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(54) Title: PREVENTION OR TREATMENT OF SUNBURN USING THE S(+) ISOMER OF FLURBIPROFEN

(57) Abstract

Ultraviolet radiation induced erythema is prevented or treated in a human mammal in need of such prevention or treatment, i.e., a mammal suffering from or seeking to avoid sunburn, by topically administering thereto a unit dosage erythema-preventing or treating effective amount of the S(+) flurbiprofen enantiomer, said enantiomer being substantially free of its R(-) flurbiprofen antipode.

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PREVENTION OR TREATMENT OF SUNBURN USING THE S(+) ISOMER OF FLURBIPROFEN

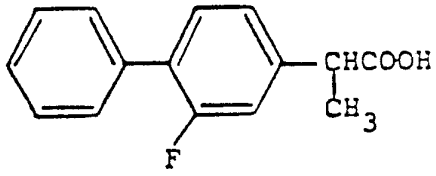
BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to the use of topically administered S(+) flurbiprofen to prevent or treat erythema induced by ultraviolet irradiation in mammalian organisms in need of such prevention or treatment, and to certain topical pharmaceutical compositions comprising unit dosage effective amounts of S(+) flurbiprofen.

Description of the Prior Art

Flurbiprofen, also known as (±)-2-fluoro-α-methyl-[1,1'-biphenyl]-4-acetic acid, as (±)-2-fluoro-α-methyl-4-biphenylacetic acid or as (±)-2-(2-fluoro-4-biphenylyl)propionic acid, is described in U.S. Patent No. 3,755,427 and has the structural formula:



The compound is well-known as a nonsteroidal anti-inflammatory drug having analgesic and antipyretic activity. Flurbiprofen is not yet marketed in the United States, but has been on the market in numerous countries overseas, including Europe, for a number of years. Tradenames and codenames by which it is known include Ansaid, Cebutid, Froben, BTS 18322 and U-27182. As Froben, the drug is available abroad as tablets containing 50 or 100 mg of flurbiprofen. For rheumatic disorders such as rheumatoid arthritis, it is recommended at a daily dose of 150 to 200 mg in divided doses of two to four per day, increased to a daily dose of 300 mg in acute conditions. See Martindale, The Extra Pharmacopoeia, 28th edition, ed. James E.F. Reynolds, London, The Pharmaceutical Press, 1982, p. 255. As an analgesic, it is usually administered at the 50 mg dosage level every 4 to 6 hours, up to 300 mg per day. Flurbiprofen has been found useful in controlling acute and chronic pain, including that associated with ankylosing spondylitis, osteoarthritis, rheumatoid arthritis, postsurgical dental pain, postsurgical gynecological pain, postpartum uterine pain, primary dysmenorrhea, cancer pain, the pain of acute gout and the pain of acute bursitis/tendinitis of the shoulder. See The American Journal of Medicine, Proceedings of a Symposium, "Control of Acute and Chronic Pain with Ansaid (Flurbiprofen)", ed. Abraham Sunshine, M.D., Volume 80 (3A), March 24, 1986.

As is apparent from its chemical nomenclature, flurbiprofen is a racemic mixture. It is only the racemic mixture which has in fact ever been marketed. There have, however, been a few isolated studies of the individual S(+) and R(-) isomers

reported in the literature. These reflect that the S(+) enantiomer, analogously to other 2-arylpropionic acids, is the active form of flurbiprofen.

Hutt et al, J. Pharm. Pharmacol., 35, 693-704 (1983), reviewed the earlier work on the metabolic chiral inversion of 2-arylpropionic acids, including ibuprofen, which they indicated was the first substituted 2-arylpropionic acid conclusively shown to undergo the inversion as well as the most studied member of the group. The authors noted that early workers found no significant difference in in vivo activity among the R(-) and S(+) isomers and the racemic mixture of flurbiprofen in three different animal models, but very large differences in vitro between the R(-) and S(+) isomers, ascribing this discrepancy to the virtually quantitative conversion of the R(-) to the active S(+) isomer in vivo.

In the same paper, Hutt et al reported that, in contrast, for several other 2-arylpropionic acids, the inactive R(-) isomer was not converted in vivo to the active S(+) isomer as readily as iubuprofen, although the conversion seemed to occur to some extent over time. Naproxen, they noted, has been the only compound marketed as the S(+) enantiomer to date. Hutt et al concluded:

> It is likely that benefits will be obtained from the use of the S(+)-enantiomer of 2-arylpropionates as drugs as opposed to the racemates. This is only found at present in the case of naproxen. In cases of rapid inversion, the inactive R(-) isomer serves merely as a prodrug for the active S(+)-antipode. Where inversion is slow, the R(-) enantiomer is an unnecessary impurity in the active S(+) form. Use of the S(+)-enantiomer would

permit reduction of the dose given, remove variability in rate and extent of inversion as a source of variability in therapeutic response and would reduce any toxicity arising from non-stereospecific mechanisms.

Thus, in cases of rapid inversion, such as flurbiprofen, where substantially equivalent in vivo responses have been reported for the individual enantiomers and the racemic drug, Hutt et al suggested that no benefits would be obtained from the use of the S(+) isomer because the inactive R(-) isomer merely acts as a prodrug for the active S(+) form. Contrariwise, in cases where chiral inversion is slow, e.g. naproxen, the use of the S(+) enantiomer is desirable for the several reasons enumerated by Hutt et al. Indeed, naproxen has been reported to be marketed as the d-isomer for one of the reasons given by Hutt et al, i.e., to reduce side effects (Allison et al, "Naproxen," Chapter 9 in Anti-inflammatory and Anti-Rheumatic Drugs, eds. Rainsford and Path, CRC Press Inc., Boca Raton, Florida, 1985, p. 172). However, the 1983 Hutt et al review is silent as to the possibility of chiral inversion in the case of flurbiprofen.

Another general report on earlier work has been provided by Hutt et al in Clinical Pharmacokinetics, 9, 371-373 (1984). In this article on the importance of stereochemical considerations in the clinical pharmacokinetics of 2-arylpropionic acids, the authors tabulated relative potencies of the enantiomers of a number of 2-arylpropionic acids in vivo and in vitro. The in vitro results showed the S or (+) isomer in each case to be the more active species. In vivo, however, the results were not

consistent across the entire class. Thus, the results for naproxen demonstrated the S or (+) isomer to be much more active in vivo, indicating a relatively slow inversion of the inactive R or (-) isomer to the active S or (+) isomer; the results for fenoprofen and flurbiprofen, on the other hand, demonstrated the inactive R or (-) and the active S or (+) isomers to be approximately equally effective in vivo, indicating a rapid inversion of R or (-) isomer to S or (+) isomer. Hutt et al indicated that flurbiprofen had an S(+)/R(-) activity ratio in vivo of 878 and in vitro 2-16; the in vitro study involved antagonism of rat SRS-A on the tracheal chain of guinea pigs and the in vivo study assessed guinea pig anaphylaxis. The reference cited by Hutt et al for the flurbiprofen studies was Greig et al, J. Med. Chem. 18, 112-116 (1975).

Greig et al, who were associated with the Upjohn Company, one of the developers of flurbiprofen, studied the antagonism of slow reacting substance in anaphylaxis (SRS-A) and other spasmogens on the guinea pig tracheal chain by hydrotropic acids. Greig et al also studied the ability of the hydrotropic acids to protect guinea pigs against anaphylaxis. Among the substances tested were racemic flurbiprofen, (+) flurbiprofen and (-) flurbiprofen.

In the in vitro testing, the (+) isomer was found to be many times more effective than the racemate; indeed, the authors found that the (-) isomer inhibited the effect of the (+) isomer in antagonism of rat SRS-A on guinea pig trachea in vitro. In the in vivo testing, Greig et al found that flurbiprofen and its isomers were active in protecting sensitized guinea pigs against anaphylactic shock when

they were challenged 4 weeks after sensitization. These results correlated well with the in vitro activity. In vivo, the (+) isomer had more than a two-fold effect over the racemate; at 80% protection, the (+) isomer was 5 to 7 times more active than the racemic mixture. The (-) isomer was the least active of the three compounds.

The Greig et al studies concerned themselves with anaphylaxis and bronchospasm; as such, they have no relevancy to analgesia inflammation, or sunburn.

Nishizawa et al, also associated with Upjohn, reported in Thrombosis Research 3, 577-588 (1973) on flurbiprofen as a potent inhibitor of platelet aggregation in animals and man. They found that the platelet anti-aggregating effect resided in the d-isomer; the l-isomer was without anti-aggregating effect and neither counteracted nor enhanced the effect of the d-isomer. The optical antipodes were tested in rats. Anti-aggregating effects, however, do not correlate with models for analgesia or inflammation.

Kulmacz et al, J. Biol. Chem. 260, 12572-12578 (1985), studied the interaction of flurbiprofen with prostaglandin H synthase. They reported that 1.2 ± 0.1 mol of S(+) flurbiprofen per mol of synthase dimer resulted in maximum inhibition of the cyclooxygenase enzyme. Racemic flurbiprofen required 2.4 ± 0.3 mol per mol synthase dimer for full effect, and the R(-) isomer was not inhibitory, even at a ratio of 2.5/dimer. From their own studies and those of Nishizawa et al in inhibiting rat platelet aggregation, Kulmacz et al concluded that the flurbiprofen isomers follow the pattern observed for

many anti-inflammatory agents, i.e., the dextrorotatory form is usually more potent pharmacologically than the levorotatory isomer. This is borne out by the teachings of Armitage et al, United States Patent No. 4,501,727, dated February 26, 1985. The Armitage et al patent relates to a novel light-stable N-methyl-D-glucamine salt of the dextrorotatory or (+) isomer. It teaches that flurbiprofen has anti-inflammatory, analgesic and antipyretic properties, and that the (+) enantiomer is the pharmacologically active isomer.

Sunshine et al, "Flurbiprofen, Flurbiprofen Dextrorotatory Component (BTS 24332), and Placebo in Postepisiotomy Pain," presented at the meeting of the Amer. Soc. Clin. Pharm. Therapeutics in Orlando, Florida in March 1987, disclosed that S(+) flurbiprofen at less than one-half the dose of the racemate was significantly more effective than the racemate for many of the analgesic parameters tested.

A considerable amount of effort has been spent in the search for a method to prevent the occurrence of, or alternatively, to treat sunburn. Sunburn is caused by certain wavelengths of ultraviolet (UV) radiation striking the skin. The ultraviolet light alters the keratinocytes in the basal layer of the epidermis. A slight alteration results in erythema, and a severe alteration causes bullae to form from the fluid collected in the epidermis. To produce a suntan, ultraviolet light stimulates the melanocytes in the germinating layer to generate more melanin and oxidizes melanin already in the epidermis. Both of these processes serve as protective mechanisms by diffusing and absorbing additional UV radiation. The effects of the sun on the skin usually begin to appear

anywhere from 1 to 24 hours after exposure and range from mild erythema to tenderness, pain, and edema. Severe reactions due to excessive exposure involve the development of vesicles or bullae as well as the constitutional symptoms of fever, chills, weakness, and shock.

Energy emissions from the sun include radiation wavelengths ranging from 200 nm to more than 18,000 nm. Ultraviolet radiation is in the 200-400 nm range, and this spectrum is subdivided into three bands.

UV-A (320-400 nm) radiation can cause tanning of the skin, but is weak in causing mild sunburn of the skin. Erythemic activity (producing redness) is relatively weak at this wavelength. The primary action of UV-A is the development of a slow natural tan. At this UV level, radiation produces some immediate pigment darkening. In addition, UV-A represents the range in which most photosensitizing chemicals are active. It is also believed that UV-A may augment the effects of UV-B.

UV-B (290-320 nm) radiation causes sunburn reaction, which also stimulates pigmentation (tanning) of the skin. It is the most effective UV radiation wavelength for producing erythema, which is why it is called sunburn radiation. It triggers new pigment formation as well as vitamin D production. In addition, it is thought to be responsible for inducing skin cancer.

UV-C (200-290 nm) radiation from sunlight does not reach the earth's surface, but artificial UV sources can emit this radiation. It does not tan the skin, but it can burn it. UV-C radiation from the sun

does not reach the surface of the earth. However, UV-C is emitted by artificial ultraviolet sources. Although it will not stimulate tanning, it causes some erythema.

Other wavelengths of light also are absorbed and, if intense enough, produce erythema and burning. This type of burning differs from sunburn in that it is due to generated heat rather than a photochemical reaction.

Thus, it has been well documented that excessive exposure to ultraviolet light will cause erythema, edema, blister formation and sloughing of the skin due to cellular damage. Ultraviolet light injury includes epidermal cell death, increase in mitotic index, hyperplasia, as well as the vascular responses of vasodilation, altered permeability and cellular exudation.

The vascular changes that occur secondary to exposure to ultraviolet light are biphasic. The immediate erythema reaction is a faint, transient reddening of the skin beginning shortly after exposure to ultraviolet light and fading within 30 minutes after the exposure ends. A delayed erythema reaction appears after 2-6 hours and peaks 10-24 hours after ultraviolet-light exposure. This erythema gradually subsides over the next 2-4 days. Peeling follows 4-7 days after a moderate to severe sunburn. The mechanisms by which these two types of erythema are produced are not understood completely. Kinins, histamine, prostaglandins, other vasoactive substances, hydrolytic enzymes, and free radicals have been implicated as mediators of the erythema caused by sunlight.

Prostaglandins have been shown to increase in erythematous skin exposed to ultraviolet B radiation. Aspirin and indomethacin which are nonsteroidal anti-inflammatory agents have been shown to inhibit the prostaglandin synthetase system in skin.

Snyder et al, "Intradermal Anti-Prostaglandin Agents and Sunburn," The Journal of Investigative Dermatology, Vol. 62, No. 1, 47-50 (1974) discussed the intradermal administration of indomethacin as well as aspirin to guinea pigs. The administration of each of those drugs was shown to decrease the intensity and delay the development of ultraviolet radiation induced erythema. Snyder et al, "Topical Indomethacin and Sunburn," British Journal of Dermatology, pp. 90-91 (1974), further demonstrated that the topical application of indomethacin in humans produced a reduction in redness, skin temperature and pain perception. It was suggested that indomethacin may be affecting sunburn by preventing biosynthesis of prostaglandins.

Likewise, several nonsteroidal anti-inflammatory drugs have been administered orally to human subjects and have been demonstrated to be effective in reducing erythema after exposure to ultraviolet radiation. In particular, Edwards et al, "Reduction of the Erythema Response to Ultraviolet Light by Nonsteroidal Anti-inflammatory Agents," Arch. Dermatol. Res., Vol. 272, pp. 263-267, studied the effect of orally administered aspirin, indomethacin and flurbiprofen on ultraviolet B induced erythema in human subjects. All three drugs were comparable in reducing the sunburn response to ultraviolet radiation.

Gomez et al, "Effect of Topical Diflumidone on Ultraviolet-Light-Induced Erythema," Dermatologica, Vol. 162, pp. 175-182 (1981) studied the topical efficacy of indomethacin and diflumidone for the suppression of ultraviolet-light-induced erythema in humans. Both indomethacin and diflumidone were found to inhibit the development of erythema; however, the indomethacin treated sites had significantly less erythema 24 hours after application.

Greenberg et al, "Orally Given Indomethacin and Blood Flow Response to UVL," Arch. Dermatol., Vol. 111, pp. 328-330 (March 1975), demonstrated that orally administered indomethacin reduced the increase in blood flow produced by ultraviolet light irradiation by one-third.

Lim et al, "Effect of Indomethacin on Alteration of ATPase-Positive Langerhans Cell Density and Cutaneous Sunburn Reaction Induced by Ultraviolet-B Radiation," Journal of Investigative Dermatology, Vol. 81, No. 5, pp. 455-458 (1983), showed that indomethacin topically applied prior to ultraviolet-B irradiation in humans resulted in protection from the sun. Topical application of indomethacin after ultraviolet-B irradiation resulted in a decrease in erythema. The protective effect of topical indomethacin applied prior to radiation may be explained by its in vitro absorption of ultraviolet-B irradiation. The application of indomethacin after irradiation resulting in decreased erythema was probably related to its effect on prostaglandin synthetase inhibition. The authors concluded that indomethacin applied topically could be useful as a sunscreen agent. Its clinical safety and efficacy, however, remain to be determined.

Flowers et al, "A Comparative Study of the Effect of Flurbiprofen and Indomethacin on Sunburn," Current Therapeutic Research, Vol. 36, No. 4, pp. 787-791 (October 1984), evaluated the efficacy of ultraviolet-B induced erythema in humans when the subjects were treated with a test solution containing 2.5% indomethacin, 2.5% flurbiprofen or vehicle alone. The authors concluded that flurbiprofen showed more promise than indomethacin in the suppression of early ultraviolet-B irradiation induced erythema.

Tas et al, "Effect of Topically Applied Flurbiprofen on Ultraviolet-Induced Erythema," Drug Intelligence and Clinical Pharmacy, Vol. 20, 496-499 (1986), studied the effect of flurbiprofen on ultraviolet-B induced erythema in humans. The authors concluded that topical flurbiprofen decreased the dermal symptoms of sunburn. The optimum maximum concentration of flurbiprofen appeared to be approximately 3% and more than two applications appeared to have no added advantage.

In summary, the current state of the art assumes that, in mammals, analogously to other 2-arylpropionic acid NSAID's, the S(+) form is the active enantiomer of flurbiprofen.

SUMMARY OF THE INVENTION

Surprisingly, the present inventors now find that S(+) flurbiprofen can be advantageously topically administered to mammals, especially humans, to prevent or treat ultraviolet radiation-induced erythema and to evoke such prevention or treatment more effectively than possible by administration of the same dose of flurbiprofen in its racemic form. S(+) flurbiprofen is

more potent than an equal amount of the racemic mixture.

This is particularly surprising in light of the art's failures to attribute any difference in activity for S(+) flurbiprofen versus the racemic mixture.

In one aspect, the present invention thus provides a method for preventing ultraviolet radiation-induced erythema in a mammal, said method comprising topically administering to a mammal exposed to ultraviolet radiation an amount effective to prevent ultraviolet radiation of S(+) flurbiprofen substantially free of R(-) flurbiprofen.

In another aspect, the present invention provides a method for treating ultraviolet radiation-induced erythema in a mammal, said method comprising topically administering to a mammal in need of such treatment an amount effective to treat ultraviolet radiation-induced erythema of S(+) flurbiprofen substantially free of R(-) flurbiprofen.

In yet another aspect, the present invention provides a pharmaceutical composition of matter for use in preventing or treating ultraviolet radiation-induced erythema in mammals, especially humans, said composition comprising an amount effective to prevent or treat ultraviolet radiation-induced erythema of S(+) flurbiprofen substantially free of R(-) flurbiprofen. Typically, S(+) flurbiprofen is associated with a nontoxic topical pharmaceutically acceptable inert carrier or diluent therefor.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS OF THE INVENTION

The term "flurbiprofen" or "racemic flurbiprofen" as used herein is intended to encompass not only (±)-2-fluoro-α-methyl-[1,1'-biphenyl]-4-acetic acid itself but also any pharmaceutically acceptable salt thereof.

The term "S(+) flurbiprofen" as used herein is intended to encompass not only the preferred free acid dextrorotatory or S(+) isomer of 2-fluoro-α-methyl-[1,1'-biphenyl]-4-acetic acid but also includes the pharmaceutically acceptable, antierythematously effective simple metal salts thereof, e.g., Na, K and Ca. The expression "substantially free of R(-) flurbiprofen" as used in conjunction with the term "S(+) flurbiprofen" means that the S(+) flurbiprofen is sufficiently free of R(-) flurbiprofen [which is the levorotatory form or R(-) isomer of 2-fluoro-α-methyl-[1,1'-biphenyl]-4-acetic acid or salt thereof] to exert the desired sustained and enhanced analgesic effect. Practically speaking, this means that the active ingredient should contain at least 90% by weight S(+) flurbiprofen and 10% or less by weight R(-) flurbiprofen. Preferably, the weight ratio of S(+) flurbiprofen to R(-) flurbiprofen is greater than or equal to 20:1, more preferably greater than 97:3. Ideally the S(+) flurbiprofen is 98, 99 or more % by weight free of R(-) flurbiprofen, i.e., the weight ratio of S to R is approximately equal to or greater than 98:2 or 99:1.

Where specific amounts of S(+) flurbiprofen are set forth below, it should be understood that, unless otherwise specified, the amounts are given in mg of the acid, not of a salt. Moreover, unless otherwise

specified, for simplicity's sake the amounts given represent total flurbiprofen content, most of which is in the S(+) form. For example, "3 wt. % flurbiprofen" means 3 wt. % of total flurbiprofen at least 90% of which is in the S(+) form, preferably at least 95%, more preferably at least 97% and most preferably 99% or more.

Topical S(+) flurbiprofen, in accord with the present invention, produces the following unexpected results:

(1) the S(+) isomer of flurbiprofen is more potent than racemic flurbiprofen for topical administration on a mammal since the flurbiprofen is substantially, or in large part, in the active form; and

(2) in the case of flurbiprofen, in man, the R(-) isomer is not active and would not substantially overcome the effects of ultraviolet-induced erythema or sunburn because there would probably be little if any chiral conversion in the skin.

These unexpected results can be achieved in the treatment of sunburn responsive to an NSAID (non-steroidal anti-inflammatory drug).

In a group responsive to a given dose of the racemate, it is believed that S(+) flurbiprofen applied in the same amount as racemic flurbiprofen would provide a better response for preventing or treating ultraviolet radiation-induced erythema. S(+) flurbiprofen would be at least twice as potent.

The precise amount of topical S(+) flurbiprofen for use in accord with the present invention will vary depending, for example, on the size

and kind of the mammal and the condition for which the drug is administered. For use in humans, the amount effective to prevent or treat ultraviolet radiation-induced erythema of S(+) flurbiprofen will typically be from about 0.5 wt. % to about 10 wt. % although greater amounts (e.g., 15 wt. %) may be employed if needed or if tolerated by the patient. The preferred composition contains about 1 wt. % to about 5 wt. %, more preferably about 2.5 to 3.5 wt. % flurbiprofen. The most preferred composition would likely contain about 3.0 wt. % flurbiprofen. It should be noted, however, that lesser amounts may be useful on patients with particularly sensitive skin and/or on the skin of children.

The S(+) flurbiprofen of the present invention may be applied in any vehicle or in any fashion suitable for topical administration. Topical preparations typically include solutions, e.g., clear or milky lotions, gels, creams, ointments, sprays, lip balm, clothwipe, impregnated bandages and other topical and transdermal delivery devices.

According to the FDA advisory review panel, "[a]n ideal sunscreen vehicle would be stable, neutral, nongreasy, nondegreasing, nonirritating, nondehydrating, nondrying, odorless, and efficient on all kinds of human skin. It should also hold at least 50% water, be easily compounded of known chemicals, and have infinite stability during storage". Federal Register, 43, 38218 (1978).

S(+) flurbiprofen may be formulated with any suitable nontoxic topical pharmaceutically acceptable inert carrier material. Such topical carrier materials are well known to those skilled in the art of

pharmaceutical formulations. For those not skilled in the art, reference is made to the text entitled Remington's Pharmaceutical Sciences, 17th edition, 1985, ed. Alfonso R. Gennaro, Mack Publishing Company, Easton, Pennsylvania 18042.

Suitable solvents or vehicles, for instance, for the topical S(+) flurbiprofen composition of the present invention includes methanol, ethanol, propyl alcohol, acetone, n-butyl alcohol, isobutyl alcohol and the like.

The primary uses of sunscreens are to prevent sunburn and aid in the development of a tan. Secondarily, they serve to protect exposed areas of the body in susceptible individuals from the long-term hazards of skin cancer and premature aging. In addition, sunscreens can be used to protect against drug-related ultraviolet-induced photosensitivity.

For purposes of the present invention, the term "sunscreen agent" shall refer to the use of S(+)-flurbiprofen as a sunscreen-sunburn preventive agent, a sunscreen-suntanning agent and/or a sunscreen-opaque sunblock agent. Each of those type of agents has been defined by the FDA advisory review panel as nonprescription topical analgesic, antirheumatic, otic, burn and sunburn prevention and treatment drug products as follows:

A sunscreen-sunburn preventive agent contains an active ingredient that absorbs 95% or more of the radiation in the ultraviolet range at wavelengths from 290-320 nm and thereby removes the sunburning rays;

A sunscreen-suntanning agent contains an active ingredient that absorbs at least 85% of the radiation in the ultra-violet range at wavelengths from

290-320 nm, but transmits ultraviolet wavelengths longer than 320 nm (such agents permit tanning in the average individual and also permits some erythema without pain);

A sunscreen-opaque sunblock agent has an opaque agent that reflects or scatters all radiation in the ultraviolet and visible range from 290-777 nm and thereby prevents or minimizes suntan and sunburn.

The following pharmaceutically acceptable topical ingredients are present in commercial sunscreens or sunblocks:

titanium dioxide, petrolatum, red petrolatum, benzophenone-3, isopropyl myristate, aloe vera extract, synthetic beeswax, cetyl palmitate, ceresin, lanolin, cetyl alcohol, alcohol, oleth-3 phosphate, synthetic spermaceti, glycerin, mineral oil, lanolin alcohol, cetyl stearyl glycol, lanolin oil, triethanolamine, carbomer 934, benzyl alcohol, menthol, camphor, essential oils, acrylic-acrylate copolymer, ammonium hydroxide, carbomer 934P, dimethicone, quaternium-15, stearic acid, stearyl alcohol, water, xanthan gum, SD alcohol 40, animal protein derivative, hydroxyethyl cellulose, choleth-24, hydroxypropyl cellulose, PPG-15 stearyl ether, propylene glycol dioctanoate, stearic acid, ozokerite, PEG-4 dilaurate, propylparaben, dihydroxyacetone, hydrocarbon oil, ointment base zinc oxide, opaque base, water-repellent cream base, caramel, perfume and flavors.

It would be advantageous for the topical composition of the present invention to have sufficient substantivity to withstand exposure of the skin to swimming, high humidity and sweating.

Generally, sunscreens should be applied approximately 30 minutes before exposure to the sun. However, there are exceptions, for instance, aminobenzoic acid and its esters are more effective if applied two hours before exposure. Pre-application of the topical S(+) flurbiprofen composition prior to sun exposure to the skin is advantageous because it allows the S(+) flurbiprofen to penetrate and perhaps bind with the skin.

The amount of S(+) flurbiprofen useful in the topical preparations of the present invention is an amount sufficient to prevent or treat ultraviolet radiation-induced erythema.

Typical unit dosage forms for topical administration will contain about 0.5 wt. % to about 10 wt. %, preferably about 1 wt. % to about 5 wt. %, more preferably about 2.5 wt. % to about 3.5 wt. %, most preferably 3.0 wt. %, S(+) flurbiprofen based on the entire weight of the composition per topical unit dose application. If the composition is intended for sustained release such as by using microcapsules or microspheres, much larger amounts of the active ingredient would of course be incorporated into an individual unit. As noted earlier, the composition and the method of the present invention is "substantially free of the R(-) flurbiprofen."

The topical S(+) flurbiprofen composition of the present invention may further be combined with other types of sun-protective and/or antierythema topical agents. Such agents may absorb 95 percent or more of the ultraviolet B radiation and thereby prevent or minimize the deleterious effects on human skin caused by excessive exposure to ultraviolet B (290 to

320 nm) and ultraviolet A (320 to 400 nm) radiation. Protection is afforded by the active chemical ingredients of a sunscreen through absorption, reflection and scattering of solar radiation impinging on the skin.

Topical sunscreens can fall within one of two categories: (1) chemical, and (2) physical sunscreens. Chemical sunscreens contain one or more UV-absorbing chemicals, and upon application of a thin and invisible film, act as filters and do not allow the penetration of ultraviolet radiation to the viable cells of the epidermis. Chemical sunscreens are usually colorless because they do not contain any visible light-absorbing chemicals and are, therefore, cosmetically acceptable to most persons provided they are a nonirritant to the skin and eyes, nonphotosensitizing, stable, nonvolatile, and nonstaining to skin and clothes. Most of the commercial topical sunscreens contain one or more ultraviolet B absorbing chemicals in a moisturizing base. More recently, many leading brand-name sunscreens also contain ultraviolet A absorbing chemicals, especially the different benzophenones. The most widely used chemical sunscreens contain para-aminobenzoic acid (PABA), PABA esters (amyldimethyl PABA and octyldimethyl PABA), benzophenones (oxybenzone and sulisobenzone), cinnamates (octylmethoxy cinnamate and cinoxate), salicylates (homomenthyl salicylate), and anthranilates. To date, more than 21 such chemicals have been declared by the U.S. FDA as safe, effective agents in protecting skin against sunburn (see Table 1), and are listed under Category I (safe and approved).

Table 1

SUNSCREEN AGENTS

Compound	Dose limits, %
p-aminobenzoic acid	5.0-15.0
glyceryl aminobenzoate	3.0-5.0
amyl p-dimethylamino benzoate (Padimate A)	1.0-5.0
2-ethylhexyl-p-dimethylamino benzoate (Padimate O)	1.4-8.0
2-ethoxy-ethylhexyl-p-methoxy cinnamate (cinnoxate)	1.0-3.0
diethanolamine-p-methoxycinnamate	8.0-10.0
ethylhexyl-p-methoxycinnamate	2.0-7.5
2,2-dihydroxy-4-methoxybenzophenone (dioxybenzone)	3.0
2-hydroxy-4-methoxybenzophenone (oxybenzone)	2.0-6.0
2-hydroxy-4-methoxybenzophenone-5-sulfonic acid (sulisobenzone)	5.0-10.0
2-ethyl-hexyl-2-cyano-3,3-diphenylacrylate	7.0-10.0
ethyl-4-bis-(hydroxypropyl)-amino benzoate	1.0-5.0
digalloyl trioleate	1.0-5.0
2-ethylhexyl-salicylate	3.0-5.0
lawsone + dihydroxyacetone	0.25-3.0
3,3,5-trimethylcyclohexyl salicylate (homosalate)	4.0-15.0
methylanthranilate	3.5-4.0
2-phenyl-benzimidazole-5-sulfonic acid	1.0-4.0
triethanolamine salicylate	5.0-12.0
red veterinary petrolatum	30.0-100
titanium dioxide	2.0-25.0

Several European sunscreen manufacturers often use p-methoxy-2-ethylhexylcinnamate, 2-phenylbenzimidazole-5-sulfonic acid, 2-phenyl-5-methoxybenzophenone, and 4-tert-butyl-4'-methoxy-dibenzoylmethane as ultraviolet A and B absorbing filters. The recommended concentration for each chemical may vary and is based on not only the solubility of the chemical in a given vehicle, but also the anticipated use of the sunscreen product as a total

or partial block for the prevention of sunburn or acquisition of suntan responses. The formulation base (vehicle) used include alcohol plus glycerol or glycol, oil-in-water or water-in-oil lotion, cream, or ointment. The vehicle in which the ultraviolet radiation absorbing chemical is incorporated can determine whether a sunscreen remains effective under the general use condition involving prolonged sunbathing, sweating (sporting activities), and swimming. This adherent property to skin, known as "substantivity," varies considerably among commercially available sunscreen formulations, some of which are retained on the skin and others of which are washed off easily after sweating or swimming.

Table 2 identifies several commercial chemical sunscreen preparations along with their ingredients and type of composition.

Table 2

Trade name	Ingredients	Type of sunscreen
PABA sunscreens:		
PreSun-15		Clear lotion
Pabanol	5% PABA in 50%-70% ethyl alcohol	Clear lotion
Sunbrella		Clear lotion
PreSun-15		Gel
PABA ester sunscreens:		
Block out	3.3% isoamyl-p-N,N-dimethyl amino-benzoate (padimate-A)	Lotion/gel
PABAFILM	3.3% isoamyl-p-N,N-dimethyl amino-benzoate (padimate-A)	Lotion/gel
Sundown	3.3% isoamyl-p-N,N-dimethyl amino-benzoate (padimate-A)	Lotion
Original Eclipse	3.5% padimate-A + 3.0% octyldimethyl PABA	Lotion
Aztec	5.0% homomenthyl salicylate + 2.5%	Lotion

		amyl-p-dimethyl aminobenzoate	
	Sea & Ski	3.3% octyldimethyl PABA	Cream
	Marbert Sun Creme	benzyliden-camphor phenylbenzimidazole-5-sulfonic acid + isopropyl dibenzoyl methane	Cream
PABA-ester combination sunscreens:			
	Coppertone Super Shade-15	7% octyldimethyl PABA + 3% oxybenzone	Milky lotion
	Total Eclipse-15	2.5% glyceryl PABA + 2.5% octyldimethyl PABA + 2.5% oxybenzone	Milky lotion
	MMM-What-A-Tan!	3.0% octyldimethyl PABA+ 2.5% benzophenone-3	Milky lotion
	PreSun-15 (water-resistant)	8% padimate-O + 3% oxybenzone	Milky lotion
	Clinique-19	phenyl-benzimidazole-5-sulfonic acid + 2.5% octyldimethyl PABA	Milky lotion
	Sundown-15 (sunblock)	7% padimate-O + 5% octylsalicylate + 4% oxybenzone	Milky lotion
	Bain de Soleil	7.0% padimate-O + 2.5% oxybenzone + 0.5% dioxybenzone	White cream
	Elizabeth Arden Suncare Creme-15	padimate-O + oxy-benzone	White cream
	Estee Lauder-15	phenyl-benzimidazole-5-sulfonic acid + dimethyl PABA	White cream
	Rubenstein Gold Beauty-15	ethyl-hexyl-p-methoxycinnamate + octyldimethyl PABA	Yellow gel
	Block Out-15	7% octyldimethyl PABA + 3% oxybenzone	Creamy lotion
	Shiseido-15	6.5% titanium dioxide + 2.5% octyldimethyl PABA + 0.3% benzophenone-3	Lotion

Non-PABA sunscreens:

Piz Buin-8	5% ethyl-hexyl-p-methoxycinnamate + 3% 2-hydroxy-4-methoxybenzophenone + 4% 2-phenyl-benzimidazole sulfonic acid	Cream
Piz Buin-8 TIScreen-15	5% ethyl-hexyl-p-methoxycinnamate + 3% 2-hydroxy-4-methoxybenzophenone	Milky lotion
Piz Buin-4	4.5% ethyl-hexyl-p-methoxycinnamate	Milky lotion
UVAL	10% 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid	Milky lotion
Coppertone	8% homomenthyl-salicylate	Lotion
Ultra Vera-20 (Cheesebrough-Ponds)	octylmethoxycinnamate + 2-hydroxy-4-methoxybenzophenone	Milky lotion
Piz Buin Gletscher Creme-15	cinnamide + dibenzoyl-methane	Yellow lotion
Piz Buin-12	4.5% octyl-methoxy-cinnamate + 4.5% zinc oxide + 4.5% talc + 2.2% benzophenone-3	Milky lotion

Physical sunscreens are usually opaque formulations and contain ingredients particulate in nature that do not selectively absorb ultraviolet radiation, but, when applied as a thin film, primarily reflect and scatter ultraviolet and visible radiation because of the size of the particles and the thickness of the film. These include titanium dioxide (5% to 20%), talc (magnesium silicate), magnesium oxide, zinc oxide, kaolin, ferric chloride, and ichthyol (ichthammol). Zinc oxide appears to be the most effective. These formulations are cosmetically unpleasing, unacceptable to many patients, and are often occlusive and messy to use.

Physical sunscreens are, however, essential for those patients who are unusually sensitive to ultraviolet radiation as well as visible radiation; these are usually applied to limited areas such as the nose, lips, or helix of the ear.

Table 3 identifies several commercial physical sunscreen preparations along with their ingredients and type of composition.

Table 3

Physical sunscreens

Tradename	Ingredients	Type of Sunscreen
A-Fil	titanium dioxide +	Cream
RV Paque	oxide + talc,	Cream
Shadow	kaolin, iron oxide,	Cream
Reflecta	or red veterinary	Cream
Covermark	petrolatum	Cream
Clinique		Cream

S(+) flurbiprofen may be combined along with any of the compounds identified in any of the Tables identified above as a topical vehicle for administration.

For cosmetic rather than therapeutic needs, the patient may desire a suntan product. In many cases, suntan products differ from sunscreens only by having a lower concentration of the sunscreen agent. The concentration of the active ingredient is an important factor in judging the use and effectiveness of a product. For example, SunDare Lotion, a suntan product, contains 1.75% cinoxate, while Maxafil Cream, a sunscreen product, contains 4% (about twice as much as the suntan product) and 5% menthyl anthranilate, a second sunscreen.

Further, the sunburn/sunscreen product of the present invention may include a burn or sunburn treatment component such as an anesthetic, antimicrobial or another ingredient.

The anesthetic component of commercial products presently include:

benzocaine, lidocaine hydrochloride, butamben picrate, dibucaine, tetracaine hydrochloride, tripelennamine, and menthol benzocaine.

The antimicrobial component of commercial products currently include:

benzethonium chloride, benzalkonium chloride, povidone-iodine, chloroxylenol, chlorobutanol, 8-hydroxyquinoline, phenol, 8-hydroxyquinoline sulfate, cresol-camphor complex, chlorothymol, methylbenzethonium chloride, triclosan, benzyl alcohol, and parahydracin.

S(+) flurbiprofen for use in the method and compositions of the present invention can be prepared by a variety of methods, such as by resolution of racemic flurbiprofen.

Maitre et al, J. Chromatogr. 299, 397-403 (1984) have resolved racemic flurbiprofen and a number of other arylpropionic acids by high-performance liquid chromatographic (HPLC) separation. The diastereoisomeric derivatives of the racemic acids with S(-) 1-phenylethylamine were synthesized and then separated by the HPLC method. The pure amides could then be used to regenerate the corresponding acids, now in optically pure form, as is well-known.

HPLC methods other than Maitre et al's for resolving enantiomers of NSAID's such as flurbiprofen,

ketoprofen and fenoprofen, and likely adaptable to resolution of flurbiprofen, include the method of Doyle et al, Pharm. Technol. 9(2), 28-32 (1985), which utilizes conversion of the racemate to its amide derivatives for effective resolution; that of Wainer et al, J. Chromatogr. 284(1), 117-124 (1984), which utilizes conversion of the drug to 1-naphthalenemethylamide derivatives; and that of Sallustio et al, J. Chromatogr., 374, 329-337 (1986), which employs conversion of the drug to the R and S derivatives of R-2-phenylethylamine.

A method for derivatizing flurbiprofen and other nonsteroidal anti-inflammatory drugs with optically active amphetamine (α-methylbenzeneethanamide) has been described by Singh et al, J. Chromatogr. Biomed. Appln. 378, 125-135 (1986). Those authors also provide a summary of the usual methods for resolving enantiomers, i.e., (1) by direct separation on chiral HPLC or GC (gas chromatographic) columns, or (2) by diastereoisomer formation, by reaction with an optically pure resolving agent, followed by chromatographic separation on an optically inactive column. Singh et al's method is a new version of the second approach, using optically active amphetamine as the resolving agent, followed by separation of the diastereoisomers by capillary gas chromatography with nitrogen-phosphorus detection. (The acid, now in optically pure form, could of course then be regenerated from the salt as is well-known.) The usual method in the art utilizes optically active α-methylbenzylamine and involves preparation of the diastereoisomeric NSAID-α-methylbenzylamide directly by means of a coupling agent (e.g., 1,1'-carbonyl-diimidazole) or via the NSAID acid chloride (prepared

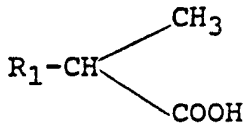
with thionyl chloride). An example of the first approach has been provided by Hermansson et al, Journal of Liquid Chromatography, 9 (2 & 3), 621-639 (1986); those authors describe direct liquid chromatographic resolution of such acidic drugs as flurbiprofen, ketoprofen, naproxen and 2-phenoxy-propionic acid, using a chiral α_1-acid glycoprotein column (Enantiopak^R).

More generally speaking, the S(+) isomer can be separated from racemic flurbiprofen by preparing a salt of flurbiprofen with an alkaloid or similar resolving agent such as cinchonidine, then separating the products by fractional crystallization from a solvent in which the dextrorotatory isomer is least soluble. The d-salt can then be acid cleaved to yield S(+) flurbiprofen. Compare, for example, Alvarez United States Patent No. 3,637,767, issued January 25, 1972, which relates to resolution of naproxen and related compounds; and Kaiser et al, J. Pharm. Sci. 65(2), 269-273 (1976), which relates to resolution of flurbiprofen.

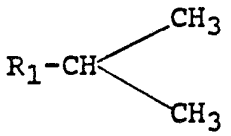
While S(+) flurbiprofen may be conveniently obtained by resolution of racemic flurbiprofen, it may also be possible to utilize a chemical or microbiological synthetic process which will provide the S(+) enantiomer directly. One such chemical process is provided by Schloemer United States Patent No. 4,542,237, which describes a process for preparing α-arylalkanoic acids utilizing novel α-hydroxy alkyl aryl ketals as intermediates. As taught in column 9 of the Schloemer patent, the process is advantageous in that the α-hydroxy ketal can be resolved by well-known methods and the optically active α-hydroxy ketal thus obtained can then be used in the subject process to

ultimately afford the desired acid in optically pure form.

Alternatively, a microbiological process such as that described in SHELL INTERNATIONALE RESEARCH MAATSCHAPPIJ B.V.'s European Patent Appln. No. 86 200987.5, published under No. 0 205215 on December 17, 1986, may be employed. According to the European application, a pharmaceutically active compound of the type



or a pharmaceutically active salt or ester thereof, which most preferably is naproxen or flurbiprofen but which may be flurbiprofen or various other NSAIDs, is prepared in stereospecific form by subjecting a compound of the formula



to the action of an appropriate microorganism. The desired acid is obtained having at least 70% by weight in the S-configuration. Preferably, a microorganism is selected such that the acid which is formed is at least 90% by weight in the S-configuration. Use of this method has afforded naproxen with enantiomeric distributions of 98.9% S and 1.1% R in one instance, and distributions of 99.5% S and 0.5% R in another. Processes of this type may be utilized to prepare S(+) flurbiprofen for use in the present invention if the S(+) isomer can be obtained in sufficient purity [ideally, at least 90% by weight S(+) isomer.]

When S(+) flurbiprofen is to be employed in the form of a pharmaceutically acceptable,

analgesically active simple metal salt thereof, such salt may be conveniently prepared by direct salification of S(+) flurbiprofen by known methods. See, for example, deVincentiis United States Patent No. 4,440,787, which describes salts of (2',4'-difluoro-4-biphenyl)oxypropionic acid with metallic ions, such as sodium, potassium, magnesium and calcium. Nonetheless, the free acid form is the preferred. Compare also Armitage et al United States Patent No. 4,501,727, issued February 26, 1985, which describes the N-methyl-D-glucamine salt of flurbiprofen. Such a salt may not only be used in oral or rectal compositions, but, because it is highly soluble in water, it may be used in the preparation of aqueous solutions of S(+) flurbiprofen salt for parenteral injection, as indicated by Armitage et al.

From the foregoing description, one of ordinary skill in the art can easily ascertain the essential characteristics of the instant invention, and without departing from the spirit and scope thereof, can make various changes and/or modifications of the invention to adapt it to various usages and conditions. As such, these changes and/or modifications are properly, equitably and intended to be within the full range of equivalents of the following claims.

WHAT IS CLAIMED IS:

1. A method for preventing or treating ultraviolet radiation-induced erythema in a human mammal exposed to ultraviolet radiation or suffering from ultraviolet radiation-induced erythema and in need of such prevention or treatment, comprising topically administering to such mammal a composition comprising a unit dosage amount effective to prevent or treat ultraviolet radiation-induced erythema of the S(+) flurbiprofen enantiomer, and said enantiomer being substantially free of its R(-) flurbiprofen antipode.

2. The method according to Claim 1, wherein the weight ratio of S(+) flurbiprofen to R(-) flurbiprofen is greater than 9:1.

3. The method according to Claim 2, wherein the weight ratio of S(+) flurbiprofen to R(-) flurbiprofen is greater than 20:1.

4. The method according to Claim 3, wherein the weight ratio of S(+) flurbiprofen to R(-) flurbiprofen is greater than 97:3.

5. The method according to Claim 4, wherein the weight ratio of S(+) flurbiprofen to R(-) flurbiprofen is approximately equal to or greater than 99:1.

6. The method according to Claim 1, comprising topically administering to such mammal from about 0.5 wt. % to about 10 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

7. The method according to Claim 1, comprising topically administering to such mammal from about 1.0 wt. % to about 5.0 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

8. The method according to Claim 1, comprising topically administering to such mammal from about 2.5 wt. % to about 3.5 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

9. The method according to Claim 2, comprising topically administering to such mammal from about 0.5 wt. % to about 10 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

10. The method according to Claim 2, comprising topically administering to such mammal from about 1.0 wt. % to about 5.0 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

11. The method according to Claim 2, comprising topically administering to such mammal from about 2.5 wt. % to about 3.5 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

12. The method according to Claim 3, comprising topically administering to such mammal from about 0.5 wt. % to about 10 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

13. The method according to Claim 3, comprising topically administering to such mammal from about 1.0 wt. % to about 5.0 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

14. The method according to Claim 3, comprising topically administering to such mammal from about 2.5 wt. % to about 3.5 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

15. The method according to Claim 4, comprising topically administering to such mammal from about 0.5 wt. % to about 10 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

16. The method according to Claim 4, comprising topically administering to such mammal from about 1.0 wt. % to about 5.0 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

17. The method according to Claim 4, comprising topically administering to such mammal from about 2.5 wt. % to about 3.5 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

18. The method according to Claim 5, comprising topically administering to such mammal from about 0.5 wt. % to about 10 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

19. The method according to Claim 5, comprising topically administering to such mammal from about 1.0 wt. % to about 5.0 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

20. The method according to Claim 5, comprising topically administering to such mammal from

about 2.5 wt. % to about 3.5 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

21. The method according to Claim 1, wherein the S(+) enantiomer is topically administered as a lotion.

22. The method according to Claim 1, wherein the S(+) enantiomer is topically administered as a gel.

23. The method according to Claim 1, wherein the S(+) enantiomer is topically administered as a solution.

24. The method according to Claim 1, wherein said composition further comprises a unit dosage amount effective to prevent or treat ultraviolet radiation-induced erythema of an additional sunscreen.

25. The method according to Claim 24, wherein said additional sunscreen is selected from the group consisting of p-aminobenzoic acid, amyldimethyl p-aminobenzoic acid, octyldimethyl p-aminobenzoic acid, octylmethoxy cinnamate, homomenthyl salicylate, glyceryl aminobenzoate, amyl p-dimethylamino benzoate 2-ethylhexyl-p-dimethylamino benzoate, 2-ethoxy-ethylhexyl-p-methoxy cinnamate, diethanolamine-p-methoxycinnamate, ethylhexyl-p-methoxycinnamate, 2,2-dihydroxy-4-methoxybenzophenone, 2-hydroxy-4-methoxybenzophenone, 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid, 2-ethyl-hexyl-2-cyano-3,3-diphenylacrylate, ethyl-4-bis-(hydroxypropyl)-amino benzoate, digalloyl trioleate, 2-ethylhexyl-salicylate,

lawsone + dihydroxyacetone, 3,3,5-trimethylcyclohexyl salicylate, methylanthranilate, 2-phenyl-benzimidazole-5-sulfonic acid, triethanolamine salicylate, red veterinary petrolatum and titanium dioxide.

26. The method according to Claim 25, wherein said additional sunscreen is selected from the group consisting of para-aminobenzoic acid, amyldimethyl para-aminobenzoic acid, octyldimethyl para-aminobenzoic acid, 2-hydroxy-4-methoxybenzophenone and 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid.

27. The method according to Claim 26, wherein said additional sunscreen is para-aminobenzoic acid.

28. A pharmaceutical composition of matter adapted for topical administration for preventing or treating ultraviolet radiation-induced erythema in a human mammal exposed to ultraviolet radiation or suffering from ultraviolet radiation-induced erythema, said composition comprising a unit dosage topically effective amount to prevent or treat ultraviolet radiation-induced erythema of the S(+) flurbiprofen enantiomer, said enantiomer being substantially free of its R(-) flurbiprofen antipode, and a nontoxic topical pharmaceutically acceptable carrier or diluent therefor.

29. The composition according to Claim 28, wherein the weight ratio of S(+) flurbiprofen to R(-) flurbiprofen is greater than 9:1.

30. The composition according to Claim 29, wherein the weight ratio of S(+) flurbiprofen to R(-) flurbiprofen is greater than 20:1.

31. The composition according to Claim 30, wherein the weight ratio of S(+) flurbiprofen to R(-) flurbiprofen is greater than 97:3.

32. The composition according to Claim 31, wherein the weight ratio of S(+) flurbiprofen to R(-) flurbiprofen is approximately equal to or greater than 99:1.

33. The composition according to Claim 28, comprising about 0.5 wt. % to about 10 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

34. The composition according to Claim 28, comprising about 1.0 wt. % to about 5.0 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

35. The composition according to Claim 28, comprising about 2.5 wt. % to about 3.5 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

36. The composition according to Claim 29, comprising about 0.5 wt. % to about 10 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

37. The composition according to Claim 29, comprising about 1.0 wt. % to about 5.0 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

38. The composition according to Claim 29, comprising about 2.5 wt. % to about 3.5 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

39. The composition according to Claim 30, comprising about 0.5 wt. % to about 10 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

40. The composition according to Claim 30, comprising about 1.0 wt. % to about 5.0 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

41. The composition according to Claim 30, comprising about 2.5 wt. % to about 3.5 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

42. The composition according to Claim 31, comprising about 0.5 wt. % to about 10 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

43. The composition according to Claim 31, comprising about 1.0 wt. % to about 5.0 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

44. The composition according to Claim 31, comprising about 2.5 wt. % to about 3.5 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

45. The composition according to Claim 32, comprising about 0.5 wt. % to about 10 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

46. The composition according to Claim 32, comprising about 1.0 wt. % to about 5.0 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

47. The composition according to Claim 32, comprising about 2.5 wt. % to about 3.5 wt. % S(+) flurbiprofen, based on the weight of the entire composition.

48. The composition according to Claim 28, wherein the S(+) enantiomer is topically administered as a lotion.

49. The composition according to Claim 28, wherein the S(+) enantiomer is topically administered as a gel.

50. The composition according to Claim 28, wherein the S(+) enantiomer is topically administered as a solution.

51. The composition according to Claim 28, wherein said composition further comprises a unit dosage amount effective to prevent or treat ultraviolet radiation-induced erythema of an additional sunscreen.

52. The composition according to Claim 51, wherein said additional sunscreen is selected from the group consisting of p-aminobenzoic acid, amyldimethyl p-aminobenzoic acid, octyldimethyl p-aminobenzoic acid, octylmethoxy cinnamate, homomenthyl salicylate, glyceryl aminobenzoate, amyl p-dimethylamino benzoate 2-ethylhexyl-p-dimethylamino benzoate, 2-ethoxy-ethylhexyl-p-methoxy cinnamate, diethanolamine-p-methoxycinnamate, ethylhexyl-p-methoxycinnamate, 2,2-dihydroxy-4-methoxybenzophenone, 2-hydroxy-4-methoxybenzophenone, 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid, 2-ethyl-hexyl-2-cyano-3,3-diphenylacrylate, ethyl-4-bis-(hydroxypropyl)-amino benzoate, digalloyl trioleate, 2-ethylhexyl-salicylate, lawsone + dihydroxyacetone, 3,3,5-trimethylcyclohexyl salicylate, methylanthranilate, 2-phenyl-benzimidazole-5-sulfonic acid, triethanolamine salicylate, red veterinary petrolatum and titanium dioxide.

53. The composition according to Claim 52, wherein said additional sunscreen is selected from the group consisting of para-aminobenzoic acid, amyldimethyl para-aminobenzoic acid, octyldimethyl para-aminobenzoic acid, 2-hydroxy-4-methoxybenzophenone and 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid.

54. The composition according to Claim 53, wherein said additional sunscreen is para-aminobenzoic acid.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/06881

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

IPC(5): A61K 7/42; A61K 7/44; A61K 31/60; A61K 31/62; A61K 31/19

U.S. CL.: 424/59; 424/60; 514/159; 514/161; 514/570

II **FIELDS SEARCHED**

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S. CL.	424/59; 424/60; 514/159; 514/161; 514/570

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 *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	US,A, 4,393,076 (NODA et al.) 12 JULY 1983 See the entire document	1-23 and 28-54
Y	US,A, 3,019,165 (NANSOR) 30 JANUARY 1962 See the entire document	24-27
Y	US,A, 3,068,153 (MOREHOUSE) 11 DECEMBER 1962 See the entire document	24-27
Y	US,,A 3,275,520 (SIROBEL et al.) 27 SEPTEMBER 1966 See the entire document	24-27

* Special categories of cited documents: [10]

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IV. **CERTIFICATION**

Date of the Actual Completion of the International Search

03 JANUARY 1992

Date of Mailing of this International Search Report

19 FEB 1992

International Searching Authority

ISA/US

Signature of Authorized Officer

KEVIN E. WEDDINGTON