(12) UK Patent Application (19) GB (11) 2 195 242 (13) A

(43) Application published 7 Apr 1988

(21) Application No 8722205

(22) Date of filing 21 Sep 1987

(30) Priority data
(31) 910571 (32) 23 Sep 1986 (33) US

(71) Applicant
Sandoz Ltd

(Incorporated in Switzerland)

35 Lichstrasse, CH-4002 Basle, Switzerland

(72) Inventor
William R Sterling

(74) Agent and/or Address for Service
B A Yorke & Co,
98 The Centre, Feltham, Middlesex TW13 4EP

(51) INT CL⁴
A61K 9/48

(52) Domestic classification (Edition J):
A5B 180 480 48Y 502 503 50Y 552 55Y 577 57Y 586 58Y 616 61Y 650 65Y 829 LM

(56) Documents cited
La Reforma Medica 16, 1970 pages 425–427
Neuropsychobiology 1983 pages 52–65

(58) Field of search
A5B
Selected US specifications from IPC sub-class A61K

(54) Temazepam

(57) A low dosage of temazepam is useful in the treatment of chronic and transient insomnia. Dosage is especially formulated in hard or soft gelatin capsules.

GB 2 195 242 A

SPECIFICATION

Pharmaceutical composition containing a benzodiazepin derivative

This invention relates to new pharmaceutical forms of temazepam and their use as hypnotic agents.

More particularly, it relates to low dose temazepam capsules and their use in the treatment of insomnia, especially, transient insomnia.

Temazepam, whose chemical name is 7-chloro-1, 3-dihydro-3-hydroxy-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, is a well known hypnotic agent used in the treatment of insomnia. The commercial product is sold both in the form of hard gelatin capusles containing 15 and 30 milligrams of temazepam and soft gelatin capsules containing 10 and 20 milligrams of temazepam. The hard gelatin capsule has been studied in great depth and has been found to be generally effective at doses of 15 and 30 milligrams of temazepam. At doses of 10 and 20 milligrams, the soft gelatin capsules have also been found to be effective, although Nicholson, et al. (Br. J. Clin. Pharmac., *3*,543-550, 1976) have reported that at 10 milligrams, no change in total sleep time was found, whereas at 20 milligrams, total sleep time was markedly increased. Lower dose forms of temazepam containing 5 milligrams of the compound have been used in a number of investigations (LaReforma Medica, *16*,425-427, 1970; Bombay Hosp. J., *16*,222-223, 1974; Neuropsychobiology 9(1), 52-65, 1983) but have never been found to be useful in treating insomnia. In the Neuropsychobiology publication, the authors indicate that at 5 milligrams, temazepam is known to be of no clinical importance as a hypnotic agent.

Although the side effects of temazepam are minimal, the lowest effective dose of the product would be desirable. It would be especially useful in treating transient insomnia, which occurs in healthy individuals whose sleep pattern has been temporarily disrupted, for example by airplane travel or by changing work shifts. It has now been found that a hard gelatin capsule comprising up to 10 milligrams of temazepam, in which the temazepam particles have a specific surface area of from 0.65 to 1.1 square meters per gram (m^2/g) and 95% of the particles have a particle size diameter of less than 65 microns (u), is effective in the treatment of insomnia, especially in improving sleep latency. Such a formulation is also useful for the treatment of chronic insomnia. Preferably the capsule contains the temazepam in amounts of from 5 to 10 milligrams, more preferably 6 to 8 milligrams, especially 7.5 milligrams, in combination with a pharmaceutically acceptable carrier. The capsule is normally administered just before bedtime.

It has also been found that a soft gelatin capsule comprising 5 to 9 mg of temazepam, and especially 5mg, in combination with a pharmaceutically acceptable carrier, is useful in the treatment of transient insomnia.

Crystalline temazepam can be synthesized with a purity of not less than 98% using known procedures such as that disclosed in U.S.P. 3,296,245. The bulk temazepam is milled to obtain the required particle size and surface area with an Alpine 160 UPZ mill using a stainless steel pin. The particle size is determined using a Malverne Particle Sizer Model 3600 E equipped with a 14.3 mm flow cell and a 100 mm lens. Surface area measurements are made essentially in accordance with the standard B.E.T. procedure of Brunauer, Emmet and Teller (J. Am. Chem. Soc. *59*, 2682, 1937 and J. Am. Chem. Soc., *60*, 309, 1938). The temazepam is formulated with standard hard gelatin capsule excipients and encapsulated in conventional hard gelatin capsules using known procedures.

Similarly for the formation of the soft gelatin capsules, temazepam is mixed with standard soft gelatin capsule excipients, and encapsulated using known procedures, in conventional soft gelatin capsules.

The use of low dose temazepam capsules in the treatment of transient insomnia is evaluated in a double blind, parallel group, placebo-controlled sleep laboratory study using 201 healthy subjects. Just before bedtime each subject is given a capsule containing placebo, or the appropriate amount of temazepam. Testing is carried out over a period of one night in the sleep laboratory. The key parameters of sleep latency and total sleep time are among those measured by EEG analysis (polysomnography). In the case of the hard gelatin capsule dosages of 7.5, 15 or 30 mg of temazepam per capsule are employed. The number of subjects in the four treatment groups is placebo—50; 7.5 milligrams—51; 15 milligrams - 49; and 30 milligrams—51. The mean values for sleep latency and total sleeptime obtained with the hard gelatin capsule in each treatment group were as follows:

Group	Sleep Latency (min.)	Total Sleep Time (min.)
Placebo	37	411
7.5 m.g.	26	422
15 m.g.	22	429
30 m.g.	18	441

As can be seen from the above data 7.5 milligrams of temazepam was effective in reducing both sleep latency and increasing total sleep time in the study. The most unexpected result is that the effect occurred as the dosage dropped below the 15 milligram dosage level. The usual effectno effect results, which would have been expected between 7.5 and 15 milligrams of temazepam based on previous hard gelatin capsule studies did not occur.

Similar results are obtained employing a soft gelatin capsule containing 5 mg of temazepam.

Example 1

White crystalline temazepam having a purity of not less than 98% is prepared according to the procedure described in USP 3,296,245. The bulk temazepam obtained is fed into an Alpine 160 UPZ mill with a stainless steel pin at a rate of about 40 kilograms (kg) per hour using a mill speed of about 11,000 RPM to obtain temazepam particles having a specific surface area of 0.65 to 1.1 m^2/g area and 95% of the particles having a particle size diameter of less than 65 u. The surface area measurement is made with the Quantector Gas Flow System and Quantasorb Surface Area Analyser at the temperature of liquid nitrogen (−196°C) using krypton as the absorbant and helium as the carrier gas. The particle size diameter is determined with the Malverne Particle Sizer at an obscuration value of 0.2 to 0.25 using a 0.1% Tween 80 solution in water saturated with temazepam in which 1 to 2 grams of temazepam sample to be tested has been dispersed. After the feed rate and mill speed of the Alpine mill have been set, they are monitored at regular intervals to maintain the required particle size and surface area.

Example 2

To prepare hard gelatin capsules containing 7.5 milligrams of the temazepam of example 1, 12 kg of temazepam and 12 kg of lactose are passed through an 18 mesh screen. This mixture is added to 372 kg of lactose, which has also been passed through an 18 mesh screen, and and 4 kg of magnesium stearate in a 30 cu. ft. PK Mixer without an intensity bar. The capsule ingredients mixed for 30 minutes using tumbling action only. The capsule mix is encapsulated in number 3 Lock hard gelatin capsules with opaque blue caps and opaque pink bodies, and the capsules are then passed through a capsule polisher. Each capsule contains 250 milligrams of capsule mix of which 7.5 milligrams are temazepam.

Example 3

For the preparation of the soft gelatin capsules, containing 5 mg of temazepam, 8 kg of the temazepam is dissolved in 356.8 kg of polyethylene glycol 400. When dissolved the solution is encapuslated by standard techniques in number 4 oval soft gelatin capsule shells which are opaque and maroon in colour. Each capsule contains 228 mg of capsule mix of which 5 mg are temazepam.

CLAIMS

1. The use of temazepam for the manufacture of a medicament for the treatment of insomnia characterised in that

a) the temazepam has a surface area of from 0.65 to 1.1 m^2/g and 95% thereof has a particle diameter of less than 65 microns and is present in a quantity of up to 10 mg per dosage unit

b) alternatively in the case of transient insomnia is in the form of a soft gelatin capsule containing less than 10 mg of temazepam.

2. The use of temazepam in insomnia characterised in that the temazepam

a) has a surface area of from 0.65 to 1.1 m^2/g and 95% thereof has a particle diameter of less than 65 microns and is present in a quantity of up to 10 mg per dosage unit or

b) alternatively in the case of transient insomnia is in the form of a soft gelatin capsule containing less than 10 mg of temazepam.

3. The use according to claim 1 or 2 wherein the temazepam

a) has a surface area of from 0.65 to 1.1 m^2/g and 95% thereof has a particle diameter of less than 65 microns and is present in a quantity of 5 to 10 mg or

b) alternatively in the case of transient insomnia, is in the form of a soft gelatin capsule

containing 5 to 9 mg of temazepam.

4. The use according to claim 3 wherein each dosage unit contains 6 to 8 mg of temazepam.

5. The use according to claim 3 wherein each dosage unit contains 7.5 mg of temazepam.

6. The use according to claim 3 wherein each dosage unit contains 5 mg of temazapem.

7. The use according to claims 1 to 6 for treating transient insomnia.

8. A hard gelatin capsule containing up to 10 mg of temazepam in which the temazepam has a surface area of from 0.65 to 1.1 m^2/g and 95% thereof has a particle diameter of less than 65 microns and a pharmaceutically acceptable carrier therefor.

9. A capsule according to claim 8 containing 5 to 10 mg of temazepam.

10. A capsule according to claim 8 containing 6 to 8 mg of temazepam.

11. A capsule according to claim 8 containing 7.5 mg of temazepam.

Published 1988 at The Patent Office, State House, 66/71 High Holborn, London WC1R 4TP. Further copies may be obtained from The Patent Office, Sales Branch, St Mary Cray, Orpington, Kent BR5 3RD. Printed by Burgess & Son (Abingdon) Ltd. Con. 1/87.