(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 March 2001 (22.03.2001)

PCT

(10) International Publication Number
WO 01/19346 A1

(51) International Patent Classification[7]: A61K 9/14, 9/22, 9/24, 9/26, 9/28, 9/36

(21) International Application Number: PCT/US00/25172

(22) International Filing Date:
14 September 2000 (14.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/395,884 14 September 1999 (14.09.1999) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/19346 A1

(54) Title: DELAYED RELEASE NABUMETONE FORMULATION

(57) Abstract: An enteric coated, delayed release nabumetone formulation is provided. The composition comprises a drug-containing core containing the active agent and an enteric polymer coating that provides the desired delayed release profile. A preferred enteric polymer is a copolymer of methacrylic acid and methyl methacrylate in which the ratio of free carboxyl to ester groups is approximately 1:1. Methods for using the novel formulation are provided as well; a preferred use is in the treatment of conditions

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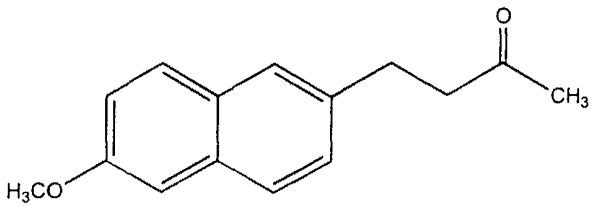
DELAYED RELEASE NABUMETONE FORMULATION

TECHNICAL FIELD

This invention relates generally to pharmaceutical formulations for oral administration of a nonsteroidal anti-inflammatory drug (NSAID), and more particularly relates to a delayed release, enterically coated nabumetone formulation. The invention additionally relates to therapeutic methods wherein the novel formulation is administered to a patient to treat an NSAID-responsive condition, disease or disorder.

BACKGROUND

Nonsteroidal anti-inflammatory drugs such as diclofenac, ibuprofen, ketoprofen, naproxen, nabumetone and piroxicam are widely used to relieve mild to moderate pain, to reduce fever, and to treat inflammatory conditions. Nabumetone (4-(6′-methoxy-2′-naphthyl)butan-2-one), for example, has been described in U.S. Patent No. 4,420,639 for use as an anti-inflammatory agent for the treatment of rheumatic and arthritic conditions.



NABUMETONE

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In addition, U.S. Patent No. 5,695,774 describes the use of nabumetone for the treatment and/or prevention of dementia, such as Alzheimer's disease.

The NSAIDs are non-habit forming drugs and thereby offer a significant advantage over the use of traditional opioid- or steroid-based drugs. However, in some cases, systematic administration of an NSAID is not recommended. NSAIDs can result in systemic toxicity in a host, and since the agent is administered systemically, its effects are also systemic. Thus, the chronic use of NSAIDs or the administration of high doses of NSAIDs has been associated with undesirable side effects such as bleeding, ulceration, and perforation. For example, chronic oral administration of aspirin can result in stomach upset and patient discomfort.

In view of the advantages of NSAIDs, steps have been undertaken to minimize the adverse effects associated with the systemic administration of these drugs. In one approach to reduce the adverse effects of NSAIDs, the agents are ingested with food or milk, or are taken in combination with antacids, histamine H_2-receptor antagonists, omeprazole, or sucraflate. In another approach, NSAIDs have been administered locally, such as by injection or topical administration, or have been co-administered with a prostaglandin.

In yet another approach to reduce the undesirable gastrointestinal effects resulting from systemic administration of NSAIDs, the agents have been enterically coated to give a delayed release formulation. In U.S. Patent Nos. 3,488,418, 3,341,416, and 3,155,590, aspirin is microencapsulated with ethylcellulose. After ingestion, the gastric fluids slowly diffuse through the encapsulant walls, dissolve the aspirin, and the dissolved aspirin diffuses out through the encapsulant walls into the body. In U.S. Patent No. 3,906,086, aspirin is coated with a non-aqueous solution of cellulose acetate phthalate. The cellulose acetate phthalate is substantially insoluble in the acidic media of the stomach and the tablet remains intact until it reaches the intestinal tract. Thus, as the cellulose acetate phthalate coating is dissolved by the alkaline intestinal fluid, aspirin is released in the intestinal tract. U.S. Patent No. 4,966,768 describes a sustained release tablet containing etodolac as the active agent and a mixture of hydroxypropylmethyl cellulose, ethyl cellulose, and dibasic sodium phosphate as a sustained release carrier.

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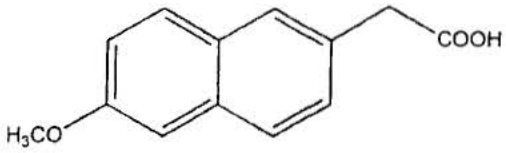
Nabumetone, disclosed in U.S. Patent No. 4,061,779, is a nonacidic prodrug that is metabolized to an active nonsteroidal antiinflammatory moiety 6-methoxy-2-naphthylacetic acid (6-MNA). 6-MNA is a structural analog of naproxen, and like other NSAIDs, possesses analgesic, antipyretic and anti-inflammatory activity.



6-MNA

See Pisko et al. (1987), "Nabumetone: a 'Nonacidic' Nonsteroidal Antiinflammatory Drug" *Pharmatherapeutica* 5:90-98. The predominant gastrointestinal reactions associated with NSAIDs, as noted above, include abdominal pain and indigestion, nausea or vomiting; however, the aforementioned publication and others suggest that with nabumetone, duodenal ulcer, gastric ulcer, and gastrointestinal bleeding occurs in less than 1% of patients taking the drug. (See, e.g., S.L. Dahl (1993), "Nabumetone: a 'Nonacidic' Nonsteroidal Antiinflammatory Drug" *Ann. Pharmacother.* 27(4): 456-463, which presents a comparative safety study of patients with osteoarthritis or rheumatoid arthritis using nabumetone, diclofenac, naproxen, piroxicam, and ibuprofen, and concluded that ulcers occurred in 0.03% of nabumetone-treated patients, and in 0.5% of patients using the other NSAIDs.) Thus, the current belief in the art is that nabumetone does not, in general, cause the gastrointestinal reactions usually associated with the administration of NSAIDs, and is therefore safe in relatively high doses and for long-term systemic administration. For this reason, controlled release nabumetone formulations, and particularly delayed release, enterically coated nabumetone compositions, have not been manufactured or made available commercially. However, applicants' own studies have shown that oral administration of an "immediate release" nabumetone formulation results in the side effects associated with other NSAIDs in significantly more patients than previously believed,

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primarily gastrointestinal reactions such as stomach upset, bleeding, ulceration, and perforation, and have now developed a novel formulation that avoids these side effects.

SUMMARY OF THE INVENTION

Accordingly, it is a primary object of the invention to address the aforementioned need in the art and provide a delayed release formulation for the administration of nabumetone.

It is another object of the invention to provide such a formulation comprising an enterically coated dosage form.

It is yet another object of the invention to provide such a formulation wherein the active agent is nabumetone.

It is still another object of the invention to provide such a formulation which significantly reduces the side effects associated with immediate release nabumetone formulations, particularly gastrointestinal reactions such as stomach upset, bleeding, ulceration, and the like.

It is an additional object of the invention to provide a method for treating a patient suffering from a disorder or condition associated with inflammation, comprising orally administering to the patient a dosage form of the invention.

It is a further object of the invention to provide such a method wherein the disorder or condition is a rheumatic or arthritic disease.

In one aspect of the invention, then, a pharmaceutical formulation is provided comprising a therapeutically effective amount of nabumetone. The formulation is an enterically coated, delayed release dosage form in which a core containing the therapeutically effective amount of nabumetone is coated with an enteric polymer effective to delay release of the active agent until the small intestine of the patient is reached. The drug-containing core of the formulation comprises:

approximately 60 wt.% to 90 wt.% nabumetone;
approximately 5 wt.% to 15 wt.% sodium starch glycolate;
approximately 0.1 wt.% to 2 wt.% surfactant;
approximately 1 wt.% to 4 wt.% hydroxypropyl methylcellulose;
approximately 2.5 wt.% to 7.5 wt.% polyethylene glycol; and

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