine 2.0 mg
IN NaOH solution to pH 8.0

water per injection ad 2,0 ml or ad 3.0 ml

EXAMPLE 4

(Analogous to Example 1 or 2)

diclofeuac sodium (Voltarol) 75.0 tog
1,2-propylene glycol 790 mg
benzyl alcohol 120 mg
mannitol 8.6 mg
ethyl lactate 0.1 tog
glutathione or N-acetylcysteine 2.0 mg
IN NaOH solution to pH 8.0
water per injection ad 2.0 ml or
ad 3.0 ml

What is claimed IS:
1. A pharmaceutical composition in the form of a parenterally administrable solution consisting essen-tially of:
a) a pharmaceutically acceptable salt of diclofenac; b) 1,2-propylene glycol or polyethylene glycol 300-400;
c) glutathione admixed with C2.3aika.necarboxylic acid C2aIkyl ester or with hydroxy-C2alk-anecarboxylic acid C2_4aikyl ester; or N-acetylcys-teine admixed with C2.3alkanecarboxylic acid C2.. 4alkyl ester or with hydroxy-C2.4alkanecarboxylic acid C24alkyl ester; and
d) a carrier liquid acceptable for injectable formula-
tions.

2. A pharmaceutical composition in the form of a parenterally administrable solution consisting essen-tially of-
a) f:a)the sodium salt of diclofenac;
b) 1,2-propylene glycol or polyethylene glycol 300; c) glutathione admixed with ethyl lactate; or N-acetylcysteine admixed with ethyl lactate; and
d) a carrier liquid acceptable for injectable formula-tions.

3. A method for treating pain, inflammation or rheu-matic diseases which consists of administering to a host in need of such treatment, a pharmaceutical composi-tion according to claim 1 in the form of a parenterally administrable injection solution.
4. A method for treating pain, inflammation or rheu-matic diseases which consists of administering to a host in need of such treatment, a pharmaceutical composi-tion according to claim 2 in the form of a parenterally administrable injection solution.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIRECCION DE NUEVAS CREACIONES

2020

Bogota, D.C.,

Abogado:
ALVARO CORREA ORDOEZ

ASUNTO RadicaciOn No
TrÆmite
Evento
ActuaciOn
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Patente de lnvención Patente de Modelo de Utilidad
Via Nacional
Via PCT (Fase Nacional) Cap.l Cap. II
No. Solicitud Internacional PCT/IN2006/000033
Fecha de Presentación Internacional 30/Enero/2006

Como resultado del Examen de Fondo, realizado con fundamento en el artIculo 45 de la DecisiOn 486 de Ia Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripciôn: Folios 21 a 35 como se radicO inicialmente.

Reivindicaciones: Folios 75 a 85 como se modificO en fase nacional.

Prioridad: IN 96/MUM/2005 (Febrero 1, 2005)

2. Objeto de la Invención

Titulo de la invenciôn: "Preparaciones inyectables de diclofenaco y sus sales farmacØuticamente aceptables"

Problema TØcnico Planteado: "Necesidad de proveer preparaciones de alta concentraciOn de sales de diclofenaco inyectables que son capaces de ser administradas por ruta intradeltoide, sobre y encima de la ruta intragluteal e intravenosa lenta."

SoluciOn: "Proveer una formulaciOn inyectable de sales solubles en agua de diclofenaco, que comprende 75 mg/ml de diclofenaco sodio o sus cantidades terapØuticamente equivalentes de sales solubles en agua de Østas y un cosolvente/solubilizador Unico, mezclas de ellos en combinación con agua como solvente principal"

El objeto de la presente Solicitud se relaciona con la ClasificaciOn Internacional de Patentes (CIP): A61 31/196, A61K47/10, A61 9/08

Exp. 2007 078 103 Primer Art. 45

3. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Concsión:

La reivindicación 17 reclama una formuiaciOn inyectable de sales solubles en agua de diclofenaco que comprende 75mg/mi de diclofenaco y un cosolvente 0 una mezcla de solventes y que presenta una viscosidad entre 1.5 y 4.7 cps y un pH entre 8 7 9. Se observa que el alcance de esta reivindicaciOn es muy ampilo e incluye un grupo amplio de solventes y no revela de forma concisa cuales son
los componentes de la formulaciOn que le otorgan las caracteristicas fisicoqulmicas reclamadas. Se sugiere que el solicitante restrinja el aicance de la reMndicaciôn 1 de forma concisa.

4. Determinación del Estado de la TØcnica

El Estado de la TØcnica se determinO con base en la fecha de prioridad Febrero

18 1, 2005 y se encontraron los siguientes documentos que anticipan el objeto de

esta solicitud:

Item Documento TItulo Fecha de

Publicaciôn

Dl US5554650 Antiphiogistic, analgesic, antipyretic Sep. 10, 1996 injection preparation
02 US5389681 Parenteral solutions for diclofenac Feb. 14, 1995 salts

Dl presenta una preparaciOn parenteral que comprende diclofenaco o sus sales (portada; col.l, In.5-20); pH de 3 - 10 (col.1, In.65; coL3, In.50-55); alcohol monohIdrico como benzllalcohol, etilalcohol o alcohol polihIdrico como glicerina, 1,3 butilenglicol o polietilenglicoles (col.2, In. 50 - 65; coL7, Rv. 4). Enseæa que el propilenglicol puede causar dolor al inyectar esta composición. Revela ejemplos de composiciones que contienen diclofenaco y bencflalcohol en 10% (col. 5, ej. 2)

D2 presenta una composiciOn farmacØutica estØril que contienen diclofenaco (portada, colA, In. 5-10), y revela ejemplos de composiciones que contienen 75 mg en 3 ml de preparaciôn (coL5; ej. 2) que tienen un pH aproximado de 8.3 (col.5, In. 17).

AnÆlisis de Patentabilidad (Art 14D486)

Nivel Inventivo (Art18 D486)

La reivindicaciôn 17 nueva: Un formulaciôn inyectable de sales solubles en agua de diclofenaco, que comprende 75 mg/ml de diclofenaco sodio o sus cantidades terapØuticamente equivalentes de sales solubles en agua de estas y un cosolvente/solubilizador Unico seleccionado del grupo que consiste de alcohol monohIdrico, alcohol polihIdrico, y Øter de propilenglicol de alcohol tetrahidrofurfurilo..." (f.75)

ComparaciOn de las caracterlsticas tØcnicas esenciales, con las del Estado de la Tecnica:

Caracteristicas esenciales Dl D2

Un formulaciOn inyectable de sales solubles en agua de diclofenaco, 4 4
que comprende 75 mg/ml de diclofenaco sodio o sus cantidades
terapØuticamente eguivalentes de sales solubles en agua de estas

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un cosolvente/solubilizador ünico seleccionado del grupo que consiste

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MMI

de
alcohol monohldrico 4-25%vlv
alcohol poihidrico 27-45 v/v
Øter de propilenglicol de alcohol tetrahidrofurfurilo 18-35% v/v
en combinaciOn con agua
o combnaciones de uno o mÆs cosolventesmencionados
1.5a4.7cps
8-9 pH

El documento DI, considerado el estado de la tØcnlea mÆs cercano a la invenciôn definida en Ia reivindicación 1, divulga una preparación parenteral que comprende diclofenaco o sus sales (coLl, ln.5-20), pH de 3 - 10 (coLl, In.65); alcohol monohIdrico o polihIdrico (coL2, coL7) y que el propilenglicol puede causar dolor al inyectar esta composición. Revela ejemplos de composiciones que contienen diclofenaco 25 mg/ ml (col. 5, 6, y 7).

La diferencia entre la invenciôn, definida en la reivindicaciôn 1, y la preparación de Dl consiste en la cantidad de activo (25mg/mi de diclofenaco en DI; 75 mg/ml de diclofenaco en la solicitud) y la viscosidad alcanzada en la preparaciOn.

El efecto que logra el incluir 75 mg de diclofenaco por 1 ml de preparaciôn y una viscosidad entre 1.5 a 4.7 cps es disminuir el dolor al inyectar la preparaciOn de alta concentración de sales de diclofenaco.

Por lo tanto, el Problema TØcnico Objetivo que pretende resolver esta invenciôn se puede formular asi: "cOmo modificar la preparación conocida en Dl para obtener una preparación de alta concentraciOn de diclofenaco y con propiedades tales que ayuden a disminuir el dolor de la aplicación de la inyeccion".

Sin embargo,
sugerido para
diclofenaco.

a partir de las enseæanzas de D2 el experto habrIa sido
formular una inyecciOn con una concentraciôn alta de

En consecuencia, el experto en la materia enfrentado al problema mencionado
incluiria una concentración superior de activo (75 mg de diclofenaco) como en la

S preparaciOn de D2 en la composición de Dl -en donde ademÆs se sugiere

excluir el propilenglicol ya que causa dolor- Ilegando asI al objeto de la reivindicación I de la sollcitud. Por otro lado, se considera que la viscosidad
obtenida por la presente invenciOn no es inesperada dado que en las anterioridades se enseæan composiciones con los mismos solventes en cantidades similares a los acÆ reclamados por lo cual se considera que dicha
viscosidad es inherente de la mezcla de dichos solventes y no consiste en un resultado sorprendente o inesperado. Por lo cual se considera obvia.

Conclusion:

La reivindicaciOn 1 cumple el requisito de novedad (Art. 16), pero
no cumple con el requisito de nivel inventivo (Art. 18).

Conclusion

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados
asi:

Reivindicaciones Requisito que Documento afectadas afecta
Dl US5554650 17-46 Nivel inventivo
D2 US5389681 17-46 Nivel inventivo

Exp. 2007 078 103 - Primer Art. 45

En cumplimiento del artIcuto 45 de Ia Decision 486 de la ComisiOn de la Comunidad Andina, se le indica que debe dar respuesta dentro del tØrmino de 60 dias contados a partir de la fecha de notificaciOn de la presente comunicaciOn. En caso de no dar respuesta at presente requerimiento, 0 si a pesar de la respuesta subsistieran los impedimentos para la concesiOn, se denegara la patente.

NotifIquese el presente oficlo conforme a to dispuesto en el numeral 5.2, literal e), del capItulo quinto del titulo primero de la Circular Unica No. 10 de 2001.

JOSE LUIS SALAZAR LOPEZ

Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijaciôn en lista, de fecha

O S ABR. 20))

CONCEPTO TECNICO EXAMINADOR TECNICO

NUMERO: 833 C6digo:202092

Exp. 2007 078 103 Primer Art. 45