MEDICAMENT FOR TREATMENT OF PREGNANCY-INDUCED HYPERTENSION

THIS INVENTION relates to the manufacture of a medicament for the treatment of pregnancy-induced hypertension.

According to the invention, eicosapentaenoic acid, or a pharmaceutically acceptable salt or derivative thereof containing an eicosapentaenoate group, is used for the manufacture of a medicament for the treatment of pregnancy-induced hypertension.

By pregnancy-induced hypertension is meant hypertension or elevated blood pressure in the female mammal body which, prior to its first pregnancy, has had no history indicating any predisposition to hypertension, the hypertension manifesting itself after the onset of pregnancy and disappearing after termination of pregnancy. Such hypertension is frequently indicative of a predisposition to pre-

eclampsia and is frequently associated with an abnormal sensitivity to vascular pressors.

The eicosapentaenoic acid may be in naturally occurring form. Thus, it may be in the form as encountered in fish oil such as anchovy oil, typically as a hydroxyl group substituent on a triglyceride.

The use may thus be of a derivative of eicosapentaenoic acid which is a triglyceride at least one of whose hydroxyl groups is substituted by an eicosapentaenoate group. The triglyceride may form a constituent of a fish oil. Sufficient of the hydroxyl groups of the triglyceride may be substituted by eicosapentaenoate groups for the eicosapentaenoate groups to form about 25-30% by mass of the triglyceride. Thus, the hydroxyl groups of the triglyceride which are substituted by eicosapentaenoate groups may form 25-30% by mass of the medicament. Certain selected naturally occurring fish oils can contain up to 30% by mass or more eicosapentaenoate groups, bearing in mind that the substituted triglycerides in question will typically have other hydroxyl group substituents thereon, eg other fatty acid groups.

Instead, the eicosapentaenoic acid may be present in a semi-synthetic form, eg in the ester form,

derived from the triglyceride form, such as the ethyl ester thereof. In this case, after conversion of the triglyceride form from fish oil into the ethyl ester form, eicosapentaenoic acid concentrations of up to 98% by mass are obtainable. However, such high concentrations may be expensive, in which case, after esterification to the ethyl ester, refining up to a concentration of no more than 80% in a pharmaceutically acceptable solvent may be desirable. Accordingly, the use may be of a derivative of eicosapentaenoic acid which is an alkyl ester of eicosapentaenoic acid. The alkyl ester may have at most 5 carbon atoms, and conveniently is the ethyl ester of eicosapentaenoic acid. Preferably, the eicosapentaenoate groups of the alkyl ester form 60-80% by mass of the medicament, the ester in the medicament being dissolved in a pharmaceutically acceptable solvent.

Instead, the use may be of a salt of eicosapentaenoic acid. The salt may be magnesium eicosapentaenoate or zinc eicosapentaenoate.

In fish oils particularly, eicosapentaenoate groups are frequently encountered in the presence of docosahexaenoate groups, which may contribute to the activity of the eicosapentaenoate groups in combatting pregnancy-induced hypertension.

Said eicosapentaenoic acid or pharmaceutically acceptable salt or derivative thereof may thus be used together with docosahexaenoic acid or a pharmaceutically acceptable salt or derivative thereof containing the docosahexaenoate group for the manufacture of said medicament. Preferably, the eicosapentaenoate groups and the docosahexaenoate groups together form 28-35% by mass of the medicament. The proportion of docosahexanoate groups by mass will typically be lower than that of the eicosapentaenoate groups, the higher the proportion of the one, the lower the proportion of the other, and vice versa.

It follows that when a refined source of eicosapentaenoate groups is employed, they may be associated with docosahexaenoate groups in the same proportions as are present in the raw material such as fish oil, the docosahexaenoate groups being refined eg by esterification of triglycerides from fish oil on which they form hydroxyl group substituents, in an essentially similar fashion, and simultaneously with the refining of the eicosapentaenoate groups.

The medicament manufactured in accordance with the invention will typically, as indicated above, be in the form of a naturally occurring substance such as a fish oil, or in the form of a solution of an eicosapentaenoic acid derivative, such as the ethyl

ester thereof, in a pharmaceutically acceptable solvent, in unit dosage form in a capsule such as a soft gelatine capsule, the solvent, when used, acting as a diluent.

The use may thus be for the manufacture of the medicament in unit dosage form, eg in capsule form.

Naturally, solid diluents may be used, in which case the substance or composition may be in the form of a tablet comprising solid diluent material with which the active ingredient is mixed. The composition or substance may instead be in the form of a syrup, or it may be in admixture with foodstuffs, beverages, or the like.

The use may thus be for the manufacture of the medicament in tablet form. In particular the use may be for the manufacture of unit dosages each containing 2-4g of eicosapentaenoate groups.

Said eicosapentaenoic acid or pharmaceutically acceptable salt or derivative thereof may be used together with an anti-oxidant for the manufacture of said medicament, and the antioxidant may be Vitamin E or dodecyl gallate.

When Vitamin E is used, it may be used at levels of about 1 -2% by mass of the active ingredient, and dodecyl gallate may be used at levels of about 50-100 parts per million by mass of the active ingredient. Gelatine encapsulation also resists oxidation.

When in unit dosage form the dosage may be suitable eg for daily, twice-daily or thrice-daily administration. For an adult human of typically 50-100 kg body weight, a unit dosage for daily administration may, as indicated above, contain between 2,0 and 4,0g of active ingredient, ie of the eicosapentaenoate groups.

Suitable solvents include plant oils, isotonic saline solutions or any other liquid or aqueous solvent which is pharmaceutically acceptable. As suggested above, the Applicant believes that the most convenient forms will in fact be fish oil, a fish oil concentrate or in a concentrated semi-synthetic form such as the ethyl ester, in a capsule.

Instead, the use may be for the manufacture of an emulsion having water as its continuous phase and having a discontinuous phase which comprises eicosapentaenoic acid, triglycerides at least one of whose hydroxyl groups is substituted by an

eicosapentaenoate group, or alkyl esters of eicosapentaenoic acid.

The emulsion will be suitable for transfusion, typically for intravenous administration eg by drop infusion, and may contain a pharmaceutically acceptable emulsifier and/or one or more vegetable oils.

In a particular embodiment the emulsion may comprise a suitable pharmaceutically acceptable emulsifier and at least one vegetable oil, the active ingredient being selected from triglycerides from purified fish oil such as anchovy oil and the ethyl ester of eicosapentaenoic acid.

The use may thus be of triglycerides from purified fish oils or of the ethyl ester of eicosapentaenoic acid, used together with a suitable pharmaceutically acceptable emulsifier and at least one vegetable oil.

The medicament will be employed for the treatment or prophylaxis of pregnancy-induced hypertension in pregnant women. This will typically be effected by administering the medicament in unit dosage form, eg daily, twice-daily or thrice-daily, in the dosages mentioned above.

For an adult of 50-100 kg body mass, administration of a medicament manufactured in accordance with the present invention may be in unit dosage form on a daily, twice daily or thrice daily basis, at a dosage rate of 2 - 4 g/day of active ingredient.

Without being bound by theory, the Applicant believes that the utility of the eicosapentaenoic acid (or its derivatives or; salts containing the eicosapentaenoate group) in the prevention or treatment of pregnancy-induced hypertension arises from its effect on the dynamic balance in the warm-blooded body between the production of prostacyclin and thromboxane, prostacyclin being a vasodilator and thromboxane being a vasoconstrictor. A shift in this dynamic balance in favour of prostacyclin tends to reduce pregnancy-induced hypertension, and evidence has been found that pregnancy-induced hypertension may be associated with reduced prostacyclin generation in women, with the shift of said dynamic balance in favour of thromboxane.

The broad scheme of prostaglandin synthesis involves the conversion of membrane phospholipids by phospholipase A_2 to arachidonic acid, and conversion of this arachidonic acid by

cyclo-oxygenase to endoperoxides, which in turn are converted at the cellular level to prostacyclin, thromboxane and other prostanoids.

In the metabolization at the cellular level of fatty acids from the circulating metabolic pool to prostaglandins, different fatty acids can compete with one another. Eicosapentaenoic acid, whether derived from alpha-linoleic acid, or whether administered directly, is a precursor for the so-called 3-series of prostaglandins, with a predeliction in favour of prostacyclin production. On the other hand, linoleic acid leads to the production of dihomo-gamma-linolenic acid and then to arachidonic acid, and, ultimately, as mentioned above, to prosstacyclin and thromboxane, via the 1-series and 2-series of prostaglandins respectively. Arachidonic acid can also be obtained from red meat.

It is believed that eicosapentaenoic acid competes with arachidonic acid for the cyclo-oxygenase enzyme, leading to a reduced production of prostacyclin and thromboxane from arachidonic acid, and to an increased production of prostacyclin from the eicosapentaenoic acid, without the associated production of thromboxane.

It follows that the prostacylin/thromboxane balance is disturbed, in favour of increased prostacylcin production and

reduced thromboxane production, at the cellular level, resulting in increased vasodilator production and decreased vasoconstrictor production. This in turn reduces or prevents any sensitivity in the body undergoing treatment to vascular pressors, leading ultimately to the prevention or control of pregnancy-induced hypertension.

The use of the medicament of the invention will now be described, by way of example, with reference to the following non-limiting illustration Examples.

EXAMPLE 1

Two pregnant women suffering from pregnancy-induced hypertension were treated with the medicament of the invention in the form of a refined fish oil, containing eicosapentaenoate groups as triglyceride hydroxyl group substituents, said groups being present at a concentration of 28-35% by mass. The fish oil was administered in the form of capsules, each containing agent 0,16g of active ingredient expressed as eicosapentaenoate groups, the encapsulation being by means of soft gelatine and the fish oil containing slightly less than 100 parts per million dodecyl as antioxidant. Each patient received the capsules three times a day, divided into roughly equal dose, the daily dose being twenty capsules,

giving 3,2g of active ingredient/day in total.

In each case the pregnancy, which would otherwise have been terminated, was permitted to be extended by the treatment for a period of about three weeks, after which a successful birth took place.

Results are set out in the following table, Table 1, from which it is apparent that blood pressure and hypertension were reduced from abnormally high levels to acceptable levels; no significant changes took place in creatinin clearance; there was a slight, but not unacceptable, increase in platelet counts in the blood; and urate levels in the blood were reduced. It was also noted that no changes were observed in liver function tests performed; and no undesirable side-effects were observed.

TABLE 1

	Patient A		Patient B	
	Before Treatment	After Treatment	Before Treatment	After Treatment
Blood Pressure	150/100	130/90	155/101	130/90
Urate (milli moles/l)	0,42	0,38	0,43	0,38
Platelet count	160 000	200 000	180 000	210 000
Creatinin Clearance (ml/min)	120	120	120	119
Prolongation of Pregnancy (days)		21		19

EXAMPLES 2 - 5

In these Examples, four further pregnant women, all pregnant for the first time and suffering from pregnancy-induced hypertension and pre-eclampsia were treated with the fish oil referred to in Example 1 at the same dosage rate as in Example 1. In each case they were admitted as patients to hospital and were immediately subjected to bed rest and treatment with methyldopa (Aldomet) administered orally at a dosage rate of 250 mg doses administered every six hours.

EXAMPLE 2

The patient was 19 years old and was admitted to hospital 30

weeks pregnant, with a blood pressure level of 170/110 on admission, a platelet count of 150 000 on admission, and a urate level of 0,41 millimoles/l on admission. Treatment with the fish oil started within five days of admission. The patient's blood pressure declined on bed rest and on starting the fish oil administration. After one week of fish oil administration the methyldopa treatment was stopped. The reduction in blood pressure was maintained thereafter, the platelet count having risen to 200 000 and the urate level having fallen to 0,34 millimoles/l. Four weeks after admission, it was decided that the fetus was mature and the patient was successfully and electively induced.

EXAMPLE 3

In this case the patient was 20 years old and had a blood pressure of 160/105 upon admission. Within one week of commencement of fish oil administration, which started within 5 days of admission, blood pressure decreased and anti-hypertensive therapy by means of methyldopa was discontinued. After 10 days of treatment with fish oil, the platelet count of 200 000 on admission had increased to 300 000, and urate level had fallen from 0,39 millimoles/l to a value of 0,31 millimoles/l. The patient was successfully induced on an elective basis, three weeks after admission, as the fetus was judged to be mature.

EXAMPLE 4

In this case the patient was 24 years old and had a blood pressure of 180/120 on admission. Monohydralazine HCl (Apresoline) treatment at an oral dosage rate of 40 mg every 8 hours was commenced, together with the bed rest and methyldopamine treatment, immediately upon admission. Fish oil treatment was started within 5 days of admission. Effective reduction in blood pressure occurred within 14 days of starting the fish oil administration. Urate and platelet count values, which were 0,42 millimoles/l and 150 000 respectively upon admission, changed after said 14 days to 0,29 millimoles/l and 250 000. Five weeks after admission the fetus was judged to have reached pulmonary maturity, and the patient was successfully electively induced.

EXAMPLE 5

In this case the patient was 20 years old and was admitted 30 weeks after the start of pregnancy, with a blood pressure of 180/120, a urate level of 0,38 millimoles/l and a platelet count of 240 000. Fish oil treatment was started within 5 days of admission. Fourteen days after fish oil treatment was started, an effective reduction in blood pressure was found to have taken place, without, however, any material change in urate level or platelet count. All anti-hypertensive treatment, except the fish oil, was

stopped 21 days after fish oil administration was started. The patient fulminated four weeks after admission with a dramatic increase in blood pressure and proteinuria levels. Termination of pregnancy was judged necessary for maternal indications and the patient was successfully induced.

From the Examples it is apparent that the invention provides a substance or composition which acts to reduce pregnancy-induced hypertension, which is easily administered, and which appears to produce no undesirable side-effects. Although primarily intended for human use, there is no reason for the substance or composition not to be useful for the same purpose in any mammal, at the same dosage rate in terms of g/kg/day. Furthermore, from Examples 3 and 5 it appears that, at least for a limited period, antihypertensive treatment other than with fish oil can be discontinued, without an immediate increase in blood pressure.

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CLAIMS:

1. The use of eicosapentaenoic acid, or a pharmaceutically acceptable salt or derivative thereof containing an eicosapentaenoate group for the manufacture of a medicament for the treatment of pregnancy-induced hypertension.

2. The use of claim 1, which is of a derivative of eicosapentaenoic acid which is a triglyceride at least one of whose hydroxyl groups is substituted by an eicosapentaenoate group.

3. The use of claim 2, in which the triglyceride forms a constituent of a fish oil.

4. The use of claim 2 or claim 3, in which the hydroxyl groups of the triglyceride which are substituted by eicosapentaenoate groups form 25-30% by mass of the medicament.

5. The use of claim 1, which is of a derivative of eicosapentaenoic acid which is an alkyl ester of eicosapentaenoic acid.

6. The use of claim 5, in which the alkyl ester has at most 5 carbon atoms.

7. The use of claim 6, in which the alkyl ester is the ethyl ester of eicosapentaenoic acid.

8. The use of any one of claims 5 to 7 inclusive, in which the eicosapentaenoate groups of the alkyl ester form 60-80% by mass of the medicament, the ester in the medicament being dissolved in a pharmaceutically acceptable solvent.

9. The use of claim 1, which is of a salt of eicosapentaenoic acid.

10. The use of claim 9, in which the salt is magnesium eicosapentaenoate or zinc eicosapentaenoate.

11. The use of any one of the preceding claims, in which said eicosapentaenoic acid or pharmaceutically acceptable salt or derivative thereof is used together with docosahexaenoic acid or a pharmaceutically acceptable salt or derivative thereof containing the docosahexaenoate group for the manufacture of said medicament.

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12. The use of claim 11, in which the eicosapentaenoate groups and the docosahexaenoate groups together form 28-35% by mass of the medicament.

13. The use of any one of the preceding claims, which is for the manufacture of the medicament in unit dosage form.

14. The use of claim 13, which is for the manufacture of the medicament in capsule form.

15. The use of claim 13, which is for the manufacture of the medicament in tablet form.

16. The use of any one of claims 13 to 15 inclusive, which is for the manufacture of unit dosages each containing 2-4g of eicosapentaenoate groups.

17. The use of any one of the preceding claims, in which said eicosapentaenoic acid or pharmaceutically acceptable salt or derivative thereof is used together with an anti-oxidant for the manufacture of said medicament.

18. The use of claim 17, in which the antioxidant is Vitamin E or dodecyl gallate,

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19. The use of any one of claims 1 to 12 or 16 to 18 inclusive, which is for the manufacture of an emulsion having water as its continuous phase and having a discontinuous phase which comprises eicosapentaenoic acid, triglycerides at least one of whose hydroxyl groups is substituted by an eicosapentaenoate group, or alkyl esters of eicosapentaenoic acid.

20. The use of claim 19, which is of triglycerides from purified fish oils or of the ethyl ester of eicosapentaenoic acid, used together with a suitable pharmaceutically acceptable emulsifier and at least one vegetable oil.

21. The use of claim 1, substantially as described herein.