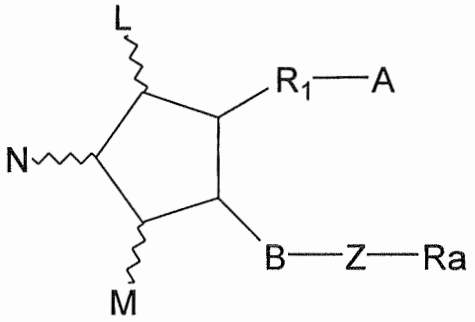
CLAIMS

1. Use of a~~A~~ pharmaceutical combination comprising:

(a) oxycodone~~an opioid~~, a pharmaceutically acceptable salt thereof or a mixture thereof~~and~~

(b) a prostaglandin (PG) compound represented by the formula (I):



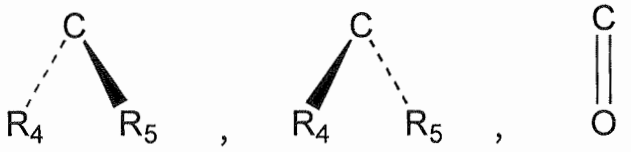
(I)

wherein L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is $-CH_3$, or $-CH_2OH$, $-COCH_2OH$, -COOH or a functional derivative thereof;

B is single bond, $-CH_2-CH_2-$, $-CH=CH-$, $-C\equiv C-$, $-CH_2-CH_2-CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-C\equiv C-CH_2-$ or $-CH_2-C\equiv C-$;

Z is



or single bond

wherein R_4 and R_5 are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R_4 and R_5 are not hydroxy and lower alkoxy at the same time;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is

unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

Ra is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or hetrocyclic-oxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclic-oxy group, provided that Ra is substituted by halogen or Z is C=O

in the manufacture of a medicament

for the treatment of a condition or disease which is one of the indications for opioid use.

2. The use according to ~~combination as described in~~ Claim 1, ~~which is used~~ for the treatment of pain.

3. The use according to ~~combination as described in~~ Claim 2, wherein the pain is chronic pain.

4. The use according to any one of ~~combination as described in~~ Claims 1 to 3, wherein said prostaglandin compound is 16-mono or dihalogen-prostaglandin compound.

5. The use according to ~~combination as described in~~ any one of Claims 1 to ~~-~~3, wherein said prostaglandin compound is 15-keto-prostaglandin compound.

6. The use according to ~~combination as described in~~ any one of Claims 1 to ~~-~~3, wherein said prostaglandin compound

is 13,14-dihydro-16-mono or dihalogen-prostaglandin compound.

7. The use according to~~combination as described in~~ any one of Claims 1 to ~~–~~3, wherein said prostaglandin compound is 13,14-dihydro-15-keto-prostaglandin compound.

8. The use according to~~combination as described in~~ any one of Claims 1 to ~~–~~3, wherein said prostaglandin compound is 13,14-dihydro-15-keto-16-mono or dihalogen-prostaglandin compound.

9. The use according to~~combination as described in~~ any one of Claims 1 to ~~–~~3, wherein said prostaglandin compound is 13,14-dihydro-16-mono or difluoro-prostaglandin compound.

10. The use according to~~combination as described in~~ any one of Claims 1 to ~~–~~3, wherein said prostaglandin compound is 15-keto-16-mono or difluoro-prostaglandin compound.

11. The use according to~~combination as described in~~ any one of Claims 1 to ~~–~~3, wherein said prostaglandin compound is 13,14-dihydro-15-keto-16-mono or difluoro-prostaglandin compound.

12. The use according to~~combination as described in~~ any one of Claims 1 to ~~–~~3, wherein said prostaglandin compound is 13,14-dihydro-16-mono or dihalogen-prostaglandin E compound.

13. The use according to ~~combination as described in~~ any one of Claims 1 to ~~–~~3, wherein said prostaglandin compound is 15-keto-16-mono or dihalogen-prostaglandin E compound.

14. The use according to ~~combination as described in~~ any one of Claims 1 to ~~–~~3, wherein said prostaglandin compound is 13,14-dihydro-15-keto-16-mono or dihalogen-prostaglandin E compound.

15. The use according to ~~combination as described in~~ any one of Claims 1 to ~~–~~3, wherein said prostaglandin compound is 13,14-dihydro-16,16-difluoro-~~-~~prostaglandin E_1 compound.

16. The use according to ~~combination as described in~~ any one of Claims 1 to ~~–~~3, wherein said prostaglandin compound is 13,14-dihydro-15-keto-prostaglandin E_1 compound.

17. The use according to ~~combination as described in~~ any one of Claims 1 to ~~–~~3, wherein said prostaglandin compound is 13,14-dihydro-15-keto-16,16-~~-~~difluoro-prostaglandin E_1 compound or 13,14-dihydro-15-keto-16,16-difluoro-18-methyl-prostaglandin E_1 compound.

18. The use according to ~~combination as described in~~ any one of Claims 1 to ~~–~~3, wherein said prostaglandin compound is 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E_1 or 13,14-dihydro-15-keto-16,16-difluoro-18-methyl-prostaglandin E_1.

~~19. The combination as described in any one of Claims 1-18, wherein the opioid is selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine,~~

~~butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dextropropoxyphene, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetylbuturate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentonil, tilidine, tramadol, a pharmaceutically acceptable salt thereof, and a mixture thereof.~~

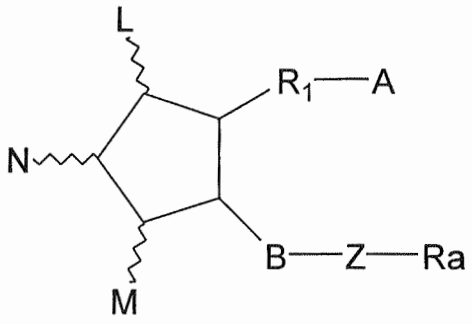
~~20. The combination as described in claim 19, wherein the opioid is oxycodone.~~

19~~21~~. The use according to~~combination as described in any one of~~ ~~c~~Claim~~s~~ 1~~–20~~, wherein components (a) and (b) are formulated for simultaneous, separate or sequential use.

20. A pharmaceutical composition comprising:

(a) oxycodone, a pharmaceutically acceptable salt thereof or a mixture thereof

(b) a prostaglandin (PG) compound represented by the formula (I):



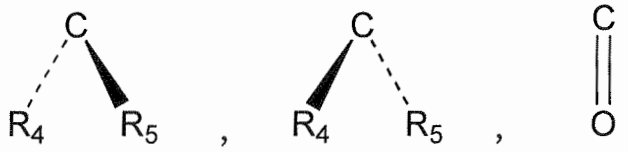
(I)

wherein L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is $-CH_3$, or $-CH_2OH$, $-COCH_2OH$, -COOH or a functional derivative thereof;

B is single bond, $-CH_2-CH_2-$, -CH=CH-, $-C\equiv C-$, $-CH_2-CH_2-CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-C\equiv C-CH_2-$ or $-CH_2-C\equiv C-$;

Z is



or single bond

wherein R_4 and R_5 are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R_4 and R_5 are not hydroxy and lower alkoxy at the same time;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

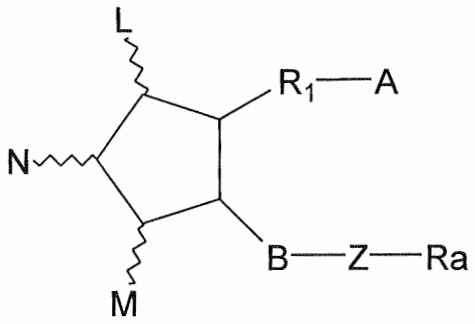
Ra is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower

alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or hetrocyclic-oxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclic-oxy group, provided that Ra is substituted by halogen or Z is C=O.

21~~22~~. A pharmaceutical combination comprising:

(a) oxycodone~~an opioid~~, a pharmaceutically acceptable salt thereof or a mixture thereof~~and~~

(b) a prostaglandin (PG) compound represented by the formula (I):



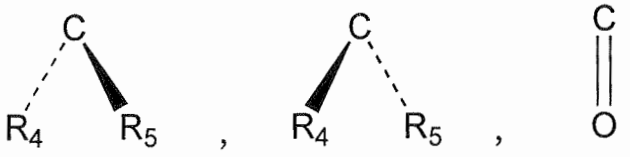
(I)

wherein L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is $-CH_3$, or $-CH_2OH$, $-COCH_2OH$, $-COOH$ or a functional derivative thereof;

B is single bond, $-CH_2-CH_2-$, $-CH=CH-$, $-C\equiv C-$, $-CH_2-CH_2-CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-C\equiv C-CH_2-$ or $-CH_2-C\equiv C-$;

Z is



or single bond

wherein R_4 and R_5 are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R_4 and R_5 are not hydroxy and lower alkoxy at the same time;

R_1 is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

Ra is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or hetrocyclic-oxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclic-oxy group, provided that Ra is substituted by halogen or Z is C=O

when used in the treatment of a condition or disease which is one of the indications for opioid use.

22~~23~~. The composition according to Claim 20 or combination according to~~as described in~~ Claim 21~~22~~, wherein said prostaglandin compound is 16-mono or dihalogen-prostaglandin compound.

23~~24~~. The composition according to Claim 20 or combination according to~~as described in~~ Claim 21~~22~~, wherein said prostaglandin compound is 15-keto-prostaglandin compound.

24~~25~~. The composition according to Claim 20 or combination according to~~as described in~~ Claim 21~~22~~, wherein said prostaglandin compound is 13,14-dihydro-16-mono or dihalogen-prostaglandin compound.

25~~26~~. The composition according to Claim 20 or combination according to~~as described in~~ Claim 21~~22~~, wherein said prostaglandin compound is 13,14-dihydro-15-keto-prostaglandin compound.

26~~27~~. The composition according to Claim 20 or combination according to~~as described in~~ Claim 21~~22~~, wherein said prostaglandin compound is 13,14-dihydro-15-keto-16-mono or dihalogen-prostaglandin compound.

27~~28~~. The composition according to Claim 20 or combination according to~~as described in~~ Claim 21~~22~~, wherein said prostaglandin compound is 13,14-dihydro-16-mono or difluoro-prostaglandin compound.

28~~29~~. The composition according to Claim 20 or combination according to~~as described in~~ Claim 21~~22~~, wherein said prostaglandin compound is 15-keto-16-mono or difluoro-prostaglandin compound.

29~~30~~. The composition according to Claim 20 or combination according to~~as described in~~ Claim 21~~22~~, wherein said prostaglandin compound is 13,14-dihydro-15-keto-16-mono or difluoro-prostaglandin compound.

30~~31~~. The composition according to Claim 20 or combination according to~~as described in~~ Claim 21~~22~~, wherein

said prostaglandin compound is 13,14-dihydro-16-mono or dihalogen-prostaglandin E compound.

31~~32~~. The composition according to Claim 20 or combination according to~~as described in~~ Claim 21~~22~~, wherein said prostaglandin compound is 15-keto-16-mono or dihalogen-prostaglandin E compound.

32~~33~~. The composition according to Claim 20 or combination according to~~as described in~~ Claim 21~~22~~, wherein said prostaglandin compound is 13,14-dihydro-15-keto-16-mono or dihalogen-prostaglandin E compound.

33~~34~~. The composition according to Claim 20 or combination according to~~as described in~~ Claim 21~~22~~, wherein said prostaglandin compound is 13,14-dihydro-16,16-difluoro -prostaglandin E_1 compound.

34~~35~~. The composition according to Claim 20 or combination according to~~as described in~~ Claim 21~~22~~, wherein said prostaglandin compound is 13,14-dihydro-15-keto-prostaglandin E_1 compound.

35~~36~~. The combination as described in Claim 21~~22~~, wherein said prostaglandin compound is 13,14-dihydro-15-keto-16,16- difluoro-prostaglandin E_1 compound or 13,14-dihydro-15-keto-16,16-difluoro-18-methyl-prostaglandin E_1 compound.

36~~37~~. The composition according to Claim 20 or combination according to~~as described in~~ Claim 21~~22~~, wherein said prostaglandin compound is 13,14-dihydro-15-keto-16,16-

difluoro-prostaglandin E_1 or 13,14-dihydro-15-keto-16,16-difluoro-18-methyl--prostaglandin E_1.

~~38. The combination as described in any one of Claims 22-37, wherein the opioid is selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dextropropoxyphene, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetylbuturate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethideine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentonil, tilidine, and tramadol, a pharmaceutically acceptable salt thereof, and a mixture thereof.~~

~~39. The combination as described in Claim 38, wherein the opioid is oxycodone.~~

37~~40~~. The combination according to~~as described in any one of~~ Claim~~s~~ 21~~22-39~~ when components (a) and (b) are used~~for~~ simultaneously, separately or sequentially~~ use~~.

3841. The~~A~~ pharmaceutical composition according to Claim 20 further comprising ~~the combination as described in any one of Claims 1-40 in association with a~~ pharmaceutically suitable excipient.

3942. The composition according to~~as described in e~~Claim 3841, wherein said pharmaceutically suitable excipient is orally acceptable.

4043. A commercial package comprising the~~a~~ combination according to~~as described in~~ any one of Celaims 211 to 3740 together with instructions for simultaneous, separate or sequential use thereof, when used for the treatment of a condition or disease which is one of the indications for opioid use.