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Transdermal therapeutical approach involving a combination of active substances containing oestriol

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(54) Title: TRANSDERMAL THERAPEUTICAL APPROACH INVOLVING A COMBINATION OF ACTIVE SUBSTANCES CONTAINING OESTRIOL

(54) Bezeichnung: TRANSDERMALES THERAPEUTISCHES SYSTEM MIT EINER ÖSTRIOL ENTHALTENDEN WIRKSTOFFKOMBINATION

(57) Abstract

Disclosed is a transdermal therapeutical approach involving oestriol as an active substance, characterized in that oestriol is combined with one or more active substances.

(57) Zusammenfassung

Ein transdermales therapeutisches System mit dem Wirkstoff Östriol ist dadurch gekennzeichnet, daß es eine Kombination von Östriol mit einem oder mehreren weiteren Wirkstoffen enthält.

A B S T R A C T

A transdermal therapeutic system having the active compound oestriol is characterized in that it contains a combination of oestriol with one or more other active compounds.

Transdermal therapeutic system having an active compound combination comprising oestriol

The invention relates to a transdermal therapeutic system having an active compound combination comprising oestriol.

Oestrogens are steroid hormones which are derived from the tetracyclic C_{18}-steroid oestrane. Among the natural oestrogens, oestrone, oestradiol and oestriol are distinguished, oestrone and oestriol counting as the most important physiologically.

Oestriol is one of the metabolic end products of oestradiol metabolism.

It has a number of special pharmacological and biological features which distinguish it from other oestrogens:

Even before absorption, it is almost completely conjugated. Only about 1-2 % of the oestriol taken appears as free oestriol in the circulation. The quotient of free to conjugated oestriol is 1:500.

At an oral dose of 2 mg, it exerts no proliferating action on the endometrium, since it remains bound to the receptors of the cell nucleus for only a short time. Oestrogenic actions, however, are only triggered when an oestrogenic substance remains in the nucleus for a relatively long period of time. This is only possible with oestriol when it is administered several times a day.

Another special feature of oestriol is that on taking oestriol for several months, the oestrogenic action increases.

After vaginal administration, the proportion of unconjugated oestriol in the serum is 10 to 20 times higher than after oral administration,

since intestinal metabolization does not take place. With an oestriol dose of 0.5 mg, a high serum level of 100-150 pg/ml can be counted on even 2 hours after vaginal administration. In comparison, for the same effect an oral dose of 10 mg is needed.

The above experiences enable it to be concluded that for oestriol a transdermal therapeutic system (TTS) is pharmaceutically the system of choice. By means of the system it can be ensured that oestriol is delivered to the body continuously over a period of, for example, 7 days.

The active compound oestriol has until now been credited with inadequate therapeutic activity in the context of substitution therapy (HRT). This applies particularly to the use of oestriol for the prevention of osteoporosis. Thus, in an official statement of the German Endocrinology Society the inactivity of oestriol for osteoporosis prophylaxis was specifically emphasized (cf. Deutsches Ärzteblatt - Ärztliche Mitteilungen, 85, 1322-1325, (1988)).

The inactivity of oestriol in bone has meanwhile gone into the relevant textbooks as standard knowledge (Freimut A. Leidenberger, "Klinische Endokrinologie für Frauenärzte" Springer Verlag 1992, page 356).

The inactivity of oestriol on its own for the treatment of osteoporosis is furthermore pointed out in product information for preparations which contain oestriol as active compound (e.g. Jenapharm Medicaments: Range and Prices of 01.07.1991 p. 67).

In contrast to this, the sole use of oestriol for the treatment of osteoporosis in the form of a transdermal therapeutic system is presented in the PCT Application WO 93/18774. According to this, the results support oestriol as the oestrogen of choice for continuous hormone substitution therapy and in particular for the therapy of climacteric osteoporosis.

On continuous administration, osteoporosis specifically is effectively treated or prevented on the one hand, while on the other hand the carcinogenic action observed with conventional oestrogens does not take place and an anticarcinogenic action can even be expected.

Starting from this state of medical knowledge, the invention is based on the object of specifying a significantly improved transdermal therapeutic system having an active compound combination comprising oestriol, which, without risks and harmful side effects, displays a particularly high therapeutic efficacy and acceptance in the use of oestriol for the prevention of osteoporosis, arteriosclerosis and/or cardiac insufficiency in old age.

Surprisingly, it has been found that transdermally administered oestriol assists the action of transdermally administered biphosphonates, β-blockers and Ca antagonists, and that transdermally administered oestriol in combination with β-blockers and Ca antagonists can preferably be employed for the treatment of arteriosclerosis or for the treatment of cardiac insufficiency in old age. In combination with biphosphonates, it is suitable for the treatment of osteoporosis by transdermal administration.

β-blockers and Ca antagonists in accordance with the present invention may be chosen from for example amlodopine carvedilol, pimobendon, timolol, mepindolol, verapamil nifredipine and/or nimodipine.

In further applications, it was found that in the treatment of osteoporosis the transdermal administration of biphosphonates in combination with oestriol is more advantageous than oestriol alone. A preferred dose form is one which releases 8 to 16 mg of oestriol in 24 hours and 3 to 7 mg of biphosphonate per TTS.

According to the invention, all transdermal therapeutic systems having an active compound

combination comprising oestriol which guarantee the continuous release of active compound over at least 24 hours are suitable for this. The production of such systems using the appropriate individual substances is known to the person skilled in the art and described in relevant detail.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia.

The claims defining the invention are as follows:

1. Transdermal therapeutic system having the active compound oestriol, characterized in that it contains a combination of oestriol with one or more other active compounds from the class of beta-blockers, Ca antagonists or biphosphonates.

2. Transdermal therapeutic system according to Claim 1, characterized in that in combination with oestriol it contains amlodipine, carvedilol, pimobendon, timolol, mepindolol, verapamil, nifredipine and/or nimodipine.

3. Transdermal therapeutic system for the treatment of osteoporosis, characterized in that in combination with oestriol it contains biphosphonate.

4. Transdermal therapeutic system according to claim 3, characterized by release rates of 8-16 mg of oestriol or 3-7 mg of biphosphonate per day.

5. Transdermal therapeutic system for the treatment of cardiac insufficiency in old age or arteriosclerosis, characterized by an active compound combination of oestriol with active compounds from the beta-blocker class and/or Ca antagonists class according to Claim 1 or 2.

DATED THIS 28th day of November, 2000.

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