CLAIMS

1. A stable, lyophilized, copanlisib-containing solid, in particular powder or cake, suitable for dilution and for therapeutic applications, said solid, in particular powder or cake, comprising :

- copanlisib, particularly in an amount suitable as a therapeutic dose,
- one or more pH-adjusting agents, particularly a buffering agent which in particular comprises a weak acid, such as citric acid for example, and a strong base, such as sodium hydroxide, for example, and
- a bulking agent,

said solid, in particular powder or cake, having a pH of between 4 and 5 (inclusive) when reconstituted with a suitable diluent, such as sterile water for injection or sterile aqueous sodium chloride solution, particularly 0.9% aqueous sodium chloride solution, for example.

2. The lyophilized, copanlisib-containing solid, in particular powder or cake, according to claim 1, wherein said therapeutic dose is 30, 45 or 60 mg of copanlisib.

3. The lyophilized, copanlisib-containing solid, in particular powder or cake, according to claim 1 or 2, wherein said pH-adjusting agent is a buffering agent.

4. The lyophilized, copanlisib-containing solid, in particular powder or cake, according to any one of claims 1 to 3, wherein said buffering agent is citric acid and sodium hydroxide.

5. The lyophilized, copanlisib-containing solid, in particular powder or cake, according to any one of claims 1 to 4, which contains citric acid in an amount of 0.7- 75 % w/w, particularly 1.5-30% w/w, in particular 2.98% w/w, of said lyophilized, copanlisib-containing solid.

6. The lyophilized, copanlisib-containing solid, in particular powder or cake, according to any one of claims 1 to 5, which contains sodium hydroxide in an amount of 0-6% w/w, particularly 3.3-4.0 % w/w, in particular 3.7% w/w, of said lyophilized, copanlisib-containing solid.

7. The lyophilized, copanlisib-containing solid, in particular powder or cake, according to any one of claims 1 to 6, which contains sodium hydroxide in an amount of 0.01-6% w/w, particularly 3.3-4.0 % w/w, in particular 3.7% w/w, of said lyophilized, copanlisib-containing solid.

8. The lyophilized, copanlisib-containing solid, in particular powder or cake, according to any one of claims 1 to 7, wherein said bulking agent is mannitol.

9. The lyophilized, copanlisib-containing solid, in particular powder or cake, according to claim 8, which contains mannitol in an amount of 15.4-82.1% w/w, particularly 30.8-82.1% w/w, in particular 61.6% w/w, of said lyophilized, copanlisib-containing solid.

10. The lyophilized, copanlisib-containing solid, in particular powder or cake, according to any one of claims 1 to 9, which contains said copanlisib free base in an amount of 7.7-92.4% w/w, particularly 7.7-61.6% w/w, in particular 30.8% w/w, of lyophilized, copanlisib-containing solid.

11. The lyophilized, copanlisib-containing solid, in particular powder or cake, according to any one of claims 1 to 10, wherein :

- said therapeutic dose of copanlisib is in an amount of 30.8% w/w of said lyophilized, copanlisib-containing solid,
- said citric acid is in an amount of 2.98% w/w of said lyophilized, copanlisib-containing solid,
- said sodium hydroxide is in an amount of 3.7% w/w of said lyophilized, copanlisib-containing solid, and
- said mannitol is in an amount of 61.6% w/w, of said lyophilized, copanlisib-containing solid,

said lyophilized, copanlisib-containing solid, in particular powder or cake, when reconstituted with a suitable diluent, such as sterile water for injection or sterile aqueous sodium chloride solution, particularly 0.9% aqueous sodium chloride solution, for example, having a pH of between 4 and 5 (inclusive).

12. The lyophilized, copanlisib-containing solid, in particular powder or cake, according to any one of claims 1 to 11, wherein :

- said therapeutic dose of copanlisib is in an amount of 30, 45 or 60 mg,
- said citric acid is in an amount of 5.8mg,
- said sodium hydroxide is in an amount of 6.3mg, and
- said mannitol is in an amount of 120mg,

said lyophilized, copanlisib-containing solid, in particular powder or cake, when reconstituted with a suitable diluent, such as sterile water for injection or sterile aqueous sodium chloride solution, particularly 0.9% aqueous sodium chloride solution, for example, having a pH of between 4 and 5 (inclusive).

13. The lyophilized, copanlisib-containing solid, in particular powder or cake, according to any one of claims 1 to 11, wherein :

- said therapeutic dose of copanlisib is in an amount of 80 mg,
- said citric acid is in an amount of 7.7 mg,
- said sodium hydroxide is in an amount of 8.4 mg, and
- said mannitol is in an amount of 160 mg,

said lyophilized, copanlisib-containing solid, in particular powder or cake, when reconstituted with a suitable diluent, such as sterile water for injection or sterile aqueous sodium chloride solution, particularly 0.9% aqueous sodium chloride solution, for example, having a pH of between 4 and 5 (inclusive).

14. The lyophilized, copanlisib-containing solid, in particular powder or cake, according to any one of claims 1 to 13, which is contained in one container, particularly a sealed container, particularly an injection vial, more particularly a 6 ml injection vial.

15. The lyophilized, copanlisib-containing solid, in particular powder or cake, according to any one of claims 1 to 14, containing copanlisib in an amount of 68.4 mg.

16. A method of preparing the lyophilized, copanlisib-containing solid, in particular powder or cake, according to any one of claims 1 to 15,

said method including :

- preparing a stable, copanlisib-containing aqueous bulk solution of increased solubility which is directly suitable for lyophilisation, said bulk solution comprising :

    - copanlisib, particularly in an amount suitable as a therapeutic dose,
    - one or more pH-adjusting agents, particularly a buffering agent which in particular comprises a weak acid, such as citric acid for example, and a strong base, such as sodium hydroxide, for example, and
    - a bulking agent,

said bulk solution having a pH of between 4 and 5 (inclusive).

- freezing, annealing, primary and secondary drying steps ;

said method thus providing a stable, lyophilized, copanlisib-containing solid, in particular powder or cake, suitable for dilution and for therapeutic applications, according to any one of claims 1 to 15.

17. A stable, copanlisib-containing aqueous bulk solution of increased solubility which is directly suitable for lyophilisation, said bulk solution comprising :

- copanlisib, particularly in an amount suitable as a therapeutic dose,
- one or more pH-adjusting agents, particularly a buffering agent which in particular comprises a weak acid, such as citric acid for example, and a strong base, such as sodium hydroxide, for example, and
- a bulking agent,

said bulk solution having a pH of between 4 and 5 (inclusive),

which particularly contains copanlisib in an amount of 40 mg/ml.

18. The bulk copanlisib-containing solution according to claim 17, wherein :

- said therapeutic dose of copanlisib is in an amount of 3.8% w/w of said bulk solution,
- said citric acid is in an amount of 0.37% w/w of said bulk solution,
- said sodium hydroxide is in an amount of 0.4 % w/w, of said bulk solution, and
- said bulking agent, which is mannitol is in an amount of 7.7% w/w, of said bulk solution,

said copanlisib-containing solution having a pH of between 4 and 5 (inclusive).

19. A method of preparing the stable, copanlisib-containing aqueous bulk solution according to claim 17 or 18,

said method comprising :

- charging a suitable vessel with water for injection ;
- transferring copanlisib, in the form of a free base, or a salt, such as a hydrochloride, in particular a monohydrochloride or a dihydrochloride, or a tosylate, for example, to said vessel ;
- allowing said copanlisib to dissolve, optionally by stirring for example, at a pH of between 2 and 3 (inclusive), thus forming a copanlisib-containing solution ;
- adding said buffering agent and said bulking agent to said copanlisib-containing solution ;
- allowing said buffering agent and said bulking agent to dissolve, optionally by stirring for example ;
- adjusting the pH of the thus-formed solution to a pH of 4 to 5 with an appropriate amount of sodium hydroxide solution, thus forming a bulk solution ;
- filtering said bulk solution in a sterile manner,

thus providing a stable, copanlisib-containing aqueous bulk solution suitable for direct lyophilisation and therapeutic applications ; and

- filling the thus-formed filtered bulk solution in one or more vials.

20. The method according to claim 19, wherein said copanlisib transferred to said vessel is copanlisib dihydrochloride.

21. The lyophilized, copanlisib-containing solid, in particular powder or cake, according to any one of claims 1 to 15, which is prepared according to the method according to claim 16, particularly from a stable, copanlisib-containing aqueous bulk solution according to claim 17 or 18, said bulk solution having been prepared in particular by the method according to claim 19 or 20.

22. A stable, reconstituted, copanlisib-containing solution of increased solubility, suitable for further dilution and for therapeutic applications, said reconstituted solution comprising :

- a lyophilized, copanlisib-containing solid, in particular powder or cake, according to any one of claims 1 to 15 or 21, and
- a suitable diluent, such as sterile water for injection or sterile aqueous sodium chloride solution, particularly 0.9% aqueous sodium chloride solution, for example,

said reconstituted solution having a pH of between 4 and 5 (inclusive).

23. The reconstituted copanlisib-containing solution according to claim 22, which contains citric acid in an amount of 0.08 – 15.0% w/v, particularly 0.15-3.0% w/v, in particular 0.15% w/v, of said reconstituted solution.

24. The reconstituted copanlisib-containing solution according to claim 22 or 23, which contains sodium hydroxide in an amount of 0-0.3% w/v, particularly 0.14-0.18 % w/v, in particular 0.16 % w/v, of said reconstituted solution.

25. The reconstituted copanlisib-containing solution according to claim 22 or 23, which contains sodium hydroxide in an amount of 0.01-0.3% w/v, particularly 0.14-0.18 % w/v, in particular 0.16 % w/v, of said reconstituted solution.

26. The reconstituted copanlisib-containing solution according to any one of claims 22 to 25, which contains mannitol in an amount of 1.5-24.0% w/v, particularly 1.5-16.0% w/v, in particular 3.0% w/v, of said reconstituted solution.

27. The reconstituted copanlisib-containing solution according to any one of claims 22 to 25, which contains said copanlisib free base in an amount of 0.5-16.0% w/v, particularly 1.0-8.0% w/v, in particular 1.5% w/v, of said reconstituted solution.

28. The reconstituted copanlisib-containing solution according to any one of claims 22 to 27, wherein :

- said therapeutic dose of copanlisib is in an amount of 1.5% w/v of said reconstituted solution,
- said citric acid is in an amount of 0.15% w/v of said reconstituted solution,
- said sodium hydroxide is in an amount of 0.16 % w/v, of said reconstituted solution, and
- said mannitol is in an amount of 3.0% w/v, of said reconstituted solution,

said diluent being 0.9% aqueous sodium chloride solution,

said copanlisib-containing solution having a pH of between 4 and 5 (inclusive).

29. The reconstituted copanlisib-containing solution according to any one of claims 22 to 27, wherein :

- said therapeutic dose of copanlisib is in an amount of 68.4 mg,
- said citric acid is in an amount of 6.6 mg,
- said sodium hydroxide is in an amount of 7.2 mg, and
- said mannitol is in an amount of 136.8 mg,
- said diluent, which is 0.9% aqueous sodium chloride solution, is in an amount of 4.4 ml,

said reconstituted copanlisib-containing solution having a pH of between 4 and 5 (inclusive),

said reconstituted copanlisib-containing solution having a volume of 4.55 ml.

30. The reconstituted copanlisib-containing solution according to any one of claims 22 to 28, which is contained in one container, particularly a sealed container, particularly an injection vial, more particularly a 6 ml injection vial.

31. The reconstituted copanlisib-containing solution according to any one of claims 22 to 30, containing copanlisib in an amount of 15 mg/ml.

32. The reconstituted copanlisib-containing solution according to any one of claims 22 to 31, which contains 60 mg of copanlisib, particularly in a volume of 4 ml.

33. The reconstituted copanlisib-containing solution according to any one of claims 22 to 32, which is further diluted with a suitable diluent, such as sterile water for injection or sterile aqueous sodium chloride solution, particularly 0.9% aqueous sodium chloride solution, for example.

34. The reconstituted copanlisib-containing solution according to claim 33, wherein said suitable diluent is 0.9% aqueous sodium chloride solution, particularly in a volume of 100 ml.

35. The reconstituted copanlisib-containing solution according to claim 34, which is contained in an infusion bag, particularly made of polyethylene (PE), polypropylene (PP), polyvinylchloride (PVC), or ethylene vinyl acetate (EVA).

36. A method of reconstituting the stable, lyophilized, copanlisib-containing solid, in particular powder or cake, suitable for dilution and for therapeutic applications, according to any one of claims 1 to 15 or 21, or as prepared by the method according to claim 16, said reconstitution method comprising :

- adding, to said stable, lyophilized solid, in particular powder, in a suitable container, particularly a sealed container, particularly an injection vial, more particularly a 6 ml injection vial, a diluent, such as sterile water for injection or sterile aqueous sodium chloride solution, particularly 0.9% aqueous sodium chloride solution, for example ;

said method thus providing a stable, reconstituted, copanlisib-containing solution, suitable for further dilution and for therapeutic applications, according to any one of claims 22 to 35.

37. A lyophilized, copanlisib-containing solid, in particular powder or cake, according to any one of claims 1 to 15 or 21, or as prepared according to the method of claim 16, or a stable, reconstituted, copanlisib-containing solution of increased solubility, suitable for further dilution and for therapeutic applications, according to any one of claims 22 to 35, or as prepared according to the method of claim 36,

for use in the treatment or prophylaxis of a cancer, particularly a non-Hodgkin's lymphoma (NHL), such as 1st line, 2nd line, or up to 9 prior treatments, relapsed, refractory, indolent NHL, in particular follicular lymphoma (FL), marginal zone lymphoma (MZL), small lymphocytic lymphoma (SLL), Lymphoplasmacytoid/Waldenström macroglobulinemia (LPL-WM), or aggressive NHL, in particular diffuse large B cell lymphoma (DLBCL), mantle cell lymphoma (MCL), peripheral T-cell lymphoma (PTCL), transformed lymphoma (TL), or chronic lymphocytic leukemia (CLL), as monotherapy or in combination with one or more immunotherapeutic, chemotherapeutic or immuno-chemotherapeutic anti-cancer agents.

38. Use of a lyophilized, copanlisib-containing solid, in particular powder or cake, according to any one of claims 1 to 15 or 21, or as prepared according to the method of claim 16, or a stable, reconstituted, copanlisib-containing solution of increased solubility, suitable for further dilution and for therapeutic applications, according to any one of claims 22 to 35, or as prepared according to the method of claim 36,

for the preparation of a medicament for the treatment or prophylaxis of a cancer, particularly a non-Hodgkin's lymphoma (NHL), such as 1st line, 2nd line, or up to 9 prior treatments, relapsed, refractory, indolent NHL, in particular follicular lymphoma (FL), marginal zone lymphoma (MZL), small lymphocytic lymphoma (SLL), Lymphoplasmacytoid/Waldenström macroglobulinemia (LPL-WM), or aggressive NHL, in particular diffuse large B cell lymphoma (DLBCL), mantle cell lymphoma (MCL), peripheral T-cell lymphoma (PTCL), transformed lymphoma (TL), or chronic lymphocytic leukemia (CLL), as monotherapy or in combination with one or more immunotherapeutic, chemotherapeutic or immuno-chemotherapeutic anti-cancer agents.

39. Use according to claim 38, wherein said copanlisib-containing solution contains 60 mg of copanlisib.

40. Use according to claim 39, wherein said copanlisib-containing solution is of a volume of 4.0 ml.

41. Use according to claim 40, wherein a fixed dose of 60 mg copanlisib is to be administered to a patient as a 1-hour intravenous infusion on days 1, 8, and 15 of a 28-day treatment cycle on an intermittent schedule (three weeks on and one week off).

42. Use according to any one of claims 38 to 40, wherein said solution is to be administered in combination with a chemotherapeutic anti-cancer agent.

43. Use according to claim 42, wherein said chemotherapeutic anti-cancer agent is selected from the group consisting of :

131I-chTNT, abarelix, abiraterone, aclarubicin, adalimumab, ado-trastuzumab emtansine, afatinib, aflibercept, aldesleukin, alectinib, alemtuzumab, alendronic acid, alitretinoin, altretamine, amifostine, aminoglutethimide, hexyl aminolevulinate, amrubicin, amsacrine, anastrozole, ancestim, anethole dithiolethione, anetumab ravtansine, angiotensin II, antithrombin III, aprepitant, arcitumomab, arglabin, arsenic trioxide, asparaginase, atezolizumab, axitinib, azacitidine, basiliximab, belotecan, bendamustine, besilesomab, belinostat, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin, blinatumomab, bortezomib, buserelin, bosutinib, brentuximab vedotin, busulfan, cabazitaxel, cabozantinib, calcitonine, calcium folinate, calcium levofolinate, capecitabine, capromab, carbamazepine carboplatin, carboquone, carfilzomib, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, ceritinib, cetuximab, chlorambucil, chlormadinone, chlormethine, cidofovir, cinacalcet, cisplatin, cladribine, clodronic acid, clofarabine, cobimetinib, crisantaspase, crizotinib, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daratumumab, darbepoetin alfa, dabrafenib, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, denosumab, depreotide, deslorelin, dianhydrogalactitol, dexrazoxane, dibrospidium chloride,

dianhydrogalactitol, diclofenac, dinutuximab, docetaxel, dolasetron, doxifluridine, doxorubicin, doxorubicin + estrone, dronabinol, eculizumab, edrecolomab, elliptinium acetate, elotuzumab, eltrombopag, endostatin, enocitabine, enzalutamide, epirubicin, epitiostanol, epoetin alfa, epoetin beta, epoetin zeta, eptaplatin, eribulin, erlotinib, esomeprazole, estradiol, estramustine, ethinylestradiol, etoposide, everolimus, exemestane, fadrozole, fentanyl, filgrastim, fluoxymesterone, floxuridine, fludarabine, fluorouracil, flutamide, folinic acid, formestane, fosaprepitant, fotemustine, fulvestrant, gadobutrol, gadoteridol, gadoteric acid meglumine, gadoversetamide, gadoxetic acid, gallium nitrate, ganirelix, gefitinib, gemcitabine, gemtuzumab, Glucarpidase, glutoxim, GM-CSF, goserelin, granisetron, granulocyte colony stimulating factor, histamine dihydrochloride, histrelin, hydroxycarbamide, I-125 seeds, lansoprazole, ibandronic acid, ibritumomab tiuxetan, ibrutinib, idarubicin, ifosfamide, imatinib, imiquimod, improsulfan, indisetron, incadronic acid, ingenol mebutate, interferon alfa, interferon beta, interferon gamma, iobitridol, iobenguane (123I), iomeprol, ipilimumab, irinotecan, Itraconazole, ixabepilone, ixazomib, lanreotide, lansoprazole, lapatinib, Iasocholine, lenalidomide, lenvatinib, lenograstim, lentinan, letrozole, leuprorelin, levamisole, levonorgestrel, levothyroxine sodium, lisuride, lobaplatin, lomustine, lonidamine, masoprocol, medroxyprogesterone, megestrol, melarsoprol, melphalan, mepitiostane, mercaptopurine, mesna, methadone, methotrexate, methoxsalen, methylaminolevulinate, methylprednisolone, methyltestosterone, metirosine, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, mogamulizumab, molgramostim, mopidamol, morphine hydrochloride, morphine sulfate, nabilone, nabiximols, nafarelin, naloxone + pentazocine, naltrexone, nartograstim, necitumumab, nedaplatin, nelarabine, neridronic acid, netupitant/palonosetron, nivolumab, pentetreotide, nilotinib, nilutamide, nimorazole, nimotuzumab, nimustine, nintedanib, nitracrine, nivolumab, obinutuzumab, octreotide, ofatumumab, olaparib, olaratumab, omacetaxine mepesuccinate, omeprazole, ondansetron, oprelvekin, orgotein, orilotimod, osimertinib, oxaliplatin, oxycodone, oxymetholone, ozogamicine, p53 gene therapy, paclitaxel, palbociclib, palifermin, palladium-103 seed, palonosetron, pamidronic acid, panitumumab, panobinostat, pantoprazole, pazopanib, pegaspargase, PEG-epoetin beta (methoxy PEG-epoetin beta),

pembrolizumab, pegfilgrastim, peginterferon alfa-2b, pembrolizumab, pemetrexed, pentazocine, pentostatin, peplomycin, Perflubutane, perfosfamide, Pertuzumab, picibanil, pilocarpine, pirarubicin, pixantrone, plerixafor, plicamycin, poliglusam, polyestradiol phosphate, polyvinylpyrrolidone + sodium hyaluronate, polysaccharide-K, pomalidomide, ponatinib, porfimer sodium, pralatrexate, prednimustine, prednisone, procarbazine, procodazole, propranolol, quinagolide, rabeprazole, racotumomab, radium-223 chloride, radotinib, raloxifene, raltitrexed, ramosetron, ramucirumab, ranimustine, rasburicase, razoxane, refametinib , regorafenib, risedronic acid, rhenium-186 etidronate, rituximab, rolapitant, romidepsin, romiplostim, romurtide, rucaparib, samarium (153Sm) lexidronam, sargramostim, satumomab, secretin, siltuximab, sipuleucel-T, sizofiran, sobuzoxane, sodium glycididazole, sonidegib, sorafenib, stanozolol, streptozocin, sunitinib, talaporfin, talimogene laherparepvec, tamibarotene, tamoxifen, tapentadol, tasonermin, teceleukin, technetium (99mTc) nofetumomab merpentan, 99mTc-HYNIC-[Tyr3]-octreotide, tegafur, tegafur + gimeracil + oteracil, temoporfin, temozolomide, temsirolimus, teniposide, testosterone, tetrofosmin, thalidomide, thiotepa, thymalfasin, thyrotropin alfa, tioguanine, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, trametinib, tramadol, trastuzumab, trastuzumab emtansine, treosulfan, tretinoin, trifluridine + tipiracil, trilostane, triptorelin, trametinib, trofosfamide, thrombopoietin, tryptophan, ubenimex, valatinib , valrubicin, vandetanib, vapreotide, vemurafenib, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, vismodegib, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin.