



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 37/30, 47/26, 47/10 A61K 9/00	A1	(11) International Publication Number: WO 93/06854 (43) International Publication Date: 15 April 1993 (15.04.93)
(21) International Application Number: PCT/EP92/02321 (22) International Filing Date: 8 October 1992 (08.10.92) (30) Priority data: MI91A002703 11 October 1991 (11.10.91) IT (71) Applicant (for all designated States except US): SMITH- KLINE BEECHAM FARMACEUTICI S.P.A. [IT/IT]; Via Zambelletti, I-20021 Baranzate di Bollate (IT). (72) Inventors; and (75) Inventors/Applicants (for US only) : CHIODINI, Laura [IT/ IT]; FONIO, Teodoro [IT/IT]; PINZA, Mario [IT/IT]; Smithkline Beecham Farmaceutici S.p.A., Via Zambellet- ti, I-20021 Baranzate di Bollate (IT).		(74) Agent: FLORENCE, Julia, A.; Corporate Patents, Smith- Kline Beecham, Mundells, Welwyn Garden City, Hert- fordshire AL7 1EY (GB). (81) Designated States: AU, BR, CA, JP, KR, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>
(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING A CALCITONIN, A GLYCYRRHIZINATE AS AB- SORPTION ENHANCER AND BENZYL (57) Abstract Pharmaceutical compositions comprising a calcitonin, an effective amount of an absorption enhancer which is a glycyrrhizinate, an effective amount of benzyl alcohol and a pharmaceutically acceptable carrier are useful in the treatment of conditions such as osteoporosis.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	LI	Liechtenstein	SK	Slovak Republic
CI	Côte d'Ivoire	LK	Sri Lanka	SN	Senegal
CM	Cameroon	LU	Luxembourg	SU	Soviet Union
CS	Czechoslovakia	MC	Monaco	TD	Chad
CZ	Czech Republic	MG	Madagascar	TG	Togo
DE	Germany	ML	Mali	UA	Ukraine
DK	Denmark	MN	Mongolia	US	United States of America
ES	Spain			VN	Viet Nam
FI	Finland				

PHARMACEUTICAL COMPOSITIONS COMPRISING A CALCITONIN, A GLYCYRRHIZINATE AS ABSORPTION ENHANCER AND BENZYL

The present invention relates to novel pharmaceutical compositions containing calcitonins, and to a novel method of enhancing the absorption of a calcitonin across a mucosal membrane.

The calcitonins are a class of pharmacologically active peptides, of both natural and synthetic origin, which contain approximately thirty two amino acids, and which have the ability to regulate serum calcium levels.

Various calcitonins, including e.g. natural human, salmon and eel calcitonins and the synthetic eel calcitonin analogue elcatonin are now commercially available and commonly employed, e.g. in the treatment of Paget's disease, Sudeck's disease and osteoporosis.

A considerable and well known problem with the administration of peptides is that they are susceptible to rapid acid and enzyme-induced degradation when administered orally. For this reason, parenteral administration has been, hitherto, the most widely used means of administration and, in the case of peptides of higher molecular weight, such as the calcitonins, has been the only significant effective means of administration.

It is widely recognised that administration by injection can be both inconvenient and unpleasant for the patient, particularly when the administration has to be repeated at regular intervals for long periods, e.g. in the treatment of post-menopausal osteoporosis with calcitonins. Thus, there has been growing interest in the administration of peptides by more acceptable non-invasive alternative routes, for example in the form of sublingual tablets, suppositories, intrapulmonary powders, intranasal drops, sprays, powders, gels, ointments and inserts.

A significant problem with many peptides, particularly those of higher molecular weights, is that they are only poorly absorbed across biological membranes, e.g. mucosal membranes, and thus the bioavailability of the peptide is often very low. Considerable research has therefore been carried out in order to find methods of improving the trans-epithelial absorption of peptides. One approach is to use an adjuvant or absorption enhancer and there are numerous published reports of compounds which are claimed to have peptide absorption-enhancing properties.

Thus, for example, choline esters (EP 214898), acyl carnitines (EP 215697), aldoses and glucosamines (Japanese Pat. Appl. No. 61 126034), ascorbates and salicylates (EP 37943), alpha-cyclodextrin (EP 0094157), pyroglutamate esters (EP 173990), chelating agents (US 4,476,116) ethanol, benzyl alcohol and polyethylene glycol 400 (EP 371010) have been proposed as absorption enhancers.

There are many published reports that surfactants can enhance the absorption of polypeptides, see for example EP 115627 (Armour), GB 2,127,689 (Sandoz), US 4,548,922 (Carey *et al*) and Hirai *et al.*, *Int. J. Pharm.*, 9, 165-184, 1981. However, a recognised problem with surfactant absorption promoters is that they can cause irritation and histolesion at the site of administration. These problems become of great importance when the peptide is administered regularly over a prolonged period.

The present applicants have previously found that glycyrrhizinic acid and its salts are excellent absorption promoters for calcitonins and do not give rise to the above-mentioned problems of local toxicity and irritation. Compositions comprising a calcitonin and a glycyrrhizinate are described in our EPA 327756, which includes both liquid and solid formulations. Liquid formulations conventionally contain a preservative and EPA 327756 refers to the use of

alkyl p-hydroxybenzoates (parabens) such as methyl and propyl p-hydroxybenzoate as suitable preservatives.

However, it has subsequently been shown that the
5 antibacterial and preservative actions of the parabens are reduced by the glycyrrhizinate component of the formulation. In addition it would be desirable to increase the absorption of calcitonins still further.

10 We have now surprisingly found that the inclusion of benzyl alcohol in a composition comprising a calcitonin and a glycyrrhizinate not only gives rise to a preservative action which is not diminished by the glycyrrhizinate, but also enhances the absorption of the calcitonin in a synergistic
15 manner. Thus the use of a glycyrrhizinate in combination with benzyl alcohol increases the transmucosal absorption of a calcitonin by more than the sum of the respective effects of benzyl alcohol and glycyrrhizinate alone.

20 In a first aspect, therefore, the present invention provides pharmaceutical compositions comprising a calcitonin; an effective amount of an absorption enhancer which is a glycyrrhizinate; an effective amount of benzyl alcohol and a pharmaceutically acceptable carrier.

25 The present invention also provides a method of enhancing the absorption of a calcitonin across a mucosal membrane, which method comprises co-administering with the calcitonin an effective amount of an absorption enhancer which is a
30 glycyrrhizinate, and an effective amount of benzyl alcohol.

Whilst preservatives are generally only used in liquid formulations, absorption enhancers are required in both liquid and solid formulations of calcitonins, and hence the
35 present invention includes within its scope both solid and liquid compositions.

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.