Claims

1. A composition comprising

(i) an amount of one or more glucocorticoids providing a hydrocortisone equivalent daily dose of 1-80 mg

(ii) 0.5-95 wt % polymer or binder

(iii) 0.5-95 wt% filler

(iv) 0.1 wt% to 10 wt% glidant

(v) 0.1 wt% to 10 wt% lubricant

(vi) 1 wt% to 5 wt% of film coating system

wherein the percentages are given as % of the total weight of the composition, said composition including a first part which provides immediate release of said glucocorticoid and a second part which provides extended release of said glucocorticoid, said first immediate release part being in the form of a coating comprising (vi) and said second extended release part being in the form of a core comprising (i) to (v), and wherein the ratio between the first immediate release part and the second extended release part is in range of 20-30% of the glucocorticoid for the coating (first part) of the total amount of glucocorticoid and 70-80% of the core (second part) of the total amount of glucocorticoid.

2. A composition according to claim 1, wherein the one or more glucocorticoids are selected from hydrocortisone, cortisone, prednisolone, prednisone, methylprednisone, triamcinolone, paramethasone, betamethasone, dexamethasone, fludrocortisone, budesonide, fluticasone, cortisone acetate, and beclometasone or any combinations thereof.

3. A composition according to claim 1, wherein the polymer or binder is selected from microcrystalline cellulose, hydroxypropylcellulose, L-hydroxypropylcellulose, hydroxypropyl methylcellulose, methylcellulose polymers, hydroxyethylcellulose, sodium carboxymethylcellulose, carboxymethylene, carboxymethylhydroxyethylcellulose or any combinations thereof.

4. A composition according to claim 1, wherein the filler is selected from cellulose, microcrystalline cellulose, powdered cellulose, silicified microcrystalline ethylcellulose, starches or modified starches or any combinations thereof.

5. A composition according to claim 1, wherein the glidant or lubricant is selected from stearic acid, magnesium stearate, calcium stearate or other metallic stearate, talc, waxes and glycerides, light mineral oil, PEG, glyceryl behenate, colloidal silica, hydrogenated vegetable oils, corn starch, sodium stearyl fumarate, polyethylene glycols, alkyl sulfates, sodium benzoate, sodium acetate, talc or any combvination thereof.

6. A composition according to claim 1, wherein the film coating system comprises methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, acrylic polymers, ethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinylalcohol, sodium carboxymethylcellulose, cellulose acetate, cellulose acetate phthalate, gelatin, methacrylic acid copolymer, polyethylene glycol, shellac, sucrose, titanium dioxide, carnauba wax, microcrystalline wax, glyceryl monostearate, talc, zein or a combinations thereof.

7. A composition according to any of the preceding claims wherein the composition is a coated tablet.

8. A composition as defined in any of claims 1-7 for use in reducing one or more side-effects of glucocorticoid therapy and undergoing glucocorticoid therapy in a subject having a diminished or disrupted endogenous glucocorticoid secretory pattern.

9. The use according to claim 8, wherein the circadian plasma concentration-time profile of cortisol after administration of one or more glucocorticoids mimics that of a healthy subject.

10. The use according to claim 8 or 9, wherein the administration is once daily.

11. The use according to any of claims 8-10, wherein the reduction of side-effect(s) is determined by comparing 12 weeks of treatment that leads to a cortisol plasma concentration-time profile, which mimics that of a healthy subject, with 12 weeks of treatment three times daily with the same glucocorticoid in a conventional dosage form, and the total daily dose being the same in the two treatment regimens.

12. The use according to claim 11, wherein the treatment that leads to a cortisol plasma concentration-time profile, which mimics that of a healthy subject, is a treatment once daily with an oral dosage form.

13. The use according to any of claims 8-12, wherein the one or more glucocorticoids is administered in form of an oral dosage, wherein from about 15 to about 35% w/w of the total amount of the glucocorticoids is immediate released upon administration and the remaining part of the glucocorticoids is modified released during a time period of at least about 8 hours such as at least about 12 hours.

14. The use according to any claims 8-13, wherein the one or more glucocorticoids is/are administered in form of a single-unit dosage form comprising a core containing a part of the glucocorticoids and the core being coated with the remaining part of the glucocorticoid.

15. The use according to claim 14, wherein the core is of a swelling matrix type.

16. The use according to any of claims 8-15, wherein the reduction of side-effect(s) is determined in a test population of 12 or more subjects with diminished or disrupted endogenous glucocorticoid secretory pattern receiving said treatment that leads to a cortisol plasma concentration-time profile, which mimics that of a healthy subject, and in a comparison population of 12 or more subjects with diminished glucocorticoid secretory pattern receiving said three times daily treatment with the same glucocorticoid in a conventional dosage form, and the total daily dose being the same in the two treatment regimens.

17. The use according to any of claims 8-16, wherein the one or more side-effects are selected from the group consisting of: gain of weight, increase in cardiovascular risk factors, increase in bone degradation, metabolic risk factors.

18. The use according to any of claims 8-17, wherein the reduction of one or more side-effect(s) or a composite risk index from such factors is statistically significant.

19. The use according to any of claims 8-18, wherein the reduction in side-effect(s) include reduction in metabolic risk factors indicative of future risk for diabetes mellitus type 2.

20. The use according to claim 16, wherein the metabolic risk factors are glucose metabolism.

21. The use according to claim 19 or 20, wherein the metabolic risk factors is measured as a reduction in HbA1c and the reduction is 0.1% or more such as 0.3% or more, or 0.5% or more after 12 weeks of treatment leading to a cortisol plasma concentration, which mimics that of a healthy subject, compared with treatment three times daily with the same glucocorticoid in a conventional dosage form, and the total daily dose is the same in the two treatments.

22. The use according to any of claims 8-21, wherein the reduction in side-effect(s) includes reduction in weight gain or reduction of body weight.

23. The use according to claim 19, wherein the weight gain after 12 weeks of treatment leading to a cortisol plasma concentration, which mimics that of a healthy subject, is reduced with at least 0.7 kg compared with treatment three times daily with the same glucocorticoid in a conventional dosage form, and the total daily dose is the same in the two treatments.

24. The use according to any of claims 8-23, wherein the reduction in side-effect(s) includes reduction in cardiovascular risk factors including one or more of the systolic blood pressure and the diastolic blood pressure.

25. The use according to claim 24, wherein the systolic blood pressure after 12 weeks treatment is reduced with 5 mmHg or more compared with treatment three times daily with the same glucocorticoid in a conventional dosage form, and the total daily dose is the same in the two treatments.

26. The use according to claim 24, wherein the diastolic blood pressure after 12 weeks treatment is reduced with 2 mmHg or more compared with treatment three times daily with the same glucocorticoid in a conventional dosage form, and the total daily dose is the same in the two treatments.

27. The use according to any of claims 8-26, wherein the reduction in side-effect(s) includes reduction in bone degradation.

28. The use according to claim 27, wherein reduction in bone degradation is determined by measuring bone marker(s) for bone formation marker and the marker PINP is increased with at least 5% or more, such as 7% or more, or 10% or more after 12 weeks of treatment compared with treatment three times daily with the same glucocorticoid in a conventional dosage form, and the total daily dose is the same in the two treatments.

29. The use according to any of claims 8-28, wherein the subject also suffers from diabetes mellitus.

30. The use according to claim 8-29, wherein the subject suffers from diabetes mellitus type I or type II with or without insulin treatment.

31. The use according to any of claims 29, wherein the subject is at increased cardiovascular risk due to presence of cardiovascular risk factors such as hypertension, dyslipidemia, glucose metabolism, renal dysfunction or cardiovascular target organ due to myocardial infarction, stroke or congestive heart failure.

32. A glucocorticoid composition as defined in any of claims 1-7 for reduction of side-effects generally observed with glucocorticoid therapy, wherein the composition is administered once daily.

33. A composition according to claim 32, wherein the composition is an immediate release and an extended release composition.

34. A composition according to claims 32 and 33, wherein the composition is administered once daily in the morning.

35. A composition according to any of claims 32, 33 and 34, wherein the composition comprises one or more glucocorticoids and wherein from about 15 to about 35% w/w of the total amount of the glucocorticoids is immediately released upon administration and the remaining part of the glucocorticoids is modified released during a time period of at least about 8 hours such as at least about 12 hours.

36. A composition according to any of claims 32, 33, 34 and 35, wherein the total daily dose of glucocorticoids, expressed as hydrocortisone equivalents, is from about 1 mg/70 kg

bodyweight to about 10 mg/70 kg bodyweight, such as about 30 mg/70 kg bodyweight, such as about 5 mg/70 kg bodyweight or such as 2.5-10 mg/70 kg bodyweight

37. A composition according to any of claims 32 33, and 34-36, wherein the composition further comprises one or more pharmaceutical excipients.

38. A composition according to claim 37, wherein the pharmaceutical excipients are e.g. fillers, diluents, disintegrants, binders, lubricants, glidants etc. or any mixture thereof

39. A composition according to any of claims 32, 33 and 34-38, wherein the composition is in form of e.g. a tablet.

40. A composition according to any of claims 32, 33 and 34-39, wherein the administration is by the oral route

41. A composition according to any of claims 32, 33 and 34-40, wherein the administration leads to a circadian plasma concentration-time profile of cortisol after administration of one or more glucocorticoids mimics that of a healthy subject.

42. A composition according to any of claims 32, 33 and 34-41, wherein the reduction of side-effect(s) is as defined in any of claims 9-27 and/or the subject treated is as defined in any of claims 28-30.

43. A composition as defined in any of claims 1-7 for use in treating or preventing a diminished or disrupted endogenous glucocorticoid secretory pattern in a subject with sufficient adrenal capacity. .

44. The use according to claim 43, wherein the diminished or disrupted endogenous glucocorticoid secretory pattern is associated with disturbed circadian plasma cortisol concentration-time profile of said subject.

45. The use according to claim 43 or 44, wherein the disturbed circadian plasma cortisol concentration-time profile arises from hypothyroidism, depression, sleep deprivation, insomnia, sleep disturbances, adrenal fatigue syndrome, chronic fatigue syndrome, obesity,

tertiary adrenal insufficiency, circadian rhythm sleep disorders, shift-work, jet-lag, obesity, cachexia or chronic stress.

46. The use according to any of claims 43-45, wherein the daily dose of said glucocorticoid (expressed as hydrocortisone equivalents) is from about 1 mg/70 kg bodyweight to about 10 mg/70 kg bodyweight, such as about 30 mg/70 kg bodyweight, such as about 5 mg/70 kg bodyweight or such as 2.5-10 mg/70 kg bodyweight.

47. The use according to any one of clams 43-46, wherein the circadian plasma concentration of cortisol after administration of one or more glucocorticoids mimics that of a healthy subject.

48. The use according to any one of claims 43-47, wherein the administration is once daily.

49. The use according to any one of claims 43-48, wherein the administration is as defined in any one of claims 12-14.

Claims

1. A composition comprising

(i) 1.5 wt % to 6.5 wt % of one or more glucocorticoids

(ii) 15 wt% to 25 wt % polymer or binder

(iii) 30 wt% to 40 wt% filler

(iv) 0.1 wt% to 0.5 wt% glidant

(v) 0.1 wt% to 0.5 wt% lubricant

(vi) 1 wt% to 5 wt% of film coating system

(vii) 25 wt% to 40 wt% solvent

wherein the percentages are given as % of the total weight of all ingredients used in the manufacture of the composition and wherein the solvent used in the manufacturing process of the compositions may wholly or partially be evaporated and wherein the ratio between a first immediate release part and a second extended release part is in the range of 20-30% of the glucocorticoid for the coating (first part) of the total amount of glucocorticoid and 70-80% of the core (second part) of the total amount of glucocorticoid.

2. A composition according to claim 1, wherein the one or more glucocorticoids are selected from hydrocortisone, cortisone, prednisolone, prednisone, methylprednisone, triamcinolone, paramethasone, betamethasone, dexamethasone, fludrocortisone, budesonide, fluticasone, cortisone acetate, and beclometasone or any combinations thereof.

3. A composition according to claim 1, wherein the polymer or binder is selected from microcrystalline cellulose, hydroxypropylcellulose, L-hydroxypropylcellulose, hydroxypropyl methylcellulose, methylcellulose polymers, hydroxyethylcellulose, sodium carboxymethylcellulose, carboxymethylene, carboxymethylhydroxyethylcellulose or any combinations thereof.

4. A composition according to claim 1, wherein the filler is selected from cellulose, microcrystalline cellulose, powdered cellulose, silicified microcrystalline ethylcellulose, starches or modified starches or any combinations thereof.

5. A composition according to claim 1, wherein the glidant or lubricant is selected from stearic acid, magnesium stearate, calcium stearate or other metallic stearate, talc, waxes and glycerides, light mineral oil, glyceryl behenate, colloidal silica, hydrogenated vegetable oils, corn starch, sodium stearyl fumarate, polyethylene glycols, alkyl sulfates, sodium benzoate, sodium acetate or any combvination thereof.

6. A composition according to claim 1, wherein the film coating system comprises methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, acrylic polymers, ethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinylalcohol, sodium carboxymethylcellulose, cellulose acetate, cellulose acetate phthalate, gelatin, methacrylic acid copolymer, polyethylene glycol, shellac, sucrose, titanium dioxide, carnauba wax, microcrystalline wax, glyceryl monostearate, talc, zein or a combinations thereof.

7. A composition according to any of the preceding claims wherein the composition is a coated tablet.

8. The use of a composition as defined in any of claims 1-7 in the manufacture of a medicament for reducing one or more side-effects of glucocorticoid therapy in a subject having diminished or disrupted endogenous glucocorticoid secretory pattern.

9. The use according to claim 8, wherein the composition is manufactured in an oral dosage form, wherein from about 15 to about 35% w/w of the total amount of glucocorticoids is immediate released upon administration and the remaining part of the glucocorticoids is modified released during a time period of at least about 8 hours.

10. The use according to claims 8 or 9, wherein the composition is manufactured in a single-unit dosage form comprising a core containing a part of the glucocorticoids and the core being coated with the remaining part of the glucocortiocid.

11. The use according to claim 10, wherein the core is of a swelling matrix type.

12. The use according to any of claims 8-11, wherein the one or more side-effects are selected from the group consisting of: gain of weight, increase in cardiovascular risk factors, increase in bone degradation, metabolic risk factors.

13. The use of a composition as defined in any of claims 1-7 for use in the manufacture of a medicament for treating or preventing a diminished or disrupted endogenous glucocorticoid secretory pattern in a subject having sufficient adrenal capacity.

14. The use according to claim 13, wherein the diminished or disrupted endogenous glucocorticoid secretory pattern is associated with disturbed circadian plasma cortisol concentration-time profile of said subject.

15. The use according to claim 13 or 14, wherein the disturbed circadian plasma cortisol concentration-time profile arises from hypothyroidism, depression, sleep deprivation, insomnia, sleep disturbances, adrenal fatigue syndrome, chronic fatigue syndrome, obesity, tertiary adrenal insufficiency, circadian rhythm sleep disorders, shift-work, jet-lag, obesity, cachexia or chronic stress.

16. The use according to claims 13-15, wherein the daily dose of said glucocortioid (expressed as hydrocortisone equivalents) is from about 1 mg/70 kg bodyweight to about 10 mg/70 kg bodyweight.