Exhibit 1005

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Plachetka

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[54] **FORMULATION OF 5-HT AGONIST AND NSAID FOR TREATMENT OF MIGRAINE**

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[58] **Field of Search** 514/415, 569, 514/629, 570

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,024,279	5/1977	Zor et al. .	
4,816,470	3/1989	Dowle et al. .	
5,360,925	11/1994	Chabrier De Lassauniere et al.	560/169
5,387,604	2/1995	McDonald et al.	514/456
5,514,168	5/1996	Friedman	607/89
5,605,917	2/1997	Ogletree .	
5,607,960	3/1997	Wythes .	
5,618,816	4/1997	Crenshaw et al. .	

FOREIGN PATENT DOCUMENTS

2162522	8/1985	United Kingdom .

OTHER PUBLICATIONS

Anderson, "Double–blind study of naproxen vs placebo in the treatment of acute migraine." (1989); *Cephalalgia,* vol. 9, 29–32.

Baumel, "Migraine: A pharmacological review with newer options and delivery modalities," (1994), *Neurology,* vol. 44Supp3, S13–S17.

Boureau, "Comparison of subcutaneous sumatriptan with usual acute treatments for migraine. French Sumatriptan Group." (1995) *Eur. Neurol.,* vol. 35(5), 264–269.

Bousser, Efficacy of subcutaneous sumatriptanin the acute treatment of early–morning migraine: a placebo–controlled trial. Early–Morning Sumatriptan Study Group (1993) *J Intern Med,* vol. 234(2), 211–216.

Cady, "Treatment of Acute Migraine With Subcutaneous Sumatriptan." (1991) *JAMA,* vol. 265,No. 21, 2831–2835.

Cady, "Efficacy of subcutaneous sumatriptan in repreated episodes of migraine" (1993) *Neurology,* vol. 43, 1363–1368.

Centonze, "Evaluation of the efficacy of oral sumatriptan in the management of migraine attacks. Clinical Results" (1995) *La Clinica Teraputica,* vol. 146(11), 721–728 (Article in the Italian language, Citation to English language abstract only at 727).

Dechant, "Sumatriptan A review of its Pharmacodynamic Properties, and Therapeutic Efficacy in the Acute Treatment of Migraine and Cluster Headache" (1992) *Drugs,* vol. 43(5) 776–798.

Klapper, "Toward a Standard Drug Formulary for the Treatment of Headache" (1995) *Headache,* Apr., 1995, 225–227.

Oral Sumatriptan Group, "Sumatriptan—An Oral Dose–defining Study" (1991) *Eur. Neurol.,* vol. 31, 300–305.

Thomson, "A Study to Compare Oral Sumatriptan with Oral Aspirin plus Oral Metoclopramide in the Acute Treatment of Migraine" (1992) *Eur. Neurol.,* vol. 32, 177–184.

Todd, "Naproxen A reappraisal of its Pharmacology, and Therapeutic Use in Rheumatic Diseases and pain States" (1990) *Drugs,* vol. 40(1), 91–137.

Tokola, "Effects of migraine attack and metoclopramide on the absorption of tolfenamic acid" (1984) *Br. J Clin. Pharmac,* vol. 17, 67–75.

Tokola, "Tolfenamic acid, metoclopramide, caffeine and their combinations in the treatment of migraine attacks" (1984) *Cephalalgia,* vol. 4, 253–263.

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[57] **ABSTRACT**

This invention comprises a method of treating migraine in a human comprising co-timely administering of a therapeutically effective amount of a 5-HT agonist coordinated with a therapeutically effective amount of an analgesic, particularly a long-acting NSAID in doses below those ordinarily considered as minimum effective doses as to both 5-HT agonist and long-acting NSAID. Dosage forms are also included herein.

61 Claims, No Drawings

FORMULATION OF 5-HT AGONIST AND NSAID FOR TREATMENT OF MIGRAINE

RELATED APPLICATIONS

This application claims priority from Provisional Application 60/024,129 filed Aug. 16, 1996.

FILED OF THE INVENTION

This invention comprises a method of treating migraine in a human comprising co-timely administering of a therapeutically effective amount of a 5-HT agonist coordinated with a therapeutically effective amount of an analgesic, particularly a long-acting NSAID, and in some instances, doses below those ordinarily considered as minimum effective doses as to one or both 5-HT agonist and long-acting NSAID. Dosage forms are also included herein.

This invention also comprises a unit dosage form comprising a co-timely delivered therapeutically effective amount of a 5HT agonist coordinated and a therapeutically effective amount of an NSAID or non-NSAID analgesic. Particularly noted is the NSAID ibuprofen. The invention further comprises such unit dosage form wherein the NSAID is a long-acting NSAID. In some embodiments of the unit dosage form the 5HT agonist is sumatriptan, optionally in an amount of from about 1 to about 300 mg, and further wherein the amount is about 1 to about 10 mg (particularly adapted to parenteral administration). A long-acting NSAID useful in the unit dosage form is naproxen, or pharmaceutically acceptable salt thereof such as naproxen sodium. Such unit dosage form usefully contains naproxen, or pharmaceutically acceptable salt thereof in an amount of from about 100 mg to about 1500 mg, and particularly in an amount of from about 200 to about 600 mg. A unit dosage form of sumatriptan and naproxen is specifically noted. Such unit dosage form usefully comprises from about 5 to about 100 mg. sumatriptan, and from about 200 to about 600 mg naproxen.

BACKGROUND OF THE INVENTION

The compound 5-hydroxytryptamine (5-HT or 5HT), also known as serotonin or enteramine, is a known vasoactive agent and endogenous neurotransmitter acting on receptors both within and outside the central nervous system and on blood vessels. Drugs acting on these receptors are known as 5-HT agonists or antagonists. These 5-HT receptors have been further classified into several receptor sub-classes, some of which themselves contain sub-types, and are designated, for example, 5-HT1, 5-HT1-like, 5-HT1_B, 5-HT1_D, 5-HT2, 5-HT3, and so on.

5-HT1-like agonists and agonists at other 5-HT1 sites comprise a known subclass of therapeutics with a variety of uses, notably including migraine therapy. Representative members of this class of compounds include sumatriptan succinate (distributed under the name Imitrex™ by GlaxoWellcome). Sumatriptan and related 5-HT agonist heterocyclic compounds are described in U.S. Pat. No. 4,816,470 to Dowle et al., the teachings of which are incorporated by reference. Note is made of ergot alkaloids which have 5-HT receptor activity, and these drugs are distinct from sumatriptan and its analogs in their chemical structure. In addition, ergots exhibit additional pharmacological properties distinct from sumatriptan. Ergot alkaloids and related compounds such as dihydroergotamine mesylate (DHE 45) are identified with 5-HT agonist receptor activities and have been used in migraine therapy. Without being bound by any particular theory, it is believed that the efficacy of ergots in relieving migraine arises, in part, from pharmacological activity distinct from the recognized 5-HT1 agonist property. Particular reference is made to ergotamine tartrate, ergonovine maleate, and ergoloid mesylates (i.e. dihydroergocornine, dihydroergocristine, dihydroergocryptine (dihydro-α-ergocryptine and dihydro-β-ergocryptine), and dihydroergotamine mesylate.

Some of these agents are not reliably effective treatments for migraine. However, some agents are useful in the treatment of migraine, but after an initial therapeutic effect in some patients, migraine symptoms are seen again within about 1–24 hours after the initial relief. That is, after a dosage of a therapeutic agent has been administered to a subject in an amount to effectively treat a migraine, and migraine palliation has been observed, migraine symptoms occur again from as soon as about 1–8 hours after first relief to about 12 to 24 hours later. It will be appreciated that individual migraineurs display individualized symptoms and timing for this phenomenon as will treatment with particular therapeutic agents.

In some forms of migraine, certain patients have found total or partial relief with the use of analgesics such as acetaminophen and phenacetin and other non-steroidal non-opiate analgesics not generally classified as anti-inflammatory. While, these agents, when taken alone, are rarely effective in providing complete and rapid relief of all the symptoms of migraine, especially when the symptoms of the attack already include nausea or vomiting, in combination therapy of the present invention their effectiveness is surprisingly increased.

As outlined by K. M. A. Welch (*New Eng. J Med*, 1993:329; 1476–1483), the initial dosages of the analgesics useful for the treatment of migraine are: aspirin, 500–650 mg; acetaminophen, 500 mg; naproxen sodium, 750–825 mg; tolfenamic acid, 200–400 mg; and, ibuprofen 200 mg. After oral dosing, peak plasma concentrations in subjects not experiencing a migraine attack usually occur at or about 1 hour for aspirin and acetaminophen, and between 1–2 hours for naproxen sodium, tolfenamic acid, and ibuprofen.

The headache, which occurs under the circumstances described above, has been variously and interchangeably termed a "rebound," "relapse," "recurrent," or "secondary" headache. The terms not withstanding, it is presently unknown as to whether this later headache is a continuation of the physiological chain of events that caused original headache, or a new headache due to other or repeated but unrelated underlying pathology. It is also possible that the follow on headache is a response to therapeutic agents which initially were successful in treating the initial migraine symptoms. The terms "rebound", "relapse," "recurrent" and "secondary" (as defined below) are considered synonymous as used herein without inferring a mechanism or cause of the headache described above.

It has been reported that of the 50 to 70% of patients who experience migraine symptom relief within 2 hours from initial dosing with a 5-HT agonist, 30–50% experience migraine symptoms again within the next 1–24 hours. In view of the extreme discomfort and long duration of pain that characterizes migraine headaches, a therapy that reduces or avoids rebound migraine is of substantial importance.

Note is made of certain studies illuminating aspects of migraine therapy and of observed recurrent headache after treatment with a 5-HT agonist, the teachings of which are incorporated by reference.

1. Sumatriptan-A reappraisal of its pharmacology and therapeutic efficacy in the acute treatment of migraine and cluster headache. Plosker G L et al.; *Drugs* 1994:47:622–655

2. Subcutaneous Sumatriptan in a clinical setting: The first 100 consecutive patients with acute migraine in a tertiary care center. Sheftell F D et al.; *Headache* 1994:34:67–72

3. Migraine and cluster headache—their management with sumatriptan: a critical review of the current clinical experience. Wilkinson M et al.; *Cephalalgia* 1995;15:337–357

4. Treatment of the migraine attack. Silberstein S D; *Current Opinion in Neurology* 1994;7:258–263

5. Drug therapy of migraine. Welch K M A; *New Eng. J Med*; 1993;329: 1476–1483

6. Recent advances in the acute management of migraine and cluster headaches. Kumar K L; *J Gen Int Med* 1994;9:339–348

SUMMARY OF THE INVENTION

This invention comprises a method of treating migraine in a human comprising co-timely administering of a therapeutically effective amount of a 5-HT agonist coordinated with a therapeutically effective amount of an NSAID or non-NSAID analgesic, and particularly a long-acting NSAID. In some embodiments, an additional NSAID or non-NSAID analgesic is also employed in co-timely coordinated administration. Particular note is made of ibuprofen or aspirin, each with quick onset. Particular note is further made of the non-NSAID analgesic acetaminophen. Particular attention is drawn to the method of this invention wherein the 5-HT agonist is sumatriptan. In some embodiments of this method sumatriptan administered in an amount of from about 0.01 and further from about 1 to about 300 mg, and, optionally, administration is oral, intranasal, rectal, sub-lingual, injected, inhaled or buccal. In particular embodiments wherein administering of sumatriptan is parenteral, the administered amount is about 1 to about 10 mg. For subcutaneous sumatriptan, injecting so as to establish a peak blood level of from about 1 to about 150 ng/ml is contemplated, with specific reference to a peak blood level from about 10 to about 90 ng/ml, and more specifically from about 10 to about 70 ng/ml. Pharmacologically and pharmacokinetically comparable blood levels are particularly noted embodiments for other 5-HT agonists.

In the claimed method, naproxen, or pharmaceutically acceptable salt thereof is a useful NSAID, and particularly naproxen sodium, and further when the 5-HT agonist is sumatriptan. In this method naproxen or pharmaceutically acceptable salt thereof is administered to a human in an amount of from about 100 mg to about 1500 mg, with particular reference to from about 100 mg to about 1500 mg, and more particularly from about 200 to about 600 mg. Pharmacologically and pharmacokinetically comparable doses are particularly noted embodiments for other NSAIDs and non-NSAID analgesics.

In further embodiments of the method of coadministering sumatriptan with naproxen or pharmaceutically acceptable salt thereof (e.g., naproxen sodium) is establishing a blood plasma level of from about 10 to about 150 mcg/ml of blood, and optionally from about 30 to about 80 mcg/ml.

In particular embodiments of the claimed method an 5-HT agonist and an NSAID or non-NSAID analgesic are administered simultaneously, either as separate formulations or combined in a unit dosage form.

This invention is directed to both the method of treating migraine as noted and to the specific dosage form, which is, optionally a quick dissolve tablet, trochee, capsule, caplet, dragee, or lozenge. Particular quick dissolve formulations include the 5-HT agonist sumatriptan and the NSAID naproxen, and further wherein the unit dosage form comprises from about 5 to about 100 mg. sumatriptan, and from about 200 to about 600 mg naproxen.

The method of this invention also includes administering a therapeutically effective amount of NSAID as measured subject blood levels is reached by at least about 1 hour after 5-HT agonist administration and maintained for at least about 12 hours after 5-HT agonist administration.

In yet another embodiment, the invention includes a method of treating migraine in a human comprising a combination drug therapy of co-timely administration in the treatment of rebound headache by providing a rebound headache preventing therapeutically effective amount of a 5-HT agonist coordinated with a rebound headache preventing therapeutically effective amount of a long-acting NSAID or other analgesic or combination of NSAID and other analgesic.

In an additional embodiment, the method of this invention comprising 5-HT agonist administration and long-acting NSAID administration, wherein at least one of said therapeutically effective amounts of either 5-HT agonist or the dose of NSAID or non-NSAID analgesic is sub-therapeutic (sub-MED) when used alone (a sub-minimal effective dose (MED) amount). Either the 5-HT agonist or the NSAID/non-NSAID analgesic is used in sub-MED amount or NSAID in sub-MED amount or both. While this does not exclude multiple 5-HT agonists and NSAIDs being used in treatment of a single subject, it is contemplated that particular embodiments will consist of a single 5-HT agonist, and a single long-acting NSAID, wherein one or both drugs are administered in sub-MED amounts.

The invention further includes a method of treating migraine in a human comprising co-timely administering of a therapeutically effective amount of a 5-HT agonist coordinated with a therapeutically effective amount of a non-NSAID analgesic such as acetaminophen. In some embodiments co-timely administering of a therapeutically effective amount of a 5-HT agonist coordinated with a therapeutically effective amount of a quick onset analgesic such as ibuprofen, aspirin or acetaminophen is useful.

DETAILED DESCRIPTION OF THE INVENTION

It has now been discovered that a combination therapy of a 5-HT agonist, including drugs structurally similar to 5-HT agonists like sumatriptan or like members of the ergot family of compounds, combined with a long acting nonsteroidal anti-inflammatory drug (NSAID) substantially reduces or eliminates the relapse phenomenon in a significant portion of migraineurs that otherwise experience relapse and that the combination of the two agents results in an enhanced therapeutic effect allowing for greater and/or longer lasting efficacy and/or lower doses than can be obtained with the conventional doses of either individual agent. Naproxen sodium is one such long acting NSAID and sumatriptan is one such 5-HT agonist.

This invention will best be understood with reference to the following definitions:

A. "Long acting" in relation to NSAIDs shall mean a pharmacokinetic half-life of at least about 4–6 hours and preferably about 8–14 hours and a duration of

action equal to or exceeding about 6–8 hours. Particular reference is made to flurbiprofen with a half-life of about 6 hours; ketoprofen with a half-life of about 2 to 4 hours; naproxen and naproxen sodium with half-lives of about 12 to 15 hours and about 12 to 13 hours respectively; oxaprozin with a half-life of about 42 to 50 hours; etodolac with a half-life of about 7 hours; indomethacin with a half-life of about 4 to 6 hours; ketorolac with a half-life of up to about 8–9 hours; nabumetone with a half-life of about 22 to 30 hours; mefenamic acid with a half-life of up to about 4 hours; and piroxicam with a half-life of about 4 to 6 hours.

B. "Therapeutically effective amount" as to a drug dosage, shall mean that dosage that provides the specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that migraine headache is not well understood and the etiologies of particular migraine attacks vary, as does the response to particular drugs. Thus reference to "specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment" is a recognition that a "therapeutically effective amount," administered to a particular subject in a particular instance will not abort migraine onset or relieve an actual migraine headache, even though such dosage is deemed a "therapeutically effective amount" by those skilled in the art. It is to be further understood that drug dosages are, in particular instances, measured as oral dosages, or parenteral or inhaled dosages or with reference to drug levels as measured in blood.

For 5-HT agonists and NSAIDs and non-NSAID analgesics, and particularly as to those already in the marketplace, a therapeutically effective amount shall particularly include (but not be limited to) that dosage that has been determined as safe and effective for any indication. Nevertheless, in particular applications this does not exclude substantially lesser (or greater) dosages than established minimum (or maximum) dosages for which a particular 5-HT agonist or NSAID could be used to effectively treat an episode of migraine.

Particular reference is made to the following dosages of 5-HT agonists and NSAIDs, any of which are usefully combined into single dosage forms. Concerning dosages, as there is considerable variability as to the presenting condition of subjects, the skilled practitioner is expected to adjust dosages in such regard.

Sumatriptan is usefully provided as oral tablets of 25 mg, 50 mg and 100 mg and as a parenteral dosage form containing about 6 mg/ml and about 6 mg/0.5 ml for subcutaneous administration. Oral dosages of about 1–300 mg are also useful with particular reference to doses of about 10–100 mg. Peak serum levels of approximately 1–300 ng/ml are produced with doses in these ranges. Subcutaneous injections of about 1 to 8 mg of sumatriptan are useful, with particular reference to about 3 to 6 mg doses. Injections produce peak serum levels of approximately 1 to 150 ng/ml. Other dosage forms of sumatriptan include, but are not limited to, suppositories, aerosols for inhalation or intranasal administration, and nose drops, and all are contemplated in the practice of this invention.

Ergotamine tartrate in oral doses of about 1 to 5 mg with particular reference to about 1–2 mg are useful, as are doses of about 1–2 mg at 30 minute intervals, up to about 6 to 8 mg in one day. Oral inhalation of sequential doses of about 0.1 to 0.5 mg at intervals of about 5 minutes are noted, with particular reference to doses of about 0.36 mg. Suppositories of 0.1 to 5 mg with particular reference to about 2 mg are useful.

Ergonovine maleate is administrable by injection at about 0.2 mg/ml, and oral tablets of about the same strength are also administrable.

Ergoloid mesylates (i.e. dihydroergocornine, dihydroergocristine, dihydroergocryptine (dihydro-α-ergocryptine and dihydro-β-ergocryptine) are usefully provided in tablets of from about 0.2 to 2.5 mg with particular reference to about 0.5 to about 1.0 mg tablets. Such tablets contain about 0.167 mg of each of dihydroergocornine, dihydroergocristine, and dihydroergocryptine (dihydro-α-ergocryptine and dihydro-β-ergocryptine). Liquid suspensions and liquid filled capsules of about 1 mg/ml are also useful.

Concerning NSAID dosages, as there is considerable variability as to the presenting condition of subjects, the skilled practitioner is expected to adjust dosages in such regard. Nevertheless it is noted that indomethacin is particularly useful when contained in tablets of from about 25 to 75 mg, in suppositories of about 50 mg, and in oral suspensions of about 25 mg/5 ml. A typical daily oral dosage of indomethacin is three 25 mg doses taken at intervals during one day amounting to 75 mg total, though daily doses of up to about 150 mg are also useful in some subjects. Sustained release dosage forms of indomethacin are also available and provide longer lasting blood levels than conventional tablets. In particular, a 25 mg sustained release dosage form can be used as an alternative to 25 mg three times daily or 75 mg twice daily can be substituted for 50 mg three times daily.

Ibuprofen is conveniently provided in tablets or caplets of 50, 100, 200, 300, 400, 600, and 800 mg and as a suspension of 100 mg/5 ml. Daily doses should not exceed 3200 mg and doses should be individualized. In addition, 200 mg–800 mg may be particularly useful when given 3–4 times daily.

Flurbiprofen is particularly useful when contained in tablets of from about 50 to 100 mg. Daily doses of about 100 to 500 mg, and particularly about 200 to 300 mg total are useful.

Ketoprofen is particularly useful when contained in capsules of from about 25 to 75 mg. Daily doses of about 100 to 500 mg, and particularly about 100 to 300 mg are useful, as is about 25 to about 50 mg every six to eight hours.

Naproxen is particularly useful when contained in tablets of from about 250 to about 500 mg, and in oral suspensions of about 125 mg/5 ml. For naproxen sodium, tablets of about 275 or about 550 mg are particularly useful. Initial doses of about 100 to 1250 mg, and particularly 350 to 800 mg are also useful with particular note of doses of about 550 mg.

Oxaprozin is notable for having a pharmacokinetic half-life of 42–50 hours and a bioavailability of 95%. It is usefully provided as caplets of 600 mg. Daily doses of 1200 mg have been found to be particularly useful and daily doses should not exceed 1800 mg or 26 mg/kg. The lowest effective dose should always be used.

Etodolac is usefully provided in capsules of 200 mg and 300 mg and tablets of 400 mg. Useful doses for acute pain are 200–400 mg every 6–8 hours not to exceed 1200 mg/day. Patients <60kg are advised not to exceed doses of 20 mg/kg Doses for other uses are also limited to 1200 mg per day in divided doses, particularly 2, 3, or 4 times daily.

Ketorolac is usefully provided in tablets of 10 mg and as a sterile parenteral preparation for injection in 15 mg/ml and 30 mg/ml dosage forms. Oral doses of up to 40 mg with particular reference to 10–30 mg per day and parenteral doses up to 120–150 mg per day have been useful in the amelioration of pain.

Nabumetone is usefully provided in tablets of 500 mg and 750 mg. Daily doses of up to 1500–2000 mg/day after an initial dose of 1000 mg are of particular use.

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