AUSTRALIA

Patents Act 1990 674015

Notice of Entitlement

We, ASTRA AKTIEBOLAG, of S-151 85 Sodertalje, Sweden, and YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD, of 6-9, Hiranomachi 2-chome, Chuo-Ku, Osaka-Shi, Osaka 541, Japan, jointly being the Applicant and Nominated Person in respect of Application No. 45838/93, state the following:

The actual inventors of the invention of Application No. 45838/93 are Shigeo Nakanishi, Tetsuo Tominaga, Iwao Yamanaka, Takashi Higo and Toshiyuki Shibata.

The basic application listed on the PCT Request form, namely, Japanese Application No. 201203/1992, was filed in the joint names of FUJISAWA PHARMACEUTICAL CO., LTD., and YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD. as assignee of the actual inventors via: (i) contracts of employment between FUJISAWA PHARMACEUTICAL CO., LTD., and Shigeo Nakanishi, Tetsuo Tominaga, Iwao Yamanaka and Takashi Higo; and (ii) a contract of employment between YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD and Toshiyuki Shibata.

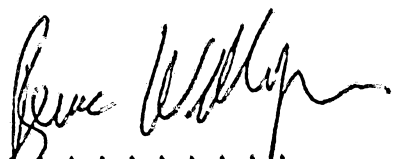
The said basic application listed in the declaration under Article 8 of the PCT was the first application made in a Convention country in respect of the invention.

The basis of our entitlement is as follows: ASTRA AKTIEBOLAG acquired the rights of FUJISAWA PHARMACEUTICAL CO., LTD., to the invention and the present application by assignment, whilst YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD acquired its rights in the invention and the present application by contracts of services as indicated above.

Our address for service is care of E. F. WELLINGTON & CO., Patent and Trade Mark Attorneys, 312 St. Kilda Road, Melbourne, Victoria, 3004.

DATED this 31st day of January, 1995

For and on behalf of
ASTRA AKTIEBOLAG and
YOSHITOMI PHARMACEUTICAL
INDUSTRIES, LTD,
By:



BRUCE S. WELLINGTON
Patent Attorney for
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To: The Commissioner of Patents,
Commonwealth of Australia

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INJECTION AND INJECTION KIT CONTAINING OMEPRAZOLE AND ITS ANALOGS

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(56) Prior Art Documents
AU 25257/84 A61K C07D
AU 70380/91 A61K C07D

(57) Claim

1. A medicament suitable for injection comprising a lyophilized product of an alkaline aqueous solution of a 2-[(2-pyridyl)methylsulfinyl]-benzimidazole compound or a salt thereof having antiulcer activity and an aqueous solvent without any nonaqueous solvent, wherein the pH of the medicament is not less than 9.5 and not more than 11.5.

4. An injection kit which is a system comprising the components (a) and (b) as follows:

(a) a lyophilized product of an alkaline aqueous solution of a 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt thereof having antiulcer activity, and

(b) an aqueous solvent without any non-aqueous solvent,

wherein components (a) and (b) are operatively

.../2

interconnected or interdependent such that component (a) can be dissolved in (b) with the pH adjusted upon dissolution of component (a) in (b) so as to be not less than pH 9.5 and not more than 11.5, in forming an aqueous injectible solution.

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(54) Title: INJECTION AND INJECTION KIT CONTAINING OMEPRAZOLE AND ITS ANALOGS

(57) Abstract

An injection comprising a 2-[(2-pyridyl)methylsulfinyl]-benzimidazole compound or a salt thereof having antiulcer activity and an aqueous solvent added with no nonaqueous solvent, wherein the pH of the injection is not less than 9.5 and not more than 11.5, and an injection kit comprising the following (a) and (b), wherein (a) and (b) are adjusted such that the pH upon dissolution of (a) in (b) is 9.5 - 11.5: (a): a lyophilized product of an alkaline aqueous solution of a 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or salt thereof having antiulcer activity; (b): an aqueous solvent added with no nonaqueous solvent. The injection of the present invention is void of the necessity to lower pH so as to prevent hemolysis and local irritation, and to add a nonaqueous solvent to an aqueous solvent for dissolution so as to prevent concomitant degradation of dissolution property. Accordingly, the injection of the present invention can secure solubility sufficient for formulation into preparation and safety for the human body.

TECHNICAL FIELD

The present invention relates to a medicament suitable for injection, comprising 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt thereof having antiulcer activity, particularly sodium salt of omeprazole, as well as relating to an injection kit thereof, which are used in clinical fields.

BACKGROUND ART

The 2-[(2-pyridyl)methylsulfinyl]benzimidazole compounds such as omeprazole or lansoprazole are potent antiulcer agents, and are used as pharmaceutical compositions for oral administration. Further, the injections thereof have recently developed.

As an injection of omeprazole, there has been known an injection prepared by dissolving sodium salt of omeprazole in sterilized water, filtering and lyophilizing the solution to give a lyophilized product, and then dissolving the lyophilized product in a mixture of polyethylene glycol 400 for injection, sodium dihydrogenphosphate and sterilized water (Japanese Patent Unexamined Publication No. 167587/1984).

Also, an injection prepared by dissolving a lyophilized product of an alkaline aqueous solution of a 2-[(2-pyridyl)-methylsulfinyl]benzimidazole compound having antiulcer activity such as lansoprazole in a mixture of (a) acid, and (b) at least one of ethanol, propylene glycol and polyethylene glycol

(Japanese Patent Unexamined Publication No. 138213/1990).

In general, the pH of injection is preferably about 4-8, and a pH above 9 has a probability of causing hemolysis and local irritation.

In the case of the 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt thereof, which is hereinafter referred to as "benzimidazole compound or salt thereof", and may be represented by sodium salt of omepazole, it shows a solubility of the level permitting formulation into preparation, in water in an alkaline range of pH 9.5 or above, whereas it shows extremely low solubility in water at a pH of not more than 9, thus rendering formulation into preparation very difficult.

While the benzimidazole compound or salt thereof is stable in the alkaline range, it poses a problem in that its stability decreases with the lowering pHs.

For this reason, in conventional injections of benzimidazole compound or salt thereof such as sodium salt of omeprazole, an acid such as hydrochloric acid or sodium dihydrogenphosphate is added to the solution to keep the pH from neutral to weak basic, and a nonaqueous solvent such as polyethylene glycol, ethanol or propylene glycol is also added, in order to obtain a certain level of solubility in such pH range.

Yet, these injections pose problems of local irritation and hemolysis caused by the nonaqueous solvent added to the solution for dissolution.

Accordingly, an object of the invention is to provide an injection of benzimidazole compound or salt thereof, particularly sodium salt of omeprazole, causing less side- effects such as hemolysis, and less local irritation, which permits easy formulation.

DISCLOSURE OF THE INVENTION

As a result of the intensive study conducted by the inventors with the aim of achieving the aforementioned object, it has now been found that a product obtained by lyophilizing an alkaline aqueous solution of benzimidazole compound or salt thereof, and dissolving same in an aqueous solvent without any non-aqueous solvent, scarcely shows hemolytic property and local irritation, notwithstanding the high pH of from 9.5 to 11.5.

Accordingly, the present invention provides a medicament suitable for injection, comprising a lyophilized product of an alkaline aqueous solution of a 2-[(2-pyridyl)methylsulfinyl]-benzimidazole compound or a salt thereof having antiulcer activity and an aqueous solvent without any nonaqueous solvent, which has a pH of not less than 9.5 and not more than 11.5.

The present invention also provides an injection kit which is a system comprising components (a) and (b) as follows:

(a) a lyophilized product of an alkaline aqueous solution of a 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt thereof having antiulcer activity, and

(b) an aqueous solvent without any non-aqueous solvent,

wherein components (a) and (b) are operatively interconnected or interdependent such that component (a) can be dissolved in (b) with the pH adjusted upon dissolution of component (a) in (b) so as to be not less than pH 9.5 and not more than 11.5, in forming an aqueous injectible solution.

The 2-[(2-pyridyl)methylsulfinyl]benzimidazole compounds having antiulcer activity which are the element constituting the present invention include, for example, the compounds described in Japanese Patent Unexamined Publication No. 62275/1977, Japanese Patent Unexamined Publication No. 1417/1979, Japanese Patent Unexamined Publication No. 53406/1982, Japanese Patent Unexamined Publication No. 135881/1983, Japanese Patent Unexamined Publication No. 192880/1983, Japanese Patent Unexamined Publication No. 181277/1984 or Japanese Patent Unexamined Publication No. 50978/1986, and omeprazole [chemical name: 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-methoxy)benzimidazole] and lansoprazole [chemical name: 2-{2-[(3-methyl-4-(2,2,2-trifluoroethoxy)]-pyridylmethylsulfinyl}-benzimidazole] are exemplified.

As the salts of said benzimidazole compounds, for example, salts of alkaline metal such as sodium salt or potassium salt or salts of alkaline earth metal such as calcium salt or magnesium salt.

In view of the solubility, it is preferable for the present invention to use the salt of benzimidazole compound.

The injection of the present invention has a pH of not less than 9.5 and not more than 11.5, preferably not less than 10 and not more than 11. Where the pH is less than 9.5, the benzimidazole compound or salt thereof does not sufficiently

dissolve in an aqueous solvent and shows poor stability, while where it is more than 11.5, hemolytic property and local irritation become prominent.

According to the present invention, an injection of the benzimidazole compound or salt thereof can be prepared by dissolving the benzimidazole compound or salt thereof in water for injection, etc. along with a strong alkaline compound such as sodium hydroxide, potassium hydroxide, sodium carbonate or L-arginine, to give an alkaline aqueous solution having a pH adjusted to not less than 10.5 and not more than 12.5, preferably not less than 11 and not more than 12. The alkaline aqueous solution may contain mannitol, glycine, sorbitol, inositol, etc. on demand for better forming of a lyophilized product.

The benzimidazole compound is contained in said alkaline aqueous solution in a proportion of 1-50 mg/ml, preferably 5-40 mg/ml on a free compound basis.

Then, this alkaline aqueous solution is filtered for sterilization, and charged in a vial by 0.5-10 ml. After nitrogen gas displacement to be conducted as necessary, the solution is lyophilized by a method known per se. The lyophilized product thus obtained is the (a): a lyophilized product of an alkaline aqueous solution of the 2-[(2-pyridyl)-methylsulfinyl]benzimidazole compounds or salt thereof having antiulcer activity to be contained in the injection kit of the present invention.

When in use, the injection of the present invention can be produced by dissolving the lyophilized product thus obtained in an aqueous solvent added with no nonaqueous solvent, such as physiological saline, aqueous solution of 5% glucose, or distilled water for injection. Said aqueous solvent corresponds to the (b) : an aqueous solvent added with no nonaqueous solvent to be contained in the injection kit of the present invention.

The injection of the present invention can be used, for example, in the form of drip infusion, intravenous injection, intramuscular injection, subcutaneous injection.

The concentration of benzimidazole compound in the injection of the present invention may vary depending upon the administration route, and generally ranges in a proportion of 0.05-10 mg/ml, preferably 0.1-5 mg/ml on a free compound basis.

The benzimidazole compound in the injection of the present invention is administered to an adult at 10-100 mg per day on a free compound basis in a single to three times divided doses, depending upon, for example, the symptoms of the patients.

[BEST MODE FOR CARRYING OUT OF THE INVENTION]

Experimental Example 1

Test preparation

1. Preparation obtained in Example 1 to be mentioned later

Test method

1. Hemolysis test

Hemolysis was evaluated by Akaishi method using whole blood

of rabbit. The result is given in Table 1.

2. Local irritation test

Local irritation was evaluated by the comparison of necrotic muscular tissue area at the injection site in 3 rabbits at 2 days after the administration of 1 ml of the test preparation by intramuscular injection, with that in the rabbits administered with 1 ml of physiological saline or 1 ml of a 1.7% acetic acid solution, respectively by intramuscular injection.

The results are summarized in Table 2.

Test results

Table 1

Test preparation	pH	Hemolysis
Ex. 1	10.5	not observed

Table 2

Test preparation	pH	Necrotic area (mm^2)
Ex. 1	10.5	63
1.7% acetic acid solution (positive comparison solution)	—	398
physiological saline (negative comparison solution)	—	31

(average of 3 rabbits)

The preparation of the present invention is desirable as an injection, since it does not cause hemolysis at all despite the high pH, and causes less local irritation.

Example 1

1N Sodium hydroxide (2.3 ml) is added to 21.3 g of sodium salt of omeprazole (20 g as omeprazole), and water for injection is added thereto to adjust the pH to 11.5 and the total amount to 1 kg.

After filtration for sterilization, this alkaline aqueous solution is charged in 10 ml vials by 2 g. A rubber plug is half driven in, and nitrogen displacement is performed. Lyophilization by a conventional method and dissolution of the lyophilized product obtained in 10 ml of physiological saline give an omeprazole injection [4 mg (free compound)/ml].

INDUSTRIAL APPLICABILITY

The injection of the present invention voids the necessity to lower pH so as to prevent hemolysis and local irritation, or to add a nonaqueous solvent such as polyethylene glycol to an aqueous solvent for dissolution so as to prevent concomitant degradation of dissolution property. As a result, irritation and hemolysis caused by the nonaqueous solvent can be avoided. Accordingly, the injection of the present invention can secure solubility sufficient for formulation into preparation and safety for the human body.

A practical example of an injection kit in accordance with the invention may employ a structurally known form of precharged hypodermic syringe, such as the so-called "Vetter Lyo-Ject" wet-dry, dual-chamber, syringe, manufactured by Arzneimittel GmbH Apotheker Vetter & Co., of Ravensburg, Germany. Components (a) and (b) of the invention are temporarily housed respectively under sterile conditions in the individual chambers of the syringe pending mixing therein under sterile conditions so as to load the syringe with the resultant injectible medicament under sterile conditions, ready for administration of the medicament to a patient. Said syringe is operated by pushing the plunger of the syringe so that a channel-form passage is opened between the individual chambers whereby the solution of component (b) in the bottom chamber of the syringe contacts the lyophilised product of component (a) in the top chamber of the syringe for dissolution of that product, so as to form a sterile injectible medicament in accordance with the invention, ready for administration to the patient.

The claims defining the invention are as follows:

1. A medicament suitable for injection comprising a lyophilized product of an alkaline aqueous solution of a 2-[(2-pyridyl)methylsulfinyl]-benzimidazole compound or a salt thereof having antiulcer activity and an aqueous solvent without any nonaqueous solvent, wherein the pH of the medicament is not less than 9.5 and not more than 11.5.

2. The medicament of Claim 1, wherein the 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt thereof is a salt of omeprazole.

3. The medicament of Claim 1 or 2, wherein the 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt thereof is the sodium salt of omeprazole.

4. An injection kit which is a system comprising the components (a) and (b) as follows:

(a) a lyophilized product of an alkaline aqueous solution of a 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt thereof having antiulcer activity, and

(b) an aqueous solvent without any non-aqueous solvent,

wherein components (a) and (b) are operatively interconnected or interdependent such that component (a) can be dissolved in (b) with the pH adjusted upon dissolution of component (a) in (b) so as to be not less than pH 9.5 and not more than 11.5, in forming an aqueous injectible solution.

5. The injection kit of Claim 4, wherein the 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or the salt thereof is a salt of omeprazole.

6. The injection kit of Claim 5, wherein the salt of omeprazole is the sodium salt of omeprazole.

DATED this 9th day of October 1996

ASTRA AKTIEBOLAG,
By its Patent Attorneys,
E. F. WELLINGTON & CO.,
By:

(Bruce Wellington)

A/KA/4025

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP 93/00998

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/44; A61K9/08

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0 382 489 (TAKEDA) 16 August 1990 see claims see page 7, line 50 - line 52 see example 2	1-5
A	EP,A,0 124 495 (AKTIEBOLAGET HÄSSLE) 7 November 1984 cited in the application see claims see page 6, line 6 - line 15 see page 7, line 31 - line 37 see page 8, line 1 - line 8 see example 13	1-5
A	EP,A,0 356 143 (TAKEDA) 28 February 1990 cited in the application see claims	1-5

[10] Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the t.

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
29 SEPTEMBER 1993	07. 10. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	SCARPONI U.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

JP 9300998
SA 76470

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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