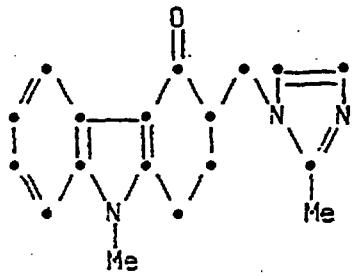
MEDICAMENTS FOR THE TREATMENT OF EMESIS

This invention relates to improvements in the treatment of gastrointestinal disorders. More particularly it relates to the use of a compound having antagonist activity at $5HT_3$ receptors and dexamethasone in the treatment of emesis, and to pharmaceutical compositions containing the two compounds.

In our UK Patent Specification No. 2153821A we disclose inter alia 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl) methyl]-4H-carbazol-4-one which may be represented by the formula (I)



(I)

and physiologically acceptable salts, solvates and physiologically acceptable equivalents thereof.

In the aforementioned specification the compounds are described as potent and selective antagonists of 5- hydroxytryptamine (5HT) at 'neuronal' 5HT receptors of the type located on terminals of primary afferent nerves, and which are also present in the central nervous system. Receptors of this type are now designated $5HT_3$ receptors. The compounds are described as being of use in the treatment of a human or animal subject suffering from a condition caused by a disturbance of neuronal 5HT function, for example in the treatment of migraine pain or a psychotic disorder such as schizophrenia. The compounds may also be useful in the treatment of conditions such as anxiety, obesity and mania.

We have found, as described in our published European Patent Specification No. 226266, that the compounds disclosed in UK Patent Specification No. 2153821A additionally promote gastric emptying, and are thus useful in the treatment of conditions which may be relieved by the promotion of gastric emptying. Such conditions include gastric

stasis and symptoms of gastrointestinal dysfunction such as dyspepsia, reflux oesophagitis, peptic ulcer and flatulence.

According to published European Patent Specification No. 226266, the compounds have also been found to be anti-emetics, and may be used in the treatment or prevention of nausea and vomiting. The use of these compounds for the treatment of emesis is also described in published European Patent Specification No. 201165, which specification additionally refers to the use of the compounds for the treatment of irritable bowel syndrome.

Studies have shown that the anti-emetic properties of the compound of formula (I) are enhanced by administering the compound in conjunction with dexamethasone. Dexamethasone is a systemic anti-inflammatory corticosteroid, which is known to have anti-emetic properties and to be useful in the treatment of emesis resulting from chemotherapy, especially cancer chemotherapy involving the use of, for example, cisplatin.

The present invention is based on a method of treating and/or preventing nausea and vomiting, which comprises administering to a human or animal subject the compound of formula (I) or a physiologically acceptable salt or solvate thereof, and dexamethasone or a physiologically acceptable salt or ester thereof.

According to one aspect the invention provides for the use of the compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for administration in conjunction with dexamethasone or a physiologically acceptable salt or ester thereof, for the treatment and/or prevention of nausea and vomiting.

Co-administration of the compound of formula (I) with dexamethasone is particularly useful for the treatment and/or prevention of nausea and vomiting associated with chemotherapy, especially cancer chemotherapy involving the use of, for example, cisplatin. Such co-administration may also reduce delayed nausea and vomiting associated with this type of chemotherapy.

The compound of formula (I) or a physiologically acceptable salt or solvate thereof, and dexamethasone or a physiologically acceptable salt or ester thereof, may be administered as a single pharmaceutical composition comprising effective amounts of the two active

ingredients. Alternatively the two active ingredients may be co-administered in the form of two separate pharmaceutical compositions for simultaneous or sequential use.

Suitable physiologically acceptable salts of the carbazolone of formula (I) for use according to the invention include acid addition salts formed with organic or inorganic acids for example, hydrochlorides, hydrobromides, sulphates, phosphates, citrates, fumarates and maleates. The solvates may, for example, be hydrates. A preferred form of the compound of formula (I) for use according to the invention is the hydrochloride, particularly in hydrated form, e.g. the dihydrate.

Dexamethasone may be administered according to the invention as dexamethasone alcohol or in the form of a physiologically acceptable salt or ester. Suitable salts and esters include the acetate, isonicotinoate, phenylpropionate, pivalate, t-butyl acetate, trioxaundecanoate, disodium metasulphobenzoate and disodium phosphate.

A proposed dosage of the compound of formula (I) for use according to the invention for administration to man (of approximately 70kg body weight), is 0.05 to 25mg, more preferably 0.05 to 20mg, and most preferably 0.1 to 10mg per unit dose, expressed as the weight of free base. A preferred dose of dexamethasone for use according to the invention is in the range of 0.5 to 20mg per dosage unit, expressed as the weight of the alcohol.

The unit doses may be administered, for example, 1 to 4 times per day. The exact dose will depend on the route of administration and the condition being treated, and it will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition to be treated.

When the two active ingredients are administered as separate preparations, they are preferably given orally or parenterally (e.g. intramuscularly or, more particularly, intravenously).

According to a further aspect the invention provides a pharmaceutical composition, for use in human or veterinary medicine, comprising the compound of formula (I) or a physiologically

acceptable salt or solvate thereof, and dexamethasone or a physiologically acceptable salt or ester thereof.

Compositions according to the invention may be formulated in conventional manner using one or more physiologically acceptable carriers or excipients. Thus the compositions may, for example, be formulated for oral, buccal, parenteral or rectal administration. Compositions for administration by the oral route, in the form of for example tablets or capsules, are preferred.

Compositions for oral use such as tablets and capsules may be prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). Tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of one or both active ingredients.

For parenteral administration the compositions may be presented in a form suitable for bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory

agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredients may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

For rectal administration the compositions may be formulated as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The pharmaceutical compositions of the invention may be prepared according to conventional techniques well known in the pharmaceutical industry. Thus, for example, the compound of formula (I) or a salt or solvate thereof and the dexamethasone or dexamethasone salt or ester may be admixed together, if desired, with suitable excipients. Tablets may be prepared, for example, by direct compression of such a mixture. Capsules may be prepared by filling the blend along with suitable excipients into gelatin capsules, using a suitable filling machine. Controlled release forms for oral or rectal administration may be formulated in a conventional manner associated with controlled release forms.

The compositions for use according to the invention may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredients. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Where the compound of formula (I) and the dexamethasone are intended for administration as two separate compositions these may be presented in the form of, for example, a twin pack.

The following examples illustrate the preparation of the compound of formula (I). Temperatures are in ^{0}C.

Example 1

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one

A solution of 3-[(dimethylamino)methyl]-1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one hydrochloride (1.7g) in water (17ml) was treated

with 2-methylimidazole (1.4g) and then heated under reflux for 20h. The cooled mixture was filtered and the residue washed with water (3x15ml) to give a product (1.7g) m.p. 221-221.5°. This material was recrystallised from methanol to give the title compound (1.4g) m.p. 231-232°.

Example 2

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one (18.3g) in a hot mixture of isopropanol (90ml) and water (18.3ml) was treated with concentrated hydrochloric acid (6.25ml). The hot mixture was filtered and the filtrate diluted with isopropanol (90ml) and stirred at room temperature for 17h, cooled to 2° and the solid filtered off (21.6g). A sample (6g) was recrystallised from a mixture of water (6ml) and isopropanol (10ml) to give the title compound as a white crystalline solid (6g) m.p. 178.5-179.5°.

Analysis Found:	C,59.45;H,6.45;N,11.5.
$C_{18}H_{19}N_3O.HCl.2H_2O$ requires	C,59.1;H,6.6;N,11.5%.
Water assay Found:	10.23%
$C_{18}H_{19}N_3O.HCl.2H_2O$ requires	9.85%

The following examples illustrate pharmaceutical compositions according to the invention, containing 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate (Compound A) and dexamethasone as the active ingredients. Other physiologically acceptable salts and/or solvates of the compound of formula (I), and dexamethasone or physiologically acceptable salts or esters thereof, may be formulated in a similar manner.

TABLETS FOR ORAL ADMINISTRATION

Tablets may be prepared by the normal methods such as direct compression or wet granulation.

The tablets may be film coated with suitable film forming materials, such as hydroxypropyl methylcellulose, using standard techniques.

Direct Compression Tablets	mg/tablet	
Compound A	5.0 *	10.0**
Dexamethasone BP	4.0	4.0
Anhydrous lactose USNF	76.05	71.05
Pregelatinised starch USNF	4.5	4.50
Magnesium stearate BP	0.45	0.45
Compression weight	90.00	90.00

* Equivalent to 4.0mg free base.

** Equivalent to 8.0mg free base.

Compound A and the dexamethasone are sieved through a suitable sieve and blended with the lactose, pregelatinised starch and magnesium stearate. The resultant mix is compressed into tablets using a suitable tablet press fitted with 6.5mm normal concave punches.

Tablets of other strengths and/or combination of doses may be prepared by appropriate alterations in the amounts of the active ingredients and the excipients and using punches to suit.

CAPSULES

	mg/capsule
Compound A	10.00
Dexamethasone BP	4.00
Pregelatinised Starch USNF	70.625
Magnesium stearate BP	0.375
Fill weight	85.00

Compound A and the dexamethasone are sieved through a 250µm sieve and blended with the pregelatinised starch and magnesium stearate. The resultant mix is filled into size 3 hard gelatin capsules using a suitable filling machine.

* C L M S *

CLAIMS:

1. A pharmaceutical composition for use in human or veterinary medicine comprising 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one or a physiologically acceptable salt or solvate thereof and dexamethasone or a physiologically acceptable salt or ester thereof.

2. A pharmaceutical composition as claimed in claim 1 wherein the 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one is used in the form of a hydrochloride salt.

3. A pharmaceutical composition as claimed in claim 2 wherein the 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one is used in the form of the hydrochloride dihydrate.

4. A pharmaceutical composition as claimed in any of claims 1 to 3 in unit dose form containing 0.05 to 25mg per unit dose of 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one expressed as the weight of free base and 0.5 to 20mg per unit dose of dexamethasone expressed as the weight of the alcohol.

5. A pharmaceutical composition as claimed in claim 4 in which the unit dose of 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one is 0.1 to 10mg.

6. A pharmaceutical composition as claimed in any of claims 1 to 5 in a form adapted for oral, buccal, parenteral or rectal administration.

7. A pharmaceutical composition as claimed in claim 6 for oral administration in the form of tablets.

8. A pharmaceutical composition as claimed in claim 6 for parenteral administration in a form suitable for injection or infusion.

9. A pharmaceutical composition as claimed in any of claims 1 to 8 containing at least one physiologically acceptable carrier or excipient.

10. A method for the manufacture of a pharmaceutical composition as claimed in any of claims 1 to 9 which comprises processing the components by conventional techniques to form a pharmaceutical composition.

11. The use of 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for administration in conjunction with dexamethasone or a physiologically acceptable salt or ester thereof in the treatment and/or prevention of nausea and vomiting.

12. The use as claimed in claim 11 wherein the 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one is used in the form of a hydrochloride salt.

13. The use as claimed in claim 12 wherein the 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one is used in the form of the hydrochloride dihydrate.

14. The use as claimed in any of claims 11 to 13 wherein the medicament is in unit dose form containing

0.05 to 25mg per unit dose of 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one expressed as the weight of free base for administration in conjunction with dexamethasone in a unit dose of 0.5 to 20mg expressed as the weight of the alcohol.

15. The use as claimed in claim 14 in which the unit dose of 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one is 0.1 to 10mg.

16. The use as claimed in any of claims 11 to 15 wherein the medicament is in a form adapted for oral, buccal, parenteral or rectal administration.

17. The use as claimed in claim 16 wherein the medicament is for oral administration in the form of tablets.

18. The use as claimed in claim 16 wherein the medicament is for parenteral administration in a form suitable for injection or infusion.

19. The use as claimed in any of claims 11 to 18 wherein the medicament is for administration in conjunction with dexamethasone but separately therefrom.

20. The use as claimed in claim 19 wherein the medicament and the dexamethasone are for parenteral administration in the form of preparations adapted to be given intravenously.

21. The use as claimed in any of claims 11 to 20 wherein the medicament contains at least one physiologically acceptable carrier or excipient.

* C L M S *

22. A twin pack comprising separate unit dose forms of 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one or a physiologically acceptable salt or solvate thereof and dexamethasone or a physiologically acceptable salt or ester thereof in association for separate administration.