1,047,822

PATENT SPECIFICATION

NO DRAWINGS

1,047,822

Date of Application and filing Complete Specification: Jan. 24, 1964.

No. 3237/64.

Application made in United States of America (No. 259,403) on Feb. 18, 1963.

Complete Specification Published: Nov. 9, 1966.

© Crown Copyright 1966.

Index at acceptance:—A5 B2S

Int. Cl.:— A 61 k 3/00

COMPLETE SPECIFICATION

Improvements in or relating to Urologic Compositions containing 5-Nitro-Furfurylidene Derivatives

We, THE NORWICH PHARMACAL COMPANY, a Company organised under the Laws of the State of New York, United States of America, of 17 Eaton Avenue, Norwich, New York, United States of America, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to compositions useful in urology. More particularly it is concerned with the provision of compositions useful in combating urologic disease. Still more particularly it is concerned with the provision of compositions containing 1 - (5-nitrofurfurylideneamino) - 2 - imidazolidone as the active ingredient which are useful in eliminating bacterial pathogens associated with urinary tract infections.

Urinary tract infections are the most common urologic disease. They manifest varying degrees of severity, being at times asymptomatic, at times they tend to make the patient very ill and sometimes they result in death. Even if initially asymptomatic or mild, infections of the urinary tract can lead, if not suitably treated, to more severe manifestations with undesirable consequences.

The bacterial organisms commonly implicated and encountered in urinary tract infections comprise the gram-negative bacilli and the micrococci. Among the gram negative group *Escherichia coli, Aerobacter aerogenes, Proteus vulgaris* and sometimes *Pseudomonas aeruginosa* are noteworthy pathogens. Of these, the Proteus and Aerobacter organisms are peculiarly resistant to known therapeutic measures.

A difficulty experienced in the treatment of bacterial urinary tract infections is a chameleon-like bacteriology in which, for instance, staphylococci may initially predominate, then colon bacilli and later on Proteus, Pseudomonas, Aerobacter or streptococcus organisms may supersede. This variegated bacteriology obviously poses a difficult problem in the management of urinary tract infections.

To successfully control urinary tract infections, the invasive bacteria must be removed by therapeutic means which are tolerable to the host. Many compositions have been provided and are available today and are widely employed for this purpose. However, no one drug is wholly satisfactory nor have combinations of drugs so formulated as to provide compositions designed to supplant and offset the shortcomings of one member completely satisfied the desiderata of urinary tract infection therapy. Failures are found in the inability of the prior compositions to control strains of the same generic organism, in the development of drug resistance, in the appearance of side reactions such as nausea, vomiting, diarrhoea, dermatitis and ulcerative staphylococcic enteritis and in their incomplete antibacterial spectrum.

We have now found that compositions comprising 1 - (5 - nitrofurfurylideneamino) - 2-imidazolidone are useful in the combating and in the control of those invasive bacteria associated with urinary tract infections. The aforesaid imidazolidone is a known compound and may be prepared by known methods of which one is described in the Journal of the American Chemical Society Volume 78 at page 5349 (1956). Hitherto the great utility of compositions comprising the said imidazolidone in the control of bacterial urinary tract infections has not been recognised. The versatility of such compositions in combating those bacteria hereinbefore recited when they are involved in urinary tract infections is most unexpected and unobvious. Not only does the urine of subjects to whom these compositions are administered in sub-toxic dosages contain a concentration of active ingredient

inimical to micrococci and gram-negative bacteria including the resistant Aerobacter and Proteus organisms but also a concentration of the active ingredient is present in the serum thus providing conditions considered advantageous in urologic disease.

The urologic compositions to which this invention is directed as hereinabove disclosed comprise suitable and conveniently administered dosage unit forms. Of these, ingestible capsules, for instance of the gelatin type, or compressed tablets containing a dosage unit quantity of the aforesaid imidazolidone are most expeditiously prepared and used: it will be realised that the capsule constitutes a pharmaceutical carrier.

As used herein the term dosage unit signifies a physically discrete unit containing an individual quantity of the active component in association with a pharmaceutical diluent or carrier, the quantity of active compound being such that one or more units are required for a single therapeutic administration. It does not include mere solutions in water or other common solvent except when such are packaged in ingestible containers.

According to the present invention there is provided a urologic composition for combating urinary tract infections upon oral administration comprising an effective and host tolerable quantity of 1 - (5 - nitrofurfurylideneamino) - 2 - imidazolidone in dosage unit form, as hereinbefore defined, in association with a pharmaceutical carrier.

The dosage unit of the aforesaid imidazolidone at present regarded as preferred in the compositions of this invention ranges from about 100 mg. to about 400 mg. Administration of such compositions to subjects provokes no overt manifestations of toxicity and produces anti-bacterial urine and serum levels. The dosage regimen employed is, of course, subject to individual instances. A single tablet containing 100 mg. when administered to a host produces antibacterially active urine. Multiple or repeated doses of such a tablet in conformity with recognised radical practice can, of course, be employed where indicated and expedient.

The following descriptions of dosage unit forms of the compositions of this invention are given to illustrate the manner in which the invention may be carried into effect.

CAPSULE

A. A capsule containing 200 mg of 1-(5 - nitrofurfurylideneamino) - 2 - imidazolidone is conveniently prepared by weighing that amount into one portion of a two-piece No. 3 clear, hard gelatin capsule and slidably engaging the other portion therewith.

B. In a manner similar to A above, a 100 mg. quantity of 1 - (5 - nitrofurfurylideneamino) - 2 - imidazolidone is prepared using a two-piece No. 4 clear, hard gelatin capsule.

TABLET

1 - (5 - Nitrofurfurylideneamino) - 2-imidazolidone	100.00
Dicalcium phosphate	50.00
Cornstarch (as 10% aqueous paste)	5.00
Syrup (sugar)	5.00
Cornstarch	4.40
Magnesium stearate	0.60

The amounts of the ingredients are measured in milligrams. The manner of tableting is conventional.

The following table illustrates the production of urines antibacterial to gram-negative bacteria associated with urinary tract infections in subjects to whom compositions of this invention were orally administered. The degree of antibacterial activity is expressed in terms of the reciprocal of the minimum bacterial inhibitory dilution of the urine. The compositions employed were:

Capsule A containing 100 mg. of 1 - (5-nitrofurfurylideneamino) - 2 - imidazolidone, Capsule B containing 200 mg, Capsule C containing 300 mg and Capsule D containing 400 mg, each in a hard gelatin capsule. These were administered to each of five subjects with sufficient hiatus between dosage levels.

Composition	Subject No.	Urine Sample (Hours Post Dosing)	Reciprocal Inhibitory Dilution Of Urine vs.			
			E. coli	A. aerogenes	P. Vulgaris	Ps. aeruginosa
Capsule A	1	4—6	32	2	<2	<2
„	2	2—4	32	2	<2	<2
„	3	2—4	8	<2	<2	<2
„	4	0—2	32	2	<2	<2
„	5	2—4	8	<2	<2	<2
Capsule B	1	0—2	128	8	2	<2
„	2	2—4	64	4	<2	<2
„	3	0—2	128	8	2	<2
„	4	0—2	128	8	2	<2
„	5	0—2	256	16	4	2
Capsule C	1	0—2	256	16	4	2
„	2	2—4	128	8	2	<2
„	3	0—2	512	32	4	2
„	4	0—2	2048	64	8	4
„	5	2—4	512	32	4	2
Capsule D	1	0—2	128	8	2	<2
„	2	4—6	128	8	2	<2
„	3	0—2	128	8	2	<2
„	4	2—4	1024	32	4	2
„	5	0—2	1024	32	4	2

WHAT WE CLAIM IS:—

1. A urologic composition for combating urinary tract infections upon oral administration comprising an effective and host tolerable quantity of 1 - (5 - nitrofurfurylideneamino)-2 - imidazolidone in dosage unit form, as hereinbefore defined in association with a pharmaceutical carrier.

2. A urologic composition according to claim 1 in the form of a pharmaceutical capsule or tablet.

3. A composition according to claim 1 or claim 2 in which the dosage unit contains from 100—400 mg of the said imidazolidone compound.

4. A composition according to any of the preceding claims in which the pharmaceutical carrier is a finely divided solid.

5. Urologic compositions in dosage unit form substantially as described.

STEVENS, LANGNER, PARRY & ROLLINSON,
Chartered Patent Agents,
Agents for the Applicants.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1966. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

Composition	Subject No.	Urine Sample (Hours Post Dosing)	Reciprocal Inhibitory Dilution Of Urine vs.			
			E. coli	A. aerogenes	P. Vulgaris	Ps. aeruginosa
Capsule A	1	4—6	32	2	<2	<2
„	2	2—4	32	2	<2	<2
„	3	2—4	8	<2	<2	<2
„	4	0—2	32	2	<2	<2
„	5	2—4	8	<2	<2	<2
Capsule B	1	0—2	128	8	2	<2
„	2	2—4	64	4	<2	<2
„	3	0—2	128	8	2	<2
„	4	0—2	128	8	2	<2
„	5	0—2	256	16	4	2
Capsule C	1	0—2	256	16	4	2
„	2	2—4	128	8	2	<2
„	3	0—2	512	32	4	2
„	4	0—2	2048	64	8	4
„	5	2—4	512	32	4	2
Capsule D	1	0—2	128	8	2	<2
„	2	4—6	128	8	2	<2
„	3	0—2	128	8	2	<2
„	4	2—4	1024	32	4	2
„	5	0—2	1024	32	4	2

WHAT WE CLAIM IS:—

1. A urologic composition for combating urinary tract infections upon oral administration comprising an effective and host tolerable quantity of 1 - (5 - nitrofurfurylideneamino)-2 - imidazolidone in dosage unit form, as hereinbefore defined in association with a pharmaceutical carrier.

2. A urologic composition according to claim 1 in the form of a pharmaceutical capsule or tablet.

3. A composition according to claim 1 or claim 2 in which the dosage unit contains from 100—400 mg of the said imidazolidone compound.

4. A composition according to any of the preceding claims in which the pharmaceutical carrier is a finely divided solid.

5. Urologic compositions in dosage unit form substantially as described.

STEVENS, LANGNER, PARRY & ROLLINSON,
Chartered Patent Agents,
Agents for the Applicants.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1966. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

* C L M S *