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(21) International Application Number: PCT/EP96/05208 (22) International Filing Date: 21 November 1996 (21.11.96) (30) Priority Data: 9523833.3 22 November 1995 (22.11.95) GB (71) Applicant (for all designated States except US): THE BOOTS COMPANY PLC [GB/GB]; 1 Thane Road West, Nottingham NG2 3AA (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BARRETT, David, Michael [GB/GB]; The Boots Company plc, 1 Thane Road West, Nottingham NG2 3AA (GB). SMITH, Carl, Simon [GB/GB]; The Boots Company plc, 1 Thane Road West, Nottingham NG2 3AA (GB). THURGOOD, David, Michael [GB/GB]; The Boots Company plc, 1 Thane Road West, Nottingham NG2 3AA (GB). (74) Agent: THACKER, Michael, Anthony; The Boots Company plc, Group Patents Dept. D31, 1 Thane Road West, Nottingham NG2 3AA (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING FLURBIPROFEN		
(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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PHARMACEUTICAL COMPOSITIONS COMPRISING FLURBIPROFEN

The present invention relates to a new medical use of flurbiprofen. Flurbiprofen [2-(2-fluoro-4-biphenyl)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.

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.

5 The solid dosage form may be a lozenge which is intended to be sucked by the patient or a masticable or suckable tablet, capsule, pastille or gum, for example chewing gum. 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
10 the active material. The term "tablet" as used herein is intended to embrace unit dosage forms made from compressed powders or granules or compressed pastes. A preferred pharmaceutical composition is a lozenge prepared by cooling a heated lozenge base comprising sugar, liquid glucose, flurbiprofen and other excipients to form solid lozenges.

15 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 antiinflammatory 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
20 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
25 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, tablets, capsules or chewing gums and may contain other ingredients known in such dosage forms such as acidity regulators, opacifiers, stabilising agents, buffering agents, flavourings, sweeteners, colouring 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. Masticable solid dose formulations may be made by the methods used to prepare chewable candy products or chewing gums. For example, a chewable solid dosage form may be prepared from an extruded mixture of sugar and glucose syrup to which the flurbiprofen has been added with optional addition of whipping agents, humectants, lubricants, flavours and colourings. (See Pharmaceutical Dosage Forms: Tablets, Volume 1, Second Edition edited by H A Lieberman, L Lachman and J B Schwartz published in 1989).

Spray formulations may be prepared by dissolving or suspending the flurbiprofen in a liquid medium which may also contain other ingredients such as stabilising agents, buffering agents, flavourings, sweeteners, colouring

agents, buffering agents, flavourings, sweeteners, colouring agents and preservatives. For example, a spray may be prepared by dissolving water soluble components in water and non-water soluble ingredients in a co-solvent (eg alcohol). The two phases are then mixed and the resulting mixture filtered
5 and placed into dispensing containers. The dispensing containers may be fitted with a metered, manually-operated spray mechanism or the dispenser may contain a pressurised propellant and be fitted with a suitable dispensing valve.

One form of preferred formulations for use in the present invention are
10 compositions which can be sucked or chewed 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
15 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.

A second form of preferred formulations for use in the present invention are sprays which are administered so that the liquid composition is
20 brought into contact with the mucus membrane of the throat so that some of the active ingredient is absorbed providing topical relief. Ingestion of the liquid composition then means that the unabsorbed flurbiprofen can be absorbed in to the blood stream to provide systemic analgesic, anti-inflammatory or antipyretic activity in addition to the relief that comes from the topical
25 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
5	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	to	to	to	to
10	and liquid glucose	2350	2350	2350	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.

20 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	Ex 7
	Racemic flurbiprofen	5	8.75	12.5
	Levomenthol	4	4	4
	Flavouring (orange)	1.645	1.645	1.645
5	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	to	to	to
10	and liquid glucose	2350	2350	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	Ex 9
	Racemic Flurbiprofen	5	12.5
	Levomenthol	1.551	1.551
	Flavouring (orange)	1.645	1.645
20	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	to	to
25	liquid glucose	2350	2350

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.

5		Ex 10	Ex 11
	Racemic Flurbiprofen	5	12.5
	Levomenthol	4	4
	Flavouring (orange)	1.645	1.645
	Flavouring (lime)	2.5	2.5
10	Aspartame	4	4
	Calcium Carbonate	7.5	7.5
	Silicone Dioxide (Aerosil 300)	0.94	1.5
	Solids from a 1:1 mixture of sugar and liquid glucose	to 2350	to 2350
15			

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.

20		Ex 12	Ex 13
	Racemic Flurbiprofen	5	12.5
	Levomenthol	4	4
	Flavouring (lime)	2.5	2.5
	Aspartame	4	4
25	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

Example 14

The following components were mixed to provide a pharmaceutical formulation which can be packed into a dispensing container fitted with a metered manually-operated spray mechanism which enables the formulation to be sprayed on to the mucus membrane of the throat as a fine spray. All percentages are by weight of the final formulation.

	Racemic Flurbiprofen	0.624%
	Alcohol	34.71%
	Sorbitol (70% solution)	13.90%
10	Glycerin	13.58%
	Colours, flavouring	qs
	Water	to 100%

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. The use of flurbiprofen for the preparation of a medicament in the form of a masticable or suckable solid dosage form or a spray intended to release a therapeutically effective amount of flurbiprofen in the oral cavity so as to
5 deliver the flurbiprofen to the surface of the throat for the treatment of sore throat.
2. 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
10 composition in the form of a masticable or suckable solid dosage form or a spray containing a therapeutically effective amount of flurbiprofen and which releases the flurbiprofen in the oral cavity so as to deliver the flurbiprofen to the surface of the sore throat.
- 15 3. A method of treating a sore throat comprising the administration of a therapeutically effective amount of flurbiprofen to the surface of the sore throat from a pharmaceutical composition in the form of a masticable or suckable solid dosage form or a spray.
- 20 4. A use or method as claimed in any preceding claim wherein the amount of flurbiprofen is from 2.5 to 20 mg per unit dose.
5. A use or method as claimed in claim 4 wherein the amount of flurbiprofen is from 5 to 12.5 mg per unit dose.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/05208

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/19 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 190 981 A (W.J.WECHTER) 2 March 1993 see claims ---	1-5
Y	US 5 206 029 A (K. BRUNE) 27 April 1993 see claims ---	1-5
Y	WO 92 00725 A (FARCON) 23 January 1992 see the whole document ---	1-5
Y	WO 91 02512 A (SEPRACOR) 7 March 1991 cited in the application see the whole document ---	1-5
Y	WO 88 03021 A (UPJOHN) 5 May 1988 see the whole document ---	1-5
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

14 April 1997

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 137 668 A (UPJOHN) 17 April 1985 cited in the application see the whole document ---	1-5
Y	US 4 389 393 A (J.M.SCHOR ET AL.) 21 June 1983 see the whole document ---	1-5
Y	DATABASE WPI Week 9145 Derwent Publications Ltd., London, GB; AN 91-328376 [45] XP002029359 see abstract & JP 03 218 308 A (LION CORP.) 25 September 1991 ---	1-5
Y	DATABASE WPI Week 8832 Derwent Publications Ltd., London, GB; AN 88-223002 [32] XP002029360 see abstract & JP 63 156 715 A (TEISAN SEIYAKU KK) 29 June 1988 -----	1-5

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 96/05208

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 3-5
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
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3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest☐ The additional search fees were accompanied by the applicant's protest.☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 96/05208

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5190981 A	02-03-93	AT 117892 T AU 645516 B AU 6171890 A CA 2064722 A DE 69016665 D DE 69016665 T EP 0486561 A ES 2067754 T JP 4507420 T WO 9102512 A	15-02-95 20-01-94 03-04-91 18-02-91 16-03-95 24-05-95 27-05-92 01-04-95 24-12-92 07-03-91
US 5206029 A	27-04-93	DE 4028906 A AU 654498 B AU 8335291 A CA 2087723 A WO 9204018 A EP 0607128 A JP 6500313 T US 5200198 A	19-03-92 10-11-94 30-03-92 13-03-92 19-03-92 27-07-94 13-01-94 06-04-93
WO 9200725 A	23-01-92	IT 1243342 B AU 8093591 A CA 2066731 A EP 0491897 A	10-06-94 04-02-92 14-01-92 01-07-92
WO 9102512 A	07-03-91	AT 117892 T AU 645516 B AU 6171890 A CA 2064722 A DE 69016665 D DE 69016665 T EP 0486561 A ES 2067754 T JP 4507420 T US 5190981 A	15-02-95 20-01-94 03-04-91 18-02-91 16-03-95 24-05-95 27-05-92 01-04-95 24-12-92 02-03-93
WO 8803021 A	05-05-88	AU 8320387 A EP 0321505 A JP 2500189 T	25-05-88 28-06-89 25-01-90

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 96/05208

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 137668 A	17-04-85	BE 900481 A DE 3428729 A JP 6047532 B JP 60061524 A	28-02-85 18-04-85 22-06-94 09-04-85
US 4389393 A	21-06-83	AR 230569 A BE 896136 A BR 8300260 A CA 1188614 A CH 655241 A DE 3309516 A FR 2523845 A GB 2117239 A,B JP 1740831 C JP 4015208 B JP 58174311 A JP 61178916 A NL 8301042 A SE 453797 B SE 8301579 A	31-05-84 01-07-83 28-08-84 11-06-85 15-04-86 01-12-83 30-09-83 12-10-83 15-03-93 17-03-92 13-10-83 11-08-86 17-10-83 07-03-88 27-09-83