What is claimed

1. ~~Lurbinectedin~~Use of lurbinectedin in the manufacture of a medicament~~,~~ for ~~use in~~ the treatment of small cell lung cancer (SCLC), said treatment comprising:

(1) administering a prophylactic dose of a corticosteroid and a serotonin antagonist effective to reduce nausea associated with administration of lurbinectedin to the patient on the day of and prior to administration of lurbinectedin to the patient; and

(2) administering lurbinectedin at a dose of 2 to 3.2 mg/m^2 to the patient by intravenous infusion;

wherein the corticosteroid is dexamethasone intravenously administered at a dose of 8 mg of dexamethasone or a dose of a corticosteroid equivalent to 8 mg of dexamethasone administered intravenously.

2. The use of claim 1, wherein the method further comprises administering one or more antiemetic agents within 2, 3, or 4 days after administration of lurbinectedin to the patient

3. The use of claim 1, wherein the serotonin antagonist is ondansetron intravenously administered at a dose of 8 mg of ondansetron or a dose of a serotonin antagonist equivalent to 8 mg of ondansetron administered intravenously.

4. The use of claim 2, wherein the one or more antiemetic agents administered after lurbinectedin administration are selected from a corticosteroid, a serotonin antagonist, and metoclopramide.

5. The use of claim 4, wherein the one or more antiemetic agents are administered at a dose of 4 mg dexamethasone, 8 mg ondansetron, or 10 mg metoclopramide, or a combination thereof.

6. The use of any one of claims 1 to 5, wherein the patient is not treated with doxorubicin in combination with the lurbinectedin.

7. The method of any one of claims 1 to 6, wherein the patient has progressed after prior platinum-containing therapy or prior immunotherapy.

8. Use of lurbinectedin in the manufacture of a medicament for the treatment of small cell lung cancer (SCLC), said treatment comprising:

(1) administering a prophylactic dose of a corticosteroid and a serotonin antagonist effective to reduce nausea associated with administration of lurbinectedin to the patient on the day of and prior to administration of lurbinectedin to the patient; and

(2) administering lurbinectedin at a dose of 2 to 3.2 mg/m^2 to the patient by intravenous infusion; and

wherein the lurbinectedin comprises deacetylated lurbinectedin at a value no greater than 0.8%, 0.7%, 0.6%, 0.5%, or 0.4% wt/wt based on the total weight of lurbinectedin.

~~2.~~9. Use of lurbinectedin in the manufacture of a medicament for~~Lurbinectedin, for use in~~ the treatment of small cell lung cancer (SCLC), including metastatic SCLC, said treatment comprising:

(1) administering a first dose of 3.2 mg/m^2 of lurbinectedin to the patient by intravenous infusion if the patient has an absolute neutrophil count of at least 1500 cells/mm^3 and a platelet count of at least 100,000/mm^3; and

(2) identifying an adverse reaction in the patient after said administering, wherein the adverse reaction is Grade 2 hepatotoxicity or other adverse reaction, ≥Grade 3 (severe) hepatotoxicity or other adverse reaction, Grade 4 thrombocytopenia (Platelet count less than 25,000 cells/mm^3), Grade 3 thrombocytopenia (Platelet count less than 50,000 cells/mm^3) with bleeding, Grade 4 neutropenia (Neutrophil count less than 500 cells/mm^3), or any grade febrile neutropenia (Neutrophil count < LLN);

(3) after the adverse reaction is identified and at the later of 21 days of the first dose or after the patient's neutrophil count is greater than 1500 cells/mm^3; platelet count is greater than about 100,000 mm^{3}and, optionally, hemoglobin levels are greater than about 9 g/dL and the hepatotoxicity or other adverse reaction is Grade 1 or less:

(i) if the identified adverse reaction consists of isolated Grade 4 neutropenia (Neutrophil count less than 500 cells/mm^3), administering to the

patient a dose of lurbinectedin that is equal to the first dose every three weeks with G-CSF prophylaxis;

(ii) if the identified adverse reaction consists of Grade 2 ~~hepatoxocity~~hepatotoxicity or other adverse reaction, administering to the patient a dose of lurbinectedin that is equal to the first dose every three weeks; or

(iii) if the identified adverse reaction is ≥Grade 3 (severe) hepatotoxicity or other adverse reaction, Grade 4 thrombocytopenia (Platelet count less than 25,000 cells/mm3), Grade 3 thrombocytopenia (Platelet count less than 50,000 cells/mm3) with bleeding, or any grade febrile neutropenia is, administering to the patient a reduced dose of lurbinectedin compared to the first dose every 3 weeks.

10. The use of claim 9, wherein the first reduced dose is 2.6 mg/m^2;

optionally wherein if the patient experiences after being administered a reduced dose of 2.6 mg/m^2, an adverse reaction of ≥Grade 3 (severe) hepatotoxicity or other adverse reaction, Grade 4 thrombocytopenia (Platelet count less than 25,000 cells/mm^3), Grade 3 thrombocytopenia (Platelet count less than 50,000 cells/mm^3) with bleeding, or any grade febrile neutropenia, then at the later of 21 days of the administration of the prior dose or after the patient's neutrophil count is greater than 1500 cells/mm^3; platelet count is greater than about 100,000 mm^{3}and, optionally, hemoglobin levels are greater than about 9 g/dL and the hepatotoxicity or other adverse reaction is Grade 1 or less, administering to the patient a second reduced dose of 2.0 mg/m^2 lurbinectedin every three weeks;

optionally further comprising discontinuing administration of lurbinectedin after identification of the adverse reaction after administration of the second reduced dose or if the patient does not recover to an absolute neutrophil count of at least 1500 cells/mm^3 and platelet count of at least 100,000/mm^3 within 2 weeks of the scheduled dose.

11. The use of any one of claims 1 to 12 in which the lurbinectedin is administered as an infusion formulation prepared by diluting a reconstituted lyophilized formulation comprising 4 mg lurbinectedin, a buffer derived from an organic carboxylic acid (e.g. lactic acid), and a disaccharide (e.g. sucrose), which, when reconstituted has a pH of 3.5 to 4.5.

3.12. A method of storing a lyophilized lurbinectedin composition comprising:

storing a lyophilized composition comprising 4 mg lurbinectedin; a buffer derived from an organic carboxylic acid; and a disaccharide at a temperature of 5º C ± 3º C for at least 48 months,

wherein the lyophilized composition is formulated such that reconstitution with 8 mL of water will yield a solution having a pH of 3.5 to 4.5 and

wherein after the at least 24 months storage, the amount of Impurity Ddeacetylated lurbinectedin present in the composition is not more than 0.8% wt./wt. of the total lurbinectedin weight.

4.13. Use of lurbinectedin in the manufacture of a medicament for Lurbinectedin and a topoisomerase inhibitor selected from SN-38 and irinotecan; for use in the treatment of solid tumor, endometrial cancer, SCLC, soft tissue sarcoma, glioblastoma, pancreatic adenocarcinoma, mesothelioma, colorectal carcinoma, or epithelial ovarian cancer in a patient in need thereof; said treatment comprising the use of lurbinectedin and a topoisomerase inhibitor selected from SN-38 and irinotecan, and comprising:

administering to the patient lurbinectedin and a topoisomerase inhibitor selected from SN-38 and irinotecan on day one of a treatment cycle;

wherein the lurbinectedin is administered at a dose of 1 to 2.5 mg/m^2 and

wherein the topoisomerase inhibitor is administered at a dose equivalent to 50 to 75 mg of irinotecan/m^2.

5.14. The use of claim 415, wherein a dose of the topoisomerase inhibitor equivalent to 50 mg to 75 mg of irinotecan/m^2 is administered on day 8 of the treatment cycle.; and/or

6. The use of claim 4 or claim 5, wherein the treatment cycle is an 18, 19, 20, 21, 22, 23, 24, or 25 day cycle; and/or.

7. The use of any one of claims 4 to 6 wherein the lurbinectedin is administered at a dose of 2 mg/m^2.; and/or

8. The use of any one of claims 4 to 7 wherein the topoisomerase inhibitor is irinotecan and is administered at a dose of 75 mg/m^2; and/or.

~~9. The use of any one of claims 4 to 8~~ wherein the treatment cycle is 21 days; and/or~~.~~

~~10. The use of any one of claims 4 to 9~~ wherein the solid tumor is SCLC, endometrial carcinoma, soft tissue sarcoma or glioblastoma; and/or~~.~~

~~11. The use of any one of claims 4 to 10~~ wherein the patient is administered G-CSF to manage the myelosuppressive effects of said treatment; and/or~~.~~

~~12. The use of any one of claims 4 to 11~~ wherein if after the administration on day 1 the patient exhibits hematological toxicity, then omitting the administration of the dose of irinotecan on day 8 of the treatment cycle.

~~13.~~15. A pharmaceutical composition prepared by:

lyophilizing an aqueous stock solution comprising lurbinectedin, an organic carboxylic acid, sodium hydroxide, and sucrose to produce a lyophilized powder,

wherein the concentration of lurbinectedin in the aqueous stock solution is 0.5 mg/mL, wherein the ratio lurbinectedin to sucrose is 1 mol of lurbinectedin to 455 to 465 mol sucrose and wherein the lyophilized powder is formulated such that reconstitution with 8 mL of water will yield a solution having a pH of 3.5 to 4.1; and

storing the lyophilized powder at 5º C ± 3º C for 30 months to 60 months to produce the pharmaceutical composition,

wherein after storage the amount of ~~Impurity D~~deacetylated lurbinectedin present in the composition is not more than 0.8% wt./wt. of the total lurbinectedin weight.

~~14.~~16. A pharmaceutical composition comprising:

a lyophilized composition comprising 4 mg lurbinectedin, a buffer derived from an organic acid, and a disaccharide,

wherein the lurbinectedin and disaccharide are present at a ratio of 1 mol lurbinectedin to 455 to 465 mol disaccharide,

wherein the lyophilized composition is formulated such that reconstitution with 8 mL of water will yield a solution having a pH of 3.5 to 4.5, and

wherein the lyophilized composition further comprises a degradation product resulting from deacetylation of lurbinectedin at a value no greater than 0.8%, 0.7%, 0.6%, 0.5%, or 0.4%. wt./wt based upon the total weight of lurbinectedin.

~~15.~~17. A method of reducing lurbinectedin degradation in a lyophilized formulation comprising lurbinectedin, the method comprising adding lactate buffer to a stock solution from which the lyophilized formulation is prepared, wherein the resulting ratio of lurbinectedin to lactate buffer is between 1 mol:44 mol and 1 mol:54mol; wherein the lurbinectedin degradation product from deacetylation does not exceed 0.8% wt./wt. of the total lurbinectedin weight when stored at 5 degree C ± 3 degree C for at least 24 months or at least 36 months or at least 48 months or at least 60 months.

~~16.~~18. Use of lurbinectedin in the manufacture of a medicament for ~~Lurbinectedin, for use in~~ the treatment of small cell lung cancer (SCLC), said treatment comprising administering lurbinectedin at a dose of 2 to 3.2 mg/m^2 to a patient by intravenous infusion every 3 weeks, wherein the lurbinectedin is provided in a lyophilized formulation comprising lurbinectedin, lactic acid, and sucrose, wherein the ratio of lurbinectedin:lactic acid:sucrose is between 1 mol:46 mol:455 mol and 1 mol:50 mol:465 mol , wherein the formulation is stable at 5 degree C ± 3 degree C for at least 24 months or at least 36 months or at least 48 months or at least 60 months such that the lurbinectedin degradation product from deacetylation does not exceed 0.8% wt./wt. of the total lurbinectedin weight.

~~17.~~19. A packaged, lyophilized composition, comprising:

4 mg lurbinectedin, a buffer derived from an organic acid and a disaccharide packaged in a vial,

wherein the dissolution of the lyophilized composition in about 8 mL of water provides a lurbinectedin solution having a pH of about 3.5 to about 4.1, and

wherein the lyophilized composition comprises less than about 0.3 % of ~~Impurity D~~deacetylated lurbinectedin (w/w based on lurbinectedin) when the composition is packaged, and wherein upon storage at about 5 degrees C for about 24 months or about 36 months or about 48 months the composition comprises not more than about 0.8% of ~~Impurity D~~deacetylated lurbinectedin (w/w based on lurbinectedin).

~~18.~~20. A packaged, lyophilized composition, comprising:

4 mg lurbinectedin, a buffer derived from an organic acid and a disaccharide packaged in a vial,

wherein the dissolution of the lyophilized composition in about 8 mL of water provides a lurbinectedin solution having a pH of about 3.8 to about 4.1, and

wherein the lyophilized composition comprises less than about 0.3 % of ~~Impurity D~~deacetylated lurbinectedin (w/w based on lurbinectedin) when the composition is packaged, and wherein the composition comprises substantially the same amount ~~Impurity D~~deacetylated lurbinectedin (w/w based on lurbinectedin) after the packaged composition has been stored at about 25 degrees C and about 60% relative humidity for up to about 1, 2, 3, 6, 9, or 12 months.

~~19.~~21. The composition of claim ~~17~~ 19 or claim ~~18~~20, wherein the composition is prepared by a process comprising:

(a) providing a solution of lurbinectedin and an organic acid;

(b) providing a solution of a base, an organic acid and a disaccharide;

(c) combining the solutions of Step (a) and Step (b);

(d) adjusting the pH of the solution of Step (c) to about 3.8 to about 4.1; and

(e) lyophilizing the solution of Step (d) to provide the lyophilized composition.

~~20.~~22. Use of lurbinectedin in the manufacture of a medicament for ~~Lurbinectedin for use in~~ the treatment of small cell lung cancer (SCLC), said treatment comprising:

1) dissolving a packaged, lyophilized composition comprising 4 mg lurbinectedin, a buffer derived from an organic acid and disaccharide in about 8 mL of water to provide a lurbinectedin solution having a pH of about 3.5 to about 4.1,

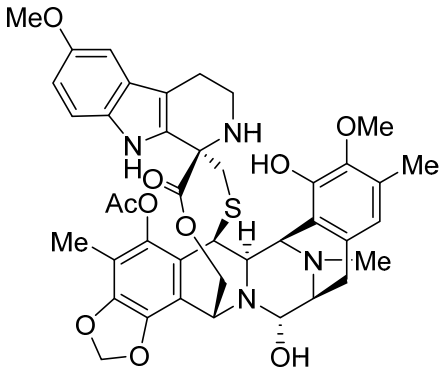
and

2) administering about 2 to 3.2 mg/m^2 of lurbinectedin to a patient whose SCLC has progressed after prior platinum-containing therapy by intravenous infusion every 3 weeks and

wherein the lyophilized composition comprises less than about 0.3 % of ~~Impurity D~~deacetylated lurbinectedin (w/w based on lurbinectedin) at packaging, and

wherein upon storage at about 5 degrees C for about 24 months the composition comprises less than about 0.8% of ~~Impurity D~~deacetylated lurbinectedin (w/w based on lurbinectedin).

~~21.~~23. Lurbinectedin Form B of the formula (I):



(I);

that exhibits a X-ray powder diffraction pattern comprising four or more peaks at 2-theta angles selected from the group consisting of 6.2 ± 0.2º, 7.6 ± 0.2º, 9.0 ± 0.2º, 10.9 ± 0.2º, 14.9 ± 0.2º and 15.3 ± 0.2º; optionally.

~~22. Lurbinectedin according to claim 21,~~ wherein the X-ray powder diffraction pattern comprises five or more peaks at 2-theta angles selected from the group consisting of 6.2 ± 0.2º, 7.6 ± 0.2º, 9.0 ± 0.2º, 10.9 ± 0.2º, 14.9 ± 0.2º and 15.3 ± 0.2º; and/or

wherein the X-ray powder diffraction pattern comprises peaks at 2-theta angles of 6.2 ± 0.2º, 7.6 ± 0.2º, 9.0 ± 0.2º, 10.9 ± 0.2º, 14.9 ± 0.2º and 15.3 ± 0.2º; and/or

wherein the X-ray powder diffraction further comprises peaks at 2-theta angles of 12.4 ± 0.2º, 19.2 ± 0.2º and 26.5 ± 0.2º; and/or

wherein the X-ray powder diffraction further comprises peaks at 2-theta angles of 18.4 ± 0.2º, 20.7 ± 0.2 and 24.9 ± 0.2º; and/or

wherein the X-ray powder diffraction further comprises peaks and relative intensities of:

Angle [2-theta]	Relative intensity [%]
6.2 ± 0.2 º	79 ± 6
7.6 ± 0.2 º	100± 3
9.0 ± 0.2 º	63 ± 3
10.9 ± 0.2 º	100 ± 3
14.9 ± 0.2 º	76 ± 3
15.3 ± 0.2 º	75 ± 3

; and/or

wherein the X-ray powder diffraction further comprises peaks and relative intensities of:

Angle[2-theta]	Relative intensity [%]	Angle [2-theta]	Relative intensity [%]
6.2 ± 0.2 º	79 ± 6	14.9 ± 0.2 º	76 ± 3
7.6 ± 0.2 º	100 ± 3	15.3 ± 0.2 º	75 ± 3
9.0 ± 0.2 º	63 ± 3	19.2 ± 0.2 º	34 ± 3
10.9 ± 0.2 º	100 ± 3	26.5 ± 0.2 º	33 ± 3
12.4 ± 0.2 º	40 ± 3		

; and/or

wherein the X-ray powder diffraction further comprises peaks and relative intensities of:

Angle [2-theta]	Relative intensity [%]	Angle [2-theta]	Relative intensity [%]
6.2 ± 0.2 º	79 ± 6	15.3 ± 0.2 º	75 ± 3
7.6 ± 0.2 º	100 ± 3	18.4 ± 0.2 º	29 ± 3
9.0 ± 0.2º	63 ± 3	19.2 ± 0.2 º	34 ± 3
10.9 ± 0.2 º	100 ± 3	20.7 ± 0.2º	32 ± 3
12.4 ± 0.2 º	40 ± 3	24.9 ± 0.2º	26 ± 3
14.9 ± 0.2 º	76 ± 3	26.5 ± 0.2 º	33 ± 3

; and/or

wherein the X-ray powder diffraction is substantially the same as any one of the X-ray powder diffraction patterns shown in Figure 2a or 2b; and/or

further characterized by an IR spectrum comprising peaks at wavelengths (cm^{-1}) of 2928, 1755, 1626, 1485, 1456, 1370, 1197, 1150, 1088, 1003, 959, 916, and 587; and/or

further characterized by a TG-FTIR degradation above 150˚C; and/or characterized by a TG-FTIR mass change to 150˚C being due to loss of water; and/or characterized by a TG-FTIR mass change to 150˚C being due to loss of less than about 5%, less than about 4%, or less than about 3% water; and/or characterized by TG-FTIR indicating a loss of water, preferably around 2-3% water, more preferably 2.6% water; and/or

further characterized by DSC wherein degradation begins above 130˚C; and/or.

~~23. Lurbinectedin according to claim 21 or claim 22,~~ further characterized by an average charge density of not more than about 30 nC/g, not more than about 20 nC/g, not more than about 10 nC/g, not more than about 6 nC/g, not more than about 5 nC/g, about 5 ± 2 nC/g, about 4 ± 2 nC/g, about 4-5 nC/g, about 5 nC/g, or about 4 nC/g; and/or

further characterized by a dispersion of charge density of less than 4.8 nC/g, of between about 0.7 nC/g to less than 4.8 nC/g, or 2.4 ± 2 nC/g.

24. Partially crystalline lurbinectedin; including wherein said partially crystalline lurbinectedin comprises at least a detectible amount of crystalline lurbinectedin, up to 1% w/w crystalline lurbinectedin, up to 5% w/w crystalline lurbinectedin, up to 10% w/w crystalline lurbinectedin, up to 20% w/w crystalline lurbinectedin, up to 30% w/w crystalline lurbinectedin, up to 40% w/w crystalline lurbinectedin, up to 50% w/w crystalline lurbinectedin, up to 60% w/w crystalline lurbinectedin, up to 70% w/w crystalline lurbinectedin, up to 80% w/w crystalline lurbinectedin, up to 90% w/w crystalline lurbinectedin, up to 95% w/w crystalline lurbinectedin, up to 98% w/w crystalline lurbinectedin, or substantially pure crystalline lurbinectedin;

~~optionally~~ wherein said partially crystalline lurbinectedin comprises lurbinectedin Form B as defined in ~~any one of claims 21 to~~claim 23; wherein said Form B may be

present as at least a detectible amount of Form B, up to 1% w/w Form B, up to 5% w/w Form B, up to 10% w/w Form B, up to 20% w/w Form B, up to 30% w/w Form B, up to 40% w/w Form B, up to 50% w/w Form B, up to 60% w/w Form B, up to 70% w/w Form B, up to 80% w/w Form B, up to 90% w/w Form B, up to 95% w/w Form B, up to 98% w/w Form B, or substantially pure Form B.

25. A pharmaceutical composition made from a process including partially crystalline lurbinectedin according to claim ~~24~~34; wherein the pharmaceutical composition is optionally a lyophilized composition; optionally.

~~26. The composition of claim 25,~~ wherein the composition has a total water content of not more than 3%; and/or residual solvents of not more than 1%, 0.5%, 0.1% or substantially not detected; and/or total impurities of not more than 1.9%, 1.8%, 1.7%, 1.6%, 1.5%, 1.4%, or 1.3%; and/or not more than 0.8% of ~~impurity D~~deacetylated lurbinectedin; and/or not more than 0.3% of any unspecified impurity; and/or total related substances of not more than 2.0% and any unspecified substances (highest) not more than 0.7%.

~~27. A process for the preparation of Form B of lurbinectedin as defined in any one of claims 21 to 23, comprising the steps of:~~

~~a) preparing an acidic aqueous solution comprising lurbinectedin or a protonated form thereof; and~~

~~b) basifying the resulting acid aqueous solution with a base or a buffer to precipitate Form B of lurbinectedin.~~

~~28. A process for the manufacture of a lurbinectedin composition, said process employing lurbinectedin as defined in any one of claims 21 to 23, or partially crystalline lurbinectedin as defined in claim 24; preferably as a starting material.~~

~~29. The process according to claim 28, wherein the process comprises pre-dissolving the lurbinectedin in an organic acid, wherein the organic acid has a pH less than 4, preferably less than 3.5, more preferably less than 3, or around 3; and~~

~~optionally preparing a solution comprising an organic acid buffer and bulking agent (e.g. disaccharide) to form a buffer solution; and~~

optionally mixing the dissolved lurbinectedin solution with the buffer solution to form a final bulk solution; and

optionally undergoing sterilization filtration before filling into vials; and

optionally freeze-drying to form a lyophilized formulation.

30. Lurbinectedin as defined in any one of claims 21 to 23, or partially crystalline lurbinectedin as defined in claim 24, or a composition as defined in claim 25 or claim 26, or a method as described in any one of claims 27 to 29, for use in the manufacture of a medicament.