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(54) Titre : COMPOSITIONS PHARMACEUTIQUES COMPRENANT DU FLURBIPROFENE
(54) Title: PHARMACEUTCAL COMPOSITIONS COMPRISING FLURBIPROFEN

(57) Abrégé/Abstract:
The present invention relates to the use of flurbiprofen in the treatment of sore throats which comprises the administration to a patient in need of such treatment of a pharmaceutical composition in the form of a masticable or suckable solid dosage form or a spray containing a therapeutically effective amount of flurbiprofen which releases the flurbiprofen in the oral cavity so as to deliver the flurbiprofen to the surface of the sore throat.

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(57) Abstract

The present invention relates to the use of flurbiprofen in the treatment of sore throats which comprises the administration to a patient in need of such treatment of a pharmaceutical composition in the form of a masticable or suckable solid dosage form or a spray containing a therapeutically effective amount of flurbiprofen which releases the flurbiprofen in the oral cavity so as to deliver the flurbiprofen to the surface of the sore throat.

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TITLE: **PHARMACEUTICAL COMPOSITIONS COMPRISING FLURBIPROFEN**

PHARMACEUTICAL COMPOSITIONS COMPRISING FLURBIPROFEN

The present invention relates to a new medical use of flurbiprofen. Flurbiprofen [2-(2-fluoro-4-biphenylyl)propionic] acid is a well known non-steroidal anti-inflammatory drug which also has analgesic and antipyretic activity. The flurbiprofen molecule exists in two enantiomeric forms and the term flurbiprofen as used herein is intended to embrace the individual enantiomers and mixtures thereof in any proportion including a 1:1 mixture which is herein referred to as racemic flurbiprofen. Flurbiprofen can exist in the form of pharmaceutically acceptable salts or in the form of derivatives such as esters and such salts or esters are embraced by the term "flurbiprofen" as used herein.

Flurbiprofen and its S(+) enantiomer have been proposed for treating medical conditions of the gums.

EP 137668-A (Upjohn) describes the use of flurbiprofen for preventing or inhibiting alveolar bone resorption.

EP 486561-A (Sepracor) describes the use of S(+)-flurbiprofen to treat periodontal disease and to promote bone regrowth associated with the disease. Periodontal disease is stated to include periodontitis, gingivitis and periodontosis.

Both these documents specifically describe the treatment of the gums and do not relate to any other part of the oral cavity.

One aspect of the present invention provides a suckable solid dosage form comprising 2.5 to 20mg of flurbiprofen contained in a lozenge base formed by cooling a sugar-based or sugar alcohol-based molten mass, such that when the dosage form is administered to the oral cavity of a patent in need thereof and sucked the solid dosage form releases a therapeutically effective amount of flurbiprofen to the oral cavity so as deliver said flurbiprofen to the surface of the throat of said patient for the treatment of sore throat.

A further aspect of the present invention relates to the use of a

pharmaceutical composition in the form of a suckable solid dosage form comprising 2.5 to 20 mg of flurbiprofen formed by cooling a sugar-based or sugar alcohol-based molten mass containing the flurbiprofen, in the manufacture of a medicament for treating sore throat so that on administering the dosage form to the oral cavity of a patient in need thereof, the solid dosage form releases a therapeutically effective amount of flurbiprofen to the oral cavity so as to deliver said flurbiprofen to the surface of the throat of said patient.

The solid dosage form preferably comprises 5 to 12.5 flurbiprofen.

The solid dosage form may be a lozenge. The term "lozenge" as used herein is intended to embrace all dosage forms where the product is formed by cooling a sugar-based or sugar alcohol based (eg sorbitol) molten mass containing the active material.

A preferred solid dosage form is a lozenge prepared by cooling a heated lozenge base comprising sugar, liquid glucose, flurbiprofen and other excipients to form solid lozenges.

The therapeutically effective amount has been found to be from 5% to 40% of the normal adult dose when given by ingestion to achieve a systemic anti-inflammatory and/or analgesic effect. Flurbiprofen may therefore be present in the pharmaceutical composition in an amount from 2.5 to 20 mg preferably 5 to 12.5 mg. Where a pharmaceutically acceptable salt of flurbiprofen is used, the amount of the salt used should be such as to provide the desired amount of flurbiprofen. Suitable salts include the alkali metal salts eg the sodium salt or amino acid salts eg the lysine, arginine or meglumine salts of flurbiprofen.

Flurbiprofen would be expected, in common with other non-steroidal anti-inflammatory agents, to cause an unpleasant burning sensation at the back of the mouth when retained in the mouth. This would clearly be unacceptable to the patient being treated. The present applicants have surprisingly found that an unacceptable burning sensation is not experienced when the present invention is used to treat a sore throat but that the patient does receive relief of the symptoms of the sore throat.

Solid dosage forms may be prepared by methods which are well known in the art for the production of lozenges and may contain other ingredients known in such dosage forms such as acidity regulators, opacifiers, stabilising agents, buffering agents, flavourings, sweeteners, colouring agents, and preservatives. For example, the preferred solid formulations of the present invention may be prepared as lozenges by heating the lozenge base (eg a mixture of sugar and liquid glucose) under vacuum to remove excess water and the remaining components are then blended into the mixture. The resulting mixture is then drawn into a continuous cylindrical mass from which the individual lozenges are formed. The lozenges are then cooled, subjected to a visual check and packed into suitable packaging. One form of suitable packaging is a blister pack of a water-impermeable plastics material (eg polyvinylchloride) closed by a metallic eg aluminium foil. The patient removes the lozenge by applying pressure to the blister to force the lozenge to rupture and pass through the metal foil seal. Lozenges will normally be sucked by the patient to release the flurbiprofen.

The preferred formulations for use in the present invention are compositions which can be sucked by the patient and which slowly release the flurbiprofen. The flurbiprofen then passes over the mucous membrane of the throat where some is absorbed providing topical relief. The unabsorbed flurbiprofen is then ingested by the patient and absorbed into the blood stream. The flurbiprofen so absorbed can act systematically to provide analgesia, anti-inflammatory and anti-pyretic activity in addition to the relief that comes from the topical application of flurbiprofen to the mucous membrane of the throat.

The invention will be illustrated by the following Examples which are given by way of example only.

Examples 1 to 4

Lozenges were prepared containing the following ingredients expressed as the weight in milligrammes per lozenge.

	Ex 1	E 2	Ex 3	Ex 4
Racemic flurbiprofen	2.5	5	8.75	12.5
Flavouring (cherry)	7.05	7.05	7.05	7.05
Calcium carbonate	7.5	7.5	7.5	7.5
Silicon Dioxide (Aerosil 300*)	0.75	0.938	0.94	1.5
Solids from a 1:1 mixture of sugar and liquid glucose	to 2350	to 2350	to 2350	to 2350

The mixture of the sugar and liquid glucose was heated to 140° and a vacuum applied to reduce the water content of the mixture. The flavouring was added in a sealed vessel. The flurbiprofen, silicon dioxide (flow aid) and calcium carbonate were blended and the blend added to the remainder of the ingredients. The resulting mixture was cooled and formed into a continuous cylindrical mass from which the individual lozenges were formed. The individual solid lozenges were visually inspected and then packed.

The resulting lozenges were found to provide palatable, stable and effective treatment for sore throats.

* Trade mark

Examples 5 to 7

In a similar manner to that described in Examples 1 to 4 above, lozenges were made containing the following ingredients expressed as the weight in milligrammes per lozenge.

	Ex 5	Ex 6	Ex7
Racemic flurbiprofen	5	8.75	12.5
Levomenthol	4	4	4
Flavouring (orange)	1.645	1.645	1.645
Flavouring (grapefruit)	2.5	2.5	2.5
Sodium saccharin	2	2	2
Calcium Carbonate	7.5	7.5	7.5
Silicon Dioxide (Aerosil 300*)	0.94	1.22	1.5
Solids from a 1:1 mixture of sugar and liquid glucose	to 2350	to 2350	to 2350

Examples 8 and 9

In a similar manner to that described in Examples 1 to 4 above, lozenges were made containing the following ingredients expressed as the weight in milligrammes per lozenge.

	Ex 8	Ex9
Racemic Flurbiprofen	5	12.5
Levomenthol	1.551	1.551
Flavouring (orange)	1.645	1.645
Peppermint Oil	2	2
Aspartame	4	4
Calcium Carbonate	7.5	7.5
Silicon Dioxide (Aerosil 300*)	0.94	1.5
Solids from a 1:1 mixture of sugar and liquid glucose	to 2350	to 2350

* Trade mark

Examples 10 and 11

In a similar manner to that described in Examples 1 to 4 above, lozenges were made containing the following ingredients expressed as the weight in milligrammes per lozenge.

	Ex 10	Ex 11
Racemic Flurbiprofen	5	12.5
Levomenthol	4	4
Flavouring (orange)	1.645	1.645
Flavouring (lime)	2.5	2.5
Aspartame	4	4
Calcium Carbonate	7.5	7.5
Silicon Dioxide (Aerosil 300*)	0.94	1.5
Solids from a 1:1 mixture of sugar and liquid glucose	to 2350	to 2350

Examples 12 and 13

In a similar manner to that described in Examples 1 to 4 above, lozenges were made containing the following ingredients expressed as the weight in milligrammes per lozenge.

	Ex 12	Ex 13
Racemic Flurbiprofen	5	12.5
Levomenthol	4	4
Flavouring (lime)	2.5	2.5
Aspartame	4	4
Calcium Carbonate	7.5	7.5
Silicon Dioxide (Aerosil 300*)	0.94	1.5
A 1:1 mixture of sugar and liquid glucose	to 2350	to 2350

* Trade mark

The effectiveness of the treatment has been demonstrated by means of clinical trials in which patients suffering from sore throats are administered

the formulations described in one of Examples 2, 3 and 4 or a placebo. The patient was asked to assess the effectiveness of the treatment on parameters such as the relief of the pain associated with the sore throat, the reduction in the swelling of the throat and/or the improvement in swallowing following treatment. The patients were also examined by a clinician to determine the amount of tonsillopharyngitis.

CLAIMS

1. A suckable solid dosage form comprising 2.5 to 20 mg of flurbiprofen contained in a lozenge base formed by cooling a sugar-based or sugar alcohol-based molten mass, such that when the dosage form is administered to the oral cavity of a patient in need thereof and sucked the solid dosage form releases a therapeutically effective amount of flurbiprofen to the oral cavity so as to deliver said flurbiprofen to the surface of the throat of said patient for the treatment of sore throat.

2. A solid dosage form as claimed in claim 1 comprising 5 to 12.5 mg of flurbiprofen.

3. Use of flurbiprofen in the manufacture of a medicament for treating sore throat wherein the medicament is in the form of a suckable solid dosage form comprising 2.5 to 20 mg of flurbiprofen formed by cooling a sugar-based or sugar alcohol-based molten mass containing the flurbiprofen, so that on administering the dosage form to the oral cavity of a patient in need thereof, the solid dosage form releases a therapeutically effective amount of flurbiprofen to the oral cavity so as to deliver said flurbiprofen to the surface of the throat of said patient.

4. The use as claimed in claim 3 wherein the solid dosage form comprises 5 to 12.5 mg of flurbiprofen.