Claims

1 Use of a methylthioninium (MT)-containing compound in the manufacture of a medicament for use in a ~~A~~ method of therapeutic or prophylactic treatment of a ~~neurodegenerative~~ disorder ~~of protein aggregation~~which is mild cognitive impairment or Alzheimer's disease in a human subject,

~~which method comprises orally administering to said subject a~~wherein the methylthioninium (MT)-containing compound is to be administered orally to the subject,

wherein ~~said administration provides~~ a total daily dose of between 0.5 and 20 mg of MT is to be administered to the subject per day, optionally split into 2 or ~~more~~ 3 doses, wherein the MT-containing compound is characterised by a purity of greater than 97%, and wherein the MT-containing compound is methylthioninium chloride (MTC).

2 The use as claimed in claim 1 wherein the subject has not historically received treatment with an acetylcholinesterase inhibitor or an N-methyl-D-aspartate receptor antagonist.

~~2~~3 The use ~~A method~~ as claimed in claim 1 or claim 2 wherein the total daily dose of MT is from ~~around~~ any of 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4 mg to ~~around any of~~ 5, or 6~~, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20~~ mg.

~~3 A method as claimed in claim 1 or claim 2 wherein the total daily dosage is 1 to 20mg; 2 to 15 mg; or 3 to 10 mg.~~

~~4 A method as claimed in claim 3 wherein the total daily dosage is 3.5 to 7 mg.~~

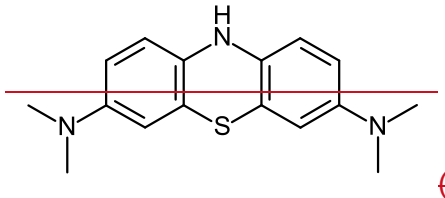
~~5 A method as claimed in claim 4 wherein the total daily dosage is 4 to 6 mg.~~

~~6~~4 The use ~~A method~~ as claimed in claim ~~2~~ 3 wherein the total daily dose of MT is ~~about~~ 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, or 6~~, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20~~mg.

~~7~~5 The use ~~A method~~ as claimed in any one of claims 1 to ~~6~~ 4 wherein the total daily dose of the MT-containing compound is to be administered as a split dose twice a day or three times a day.

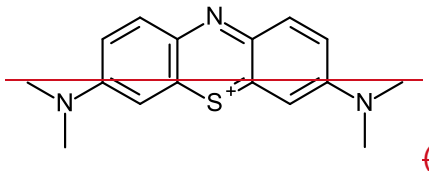
6 The use as claimed in any one of claims 1 to 4 wherein the total daily dose of the MT-containing compound is to be administered as a single dose.

~~8 A method as claimed in any one of claims 1 to 7 wherein the compound is a salt of either:~~



(LMT)

or



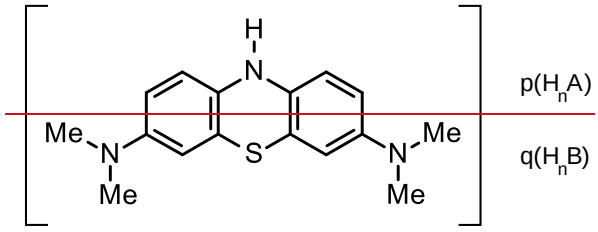
(MT+)

or a hydrate or solvate thereof.

9 A method as claimed in claim 8 wherein a mixture of LMT and MT+ containing compounds are administered.

10 A method as claimed in claim 8 wherein the compound is an LMT compound.

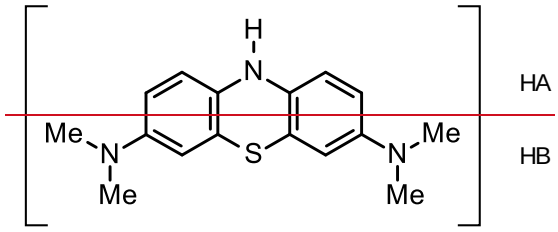
11 A method as claimed in claim 10 wherein the compound is an LMTX compound of the following formula:



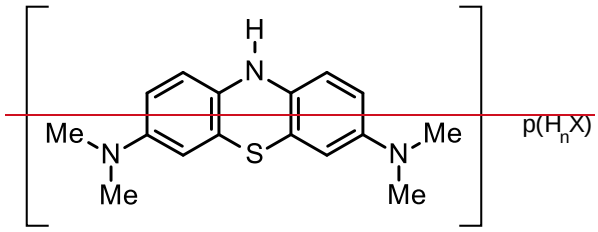
wherein each of H_nA and H_nB (where present) are protic acids which may be the same or different,

and wherein p = 1 or 2; q = 0 or 1; n = 1 or 2; (p + q) × n = 2.

12 A method as claimed in claim 11 wherein the compound has the following formula, where HA and HB are different mono-protic acids:

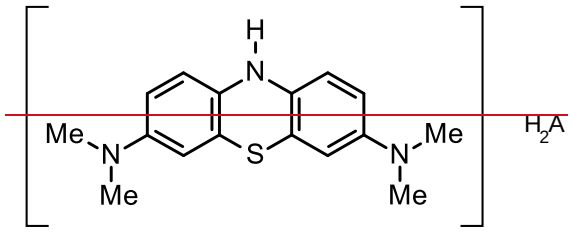


13 A method as claimed in claim 11 wherein the compound has the following formula:

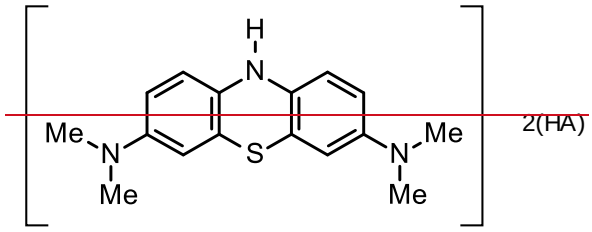


wherein each of H_nX is a protic acid.

14 A method as claimed in claim 11 wherein the compound has the following formula and H_2A is a di-protic acid:



15 A method as claimed in claim 13 wherein the compound has the following formula and is a bis-monoprotic acid:



16 A method as claimed in any one of claims 11 to 15 wherein the or each protic acid is an inorganic acid.

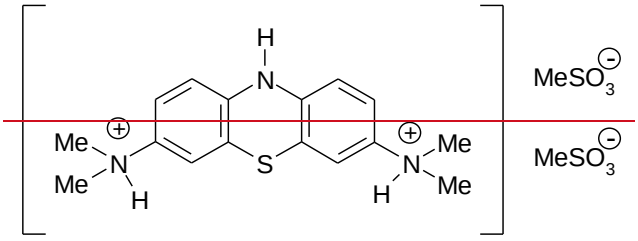
17 A method as claimed in claim 16 wherein each protic acid is a hydrohalide acid.

18 A method as claimed in claim 16 wherein the or each protic acid is selected from HCl; HBr; HNO_3; H_2SO_4.

19 A method as claimed in any one of claims 11 to 15 wherein the or each protic acid is an organic acid.

20 A method as claimed in claim 19 wherein the or each protic acid is selected from H_2CO_3; CH_3COOH; methanesulfonic acid, 1,2-ethanedisulfonic acid, ethansulfonic acid, naphthalenedisulfonic acid, p-toluenesulfonic acid.

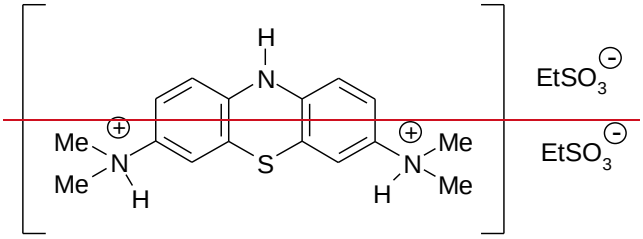
~~21 A method as claimed in claim 20 wherein the compound is LMTM:~~

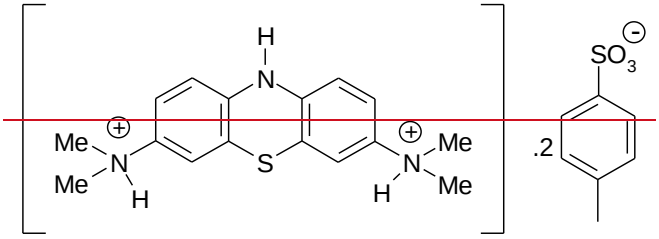


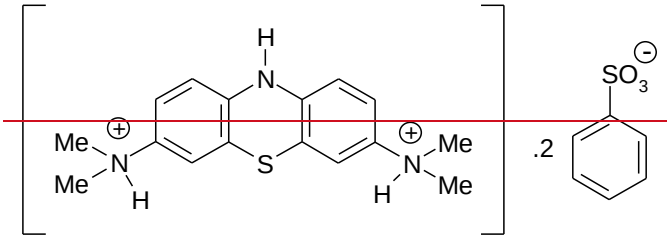
~~22 A method as claimed in claim 21 wherein the total daily dose of LMTM is around 0.8 to 33 mg/day, more preferably 6 to 12 mg/day of LMTM total.~~

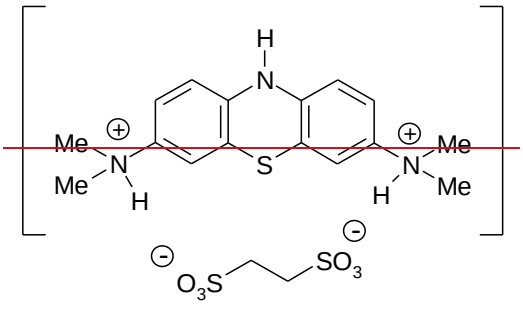
~~23 A method as claimed in claim 22 wherein the dose of LMTM is around 9 mg/once per day; 4 mg b.i.d.; 2.3 mg t.i.d.~~

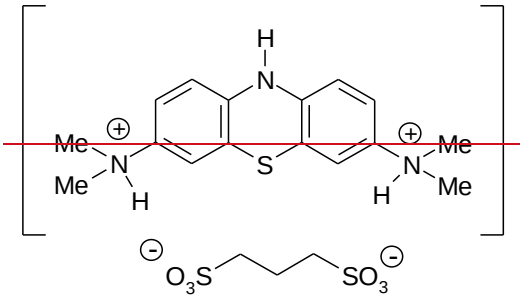
~~24 A method as claimed in claim 20 wherein the compound is selected from the list consisting of:~~

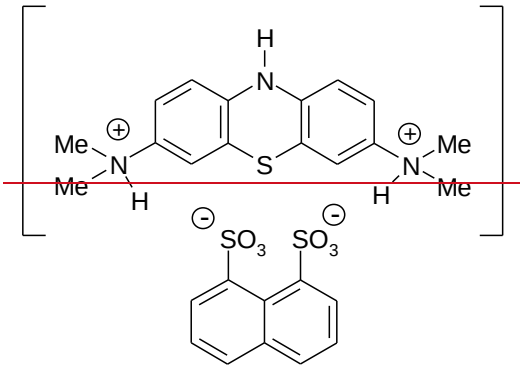




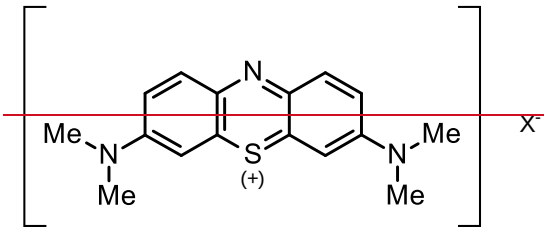








~~25 A method as claimed in claim 8 wherein the compound is an MT^+ salt having the formula or being a hydrate, solvate, or mixed salt thereof:~~



~~where X^- is an anionic counter ion.~~

~~26 A method as claimed in claim 25 wherein the compound is MTC.~~

~~27~~7 The use ~~A method~~ as claimed in ~~claim 26~~any one of claims 1 to 6 wherein the MT-containing compound is an MTC polymorph which is MTC pentahydrate.

8 The use as claimed in claim 7 wherein the total daily dose of MTC pentahydrate is 5 to 10 mg/day.

~~28~~9 The use ~~A method~~ as claimed in ~~claim 26 or claim 27~~any one of claims 1 to 8 wherein the MT-containing compound is characterised by a purity of greater than 98%.

~~29~~10 ~~A method~~The use as claimed in any one of claims ~~26 to 28~~1 to 9, wherein the MT-containing compound is characterised by a purity of greater than 98% and one or more of the following:
(i) less than 1% Azure B as impurity;
(ii) less than 0.13% MVB (Methylene Violet Bernstein) as impurity;
(iii) less than 0.15% Azure A as impurity;
(iv) less than 0.15% Azure C as impurity; or
(v) an elementals purity better than less than 100 µg/g Aluminium (Al); less than 1 µg/g Cadmium (Cd); less than 100 µg/g Chromium (Cr); less than 300 µg/g Copper (Cu); less than 10 µg/g Tin (Sn); less than 200 µg/g Iron (Fe); less than 10 µg/g Manganese (Mn); less than 1 µg/g Mercury (Hg); less than 10 µg/g Molybdenum (Mo); less than 10 µg/g Nickel (Ni); less than 10 µg/g Lead (Pb); and less than 100 µg/g Zinc (Zn).

~~30~~11 ~~A method~~The use as claimed in any one of claims ~~26 to 29~~1 to 10, wherein the MT-containing compound is characterised by a purity of greater than 98% and less than 1% Azure B as impurity.

~~31~~12 ~~A method~~The use as claimed in any one of claims ~~26 to 30~~1 to 11, wherein the MT-containing compound is characterised by a purity of greater than 98% and an elementals purity better than less than 100 µg/g Aluminium (Al); less than 1 µg/g Cadmium (Cd); less than 100 µg/g Chromium (Cr); less than 300 µg/g Copper (Cu); less than 10 µg/g Tin (Sn); less than 200 µg/g Iron (Fe); less than 10 µg/g Manganese (Mn); less than 1 µg/g Mercury (Hg); less than 10 µg/g Molybdenum (Mo); less than 10 µg/g Nickel (Ni); less than 10 µg/g Lead (Pb); and less than 100 µg/g Zinc (Zn).

~~32~~13 ~~A method~~The use as claimed in any one of claims ~~26 to 31~~1 to 12, wherein the MT-containing compound is characterised by:
(i) at least 98% purity
(i) less than 1% Azure B as impurity; and
(ii) an elementals purity better than the European Pharmacopeia limits of less than 100 µg/g Aluminium (Al); less than 1 µg/g Cadmium (Cd); less than 100 µg/g Chromium (Cr); less than 300 µg/g Copper (Cu); less than 10 µg/g Tin (Sn); less than 200 µg/g Iron (Fe); less than 10 µg/g Manganese (Mn); less than 1 µg/g Mercury (Hg); less than 10 µg/g Molybdenum (Mo); less than 10 µg/g Nickel (Ni); less than 10 µg/g Lead (Pb); and less than 100 µg/g Zinc (Zn).~~33 A method as claimed in any one of claims 27 to 32 wherein the total daily dose of MTC.5H_2O is around 0.7 to 29 mg/day, more preferably around 5 to 10 mg/day.~~

34 A method as claimed in claim 25 wherein the compound is selected from: MTC.0.5$ZnCl_2$; MTI ; MTI.HI ; MT.NO_3.

35 A method as claimed in any one of claims 25 to 34 wherein the MT^+ salt is formulated with a reducing agent which is optionally ascorbate, and then optionally lyophilized.

36 A method as claimed in any one of claims 1 to 35 wherein the duration of treatment with the MT compound is at least 7, 8, 9, 10, 11, 12 months, or longer; optionally at least 1, 2, 3, 4, 5 years, or longer.

37 A method as claimed in any one of claims 1 to 36 wherein the subject is a human who has been diagnosed as having said cognitive or CNS disorder, or wherein said method comprises making said diagnosis.

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38 A method of prophylactic treatment of a neurodegenerative disorder of protein aggregation in a subject,
which method comprises orally administering to said patient an MT containing compound, wherein said administration provides a total daily dose of between 0.5 and 20mg of MT to the subject per day, optionally split into 2 or more doses.

39 A method as claimed in claim 38 wherein the compound or dose is as defined in any one of claims 1 to 36.

40 A method as claimed in claim 38 or claim 39 wherein the subject is a human who has been assessed as being susceptible to the cognitive or CNS disorder, optionally based on familial or genetic or other data.

41 A method as claimed in any one of claims 1 to 40 wherein the subject has not historically received treatment with an acetylcholinesterase inhibitor or an N-methyl-D-aspartate receptor antagonist.

42 A method as claimed in any one of claims 1 to 40 wherein the subject has historically received treatment with an acetylcholinesterase inhibitor and\or an N-methyl-D-aspartate receptor antagonist, but ceased that medication at least 1, 2, 3, 4, 5, 6, 7 days, or 2, 3, 4, 5, 6, 7, 8, weeks etc. prior to treatment with the MT containing compound.

43 A method as claimed in any one of claims 1 to 40 wherein the subject is selected as one who is receiving treatment with an acetylcholinesterase inhibitor and\or an N-methyl-D-aspartate receptor antagonist,
wherein said treatment with the acetylcholinesterase inhibitor and\or an N-methyl-D-aspartate receptor antagonist is discontinued prior to treatment with the MT containing compound.

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44 A method as claimed in any one of claims 1 to 43 wherein the disorder is a tauopathy.

4514 The use A method as claimed in any one of claims 1 to 44 13 wherein the disorder is selected from the list consisting of: Pick's disease, progressive supranuclear palsy, frontotemporal dementia, FTD with parkinsonism linked to chromosome 17, frontotemporal lobar degeneration syndromes; disinhibition-dementia-parkinsonism-amyotrophy complex, pallido-ponto-nigral degeneration, Guam-ALS syndrome, pallido nigro luysian degeneration, cortico-basal degeneration, dementia with argyrophilic grains, dementia pugilistica or chronic traumatic encephalopathy, Down's syndrome, subacute sclerosing panencephalitis, mild cognitive impairment, Niemann-Pick disease, type C, Sanfilippo syndrome type B, or a myotonic dystrophy DM1 or DM2.

4615 The use A method as claimed in any one of claims 1 to 44 13 wherein the disorder is Alzheimer's disease.

47 A method as claimed in any one of claims 1 to 43 wherein the disorder is a polyglutamine disorder.

48 A method as claimed in claim 47 wherein the polyglutamine disorder is Huntington's disease, spinal bulbar muscular atrophy, dentatorubropallidoluysian atrophy or spinocerebellar ataxias.

49 A method as claimed in any one of claims 1 to 43 wherein the disorder is a TDP-43 proteinopathy.

50 A method as claimed in claim 49 wherein the TDP-43 proteinopathy is FTLD-TDP.

51 A method as claimed in any one of claims 1 to 43 wherein the disorder is a synucleinopathy.

52 A method as claimed in claim 51 wherein the synucleinopathy is selected from Parkinson's disease, dementia with Lewy bodies and multiple system atrophy.

53 A method as claimed in any one of claims 1 to 43 wherein the disorder is hereditary cerebral angiopathy.

54 A method as claimed in any one of claims 1 to 43 wherein the disorder is amyotrophic lateral sclerosis.

55 A method as claimed in any one of claims 1 to 43 wherein the disorder is familial encephalopathy with neuronal inclusion bodies.

5616 The use A as claimed in any one of claims 1 to 15, wherein the MT-containing compound is to be administered pharmaceutical composition comprising an MT

compound as defined in any one of claims 1 to 35, and a pharmaceutically acceptable carrier or diluent, optionally in the form of a dosage unit,

wherein the amount of MT in the composition or dosage unit is 0.5 to 104 mg.

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57 A nutraceutical composition comprising an MT compound as defined in any one of claims 1 to 35,

and a nutrient compound, optionally in the form of a dosage unit or defined portion of a foodstuff,

wherein the amount of MT in the unit is 0.5 to 10 mg,

and wherein the nutrient is selected from the list consisting of: vitamin, micronutrient, antioxidant, herb, plant extract, seed extract, vegetable or fish oil, mineral, trace element, enzyme, or amino acid.

58 A composition as claimed in claim 57 which is selected from the list consisting of:

vitamin, which is optionally vitamin B_9, B_6 or B_{12}, vitamin C, vitamin E,

micronutrient and\or antioxidant, which is optionally a flavanol, flavonol, flavone, isoflavone, flavanone, anthocyanadin, non-flavonoid polyphenol, carotenoid, crocin, diterpene;

a herb or other plant extract, which is optionally *Ginkgo biloba, Hypericum perforatum*, *Piper methysticum*. *Valeriana officinalis*, *Bacopa monniera*, *Convolvulus pluricaulis*;

a plant oil or fish oil, which is optionally a ω-3 poyunsaturated fatty acid.

59 A composition as claimed in claim 57 or claim 58 which is a defined portion of a foodstuff.

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60 A composition as claimed in any one of claims 56 to 59 which is a tablet.

61 A composition as claimed in claim 60 which is a capsule.

62 A composition as claimed in any one of claims 56 to 61 which comprises any of: 1 to 10mg; 2 to 9 mg; 3 to 8 mg; 3.5 to 7 mg; 4 to 6 mg of MT compound.

63 A composition as claimed in any one of claims 56 to 62 wherein the MT compound is at least 97% pure.

64 A composition as claimed in any one of claims 56 to 63 which comprises about any of: 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 15, 16, 17, or 18 mg of LMTM.

65 A composition as claimed in any one of claims 56 to 63 which comprises about any of: 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 15, 18, or 20 mg of MTC.$5H_20$.

66 A composition as claimed in any one of claims 56 to 65 which is an immediate release composition.

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67 A container comprising:
(i) a plurality of dosage units or defined portion foodstuffs each of which is a composition as claimed in any one of claims 56 to 66;
(ii) a label and\or instructions for their use according to a method of treatment as defined in any one of claims 1 to 55.

68 A container as claimed in claim 67, wherein the container comprises dosage units, and the dosage units are present in a blister pack which is substantially moisture-impervious.

69 A container as claimed in claim 67 or claim 68 wherein the label or instructions provide information regarding the disorder for which the composition is intended.

70 A container as claimed in any one of claims 67 to 69 wherein the label or instructions provide information regarding the maximum permitted daily dosage of the dosage units.

71 A container as claimed in any one of claims 67 to 70 wherein the label or instructions provide information regarding the suggested duration of the treatment.

72 A container as claimed in any one of claims 67 to 71 wherein the label or instructions provide information instructing that the compositions should not be used in conjunction with any of: an acetylcholinesterase inhibitor or an N-methyl-D-aspartate receptor antagonist.

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73 A method of therapeutic treatment of Alzheimer's disease (AD) in a subject, which method comprises orally administering to said subject a methylthioninium (MT)-containing compound,
wherein said treatment does not include administration of either or both of an acetylcholinesterase inhibitor or an N-methyl-D-aspartate receptor antagonist.

74 A method of prophylactic treatment of AD in a subject,
which method comprises orally administering to said patient an MT containing compound, wherein said treatment does not include administration of either or both of an acetylcholinesterase inhibitor or an N-methyl-D-aspartate receptor antagonist.

75 A method as claimed in claim 73 or claim 74 wherein the administration provides a total daily dose of between 0.5 and 300mg of MT to the subject per day, optionally split into 2 or more doses.

~~76 A method as claimed in any one of claims 73 to 75 wherein the subject has not historically received treatment with an acetylcholinesterase inhibitor or an N-methyl-D-aspartate receptor antagonist.~~

~~77 A method as claimed in any one of claims 73 to 75 wherein the subject has historically received treatment with an acetylcholinesterase inhibitor and\or an N-methyl-D-aspartate receptor antagonist, but ceased that medication at least 1, 2, 3, 4, 5, 6, 7 days, or 2, 3, 4, 5, 6, 7, 8, weeks etc. prior to treatment with the MT containing compound.~~

~~78 A method as claimed in any one of claims 73 to 75 wherein the subject is selected as one who is receiving treatment with an acetylcholinesterase inhibitor and\or an N-methyl-D-aspartate receptor antagonist,~~
~~wherein said treatment with the acetylcholinesterase inhibitor and\or an N-methyl-D-aspartate receptor antagonist is discontinued prior to treatment with the MT containing compound.~~

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~~79 A method as claimed in claim 46 or any one of claims 73 to 78 wherein the treatment is a combination treatment of a first agent which is the MT-containing compound at the specified dosage in combination with a second agent which is an inhibitor of amyloid precursor protein to beta-amyloid.~~

~~80 A method as claimed in claim 46 or any one of claims 73 to 79 wherein the treatment achieves or is for achieving an improvement in subject in one of more of the following criteria: 3, 4 or 5-point improvement on the 11-item Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) over a 52-week period; 4, 5 or 6 point improvement on the 23-item Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) over a 52-week period; a reduction in the increase of Lateral Ventricular Volume (LVV), as measured by the Ventricular Boundary Shift Integral (VBSI) of 1 or 2 cm^3 over a 52-week period.~~

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~~81 A container comprising:~~
~~(i) a plurality of dosage units each of which is a composition comprising an MT compound as defined in any one of claims 1 to 35, and a pharmaceutically acceptable carrier or diluent, wherein the amount of MT in the unit is 0.5 to 300 mg;~~
~~(ii) a label or instructions provide information that the dosage units are intended for use in treating Alzheimer's disease (AD);~~
~~(iii) a label or instructions provide information instructing that the compositions should not be used in conjunction with any of: an acetylcholinesterase inhibitor or an N-methyl-D-aspartate receptor antagonist.~~

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~~82 An MT-containing compound or composition as described in any one of claims 1 to 66, for use in a method of treatment as defined in any one of claims 1 to 55 or 73 to 80.~~

~~83 Use of an MT-containing compound or composition as described in any one of claims 1 to 66, in the manufacture of a medicament for use a method of treatment as defined in any one of claims 1 to 55 or 73 to 80~~

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~~84 A method of therapeutic or prophylactic treatment of a neurodegenerative disorder of protein aggregation in a subject, which neurodegenerative disorder is optionally Alzheimer's disease,~~
~~which method comprises orally administering to said subject a composition as defined in any one of claims 56 to 66.~~