

PATENT COOPERATION TREATY**PCT****INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference Case 26362	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/EP2010/063271	International filing date (<i>day/month/year</i>) 10.09.2010	Priority date (<i>day/month/year</i>) 11.09.2009
International Patent Classification (IPC) or national classification and IPC INV. A61K9/00		
Applicant F.Hoffmann-La Roche AG		
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>8</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ <i>sent to the applicant and to the International Bureau</i> a total of <u>7</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. ☐ (<i>sent to the International Bureau only</i>) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3bis of Annex C of the Administrative Instructions).		
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ Box No. II Priority ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement ☐ Box No. VI Certain documents cited ☐ Box No. VII Certain defects in the international application ☐ Box No. VIII Certain observations on the international application		
Date of submission of the demand 25.08.2011	Date of completion of this report 15.12.2011	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Authorized officer Kronester-Frei, A Telephone No. +49 89 2399-8555	



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2010/063271

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-81 as originally filed

Claims, Numbers

1-26 filed with the letter of

07-12-2011

Drawings, Figures

1-11 as originally filed

- ☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.

3. ☒ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☒ the claims, Nos. 17
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
5. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 70.2 (e)).
6. ☐ Supplementary international search report(s) from Authority(ies) have been received and taken into account in drawing up this report (Rule 45bis.8(b) and (c)).

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2010/063271

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-26</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-26</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-26</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- 1 The following documents (D) are referred to in this communication; the numbering corresponds to the order used in the Search Report, the numbering will be adhered to in the rest of the procedure:

- D1 WO 2007/005608 A2 (ABBOTT LAB [US]; LACY SUSAN E [US]; FUNG EMMA [US]; BELK JONATHAN P [U]) 11 January 2007 (2007-01-11)
- D2 US 2007/071675 A1 (WU CHENGBIN [US] ET AL) 29 March 2007 (2007-03-29)
- D3 WO 2006/091871 A1 (HALOZYME THERAPEUTICS INC [US]; BOOKBINDER LOI H [US]; KUNDU ANIRBAN) 31 August 2006 (2006-08-31)
- D4 WO 2009/080541 A1 (HOFFMANN LA ROCHE [CH]; ADLER MICHAEL [DE]; MAHLER HANNES-CHRISTIAN [CH]) 2 July 2009 (2009-07-02)
- D5 US 6 991 790 B1 (LAM XANTHE M [US] ET AL) 31 January 2006 (2006-01-31)
- D6 BOOKBINDER ET AL: "A recombinant human enzyme for enhanced interstitial transport of therapeutics", JOURNAL OF CONTROLLED RELEASE, ELSEVIER, AMSTERDAM, NL, vol. 114, no. 2, 28 August 2006 (2006-08-28), pages 230-241, XP005625403, ISSN: 0168-3659, DOI: DOI:10.1016/J.JCONREL.2006.05.027
- D7 WO 2005/044859 A2 (GLYCART BIOTECHNOLOGY AG [CH]; UMANA PABLO [C]; BRUENKER PETER [CH];) 19 May 2005 (2005-05-19)

Unless otherwise specified, the relevant passages of the documents cited can be taken from the International Search Report.

D1: Anti-CD20 antibody like rituximab; [0374] The pharmaceutical composition comprising the antibodies and antibody-portions of the invention prepared as an injectable solution for parenteral administration, can further comprise a particularly useful adjuvant is hyaluronidase, such as Hylenex®

(recombinant human hyaluronidase). Addition of hyaluronidase in the injectable solution improves human bioavailability following parenteral administration, particularly subcutaneous administration.

D2: Hylenex® and anti-CD20 mentioned; binding proteins incorporated in pharmaceutical composition whereby antibody or antibody-portions will be prepared as an injectable solution containing 0.1-250 mg/ml binding protein. The injectable solution can be composed of either a liquid or lyophilized dosage form in a flint or amber vial, ampule or pre-filled syringe. The buffer can be L-histidine (1-50 mM), optimally 5-10 mM, at pH 5.0 to 7.0 (optimally pH 6.0). Other suitable buffers include but are not limited to, sodium succinate, sodium citrate, sodium phosphate or potassium phosphate. Stabilizers can be used in both liquid and lyophilized dosage forms, principally 1-50 mM L-Methionine (optimally 5-10 mM). Other suitable bulking agents include glycine, arginine, can be included as 0-0.05% polysorbate-80 (optimally 0.005-0.01%). Additional surfactants include but are not limited to polysorbate 20 and BRIJ surfactants. Injectable solutions for parenteral administration can further comprise an agent useful as an adjuvant, such as those used to increase the absorption, or dispersion of a therapeutic protein (e.g., antibody). A particularly useful adjuvant is hyaluronidase, such as Hylenex® (recombinant human hyaluronidase). Addition of hyaluronidase in the injectable solution improves human bioavailability following parenteral administration, particularly subcutaneous administration.

D3: Rituximabs and Hyaluronidase; soluble hyaluronidase glycoprotein sHASEGP (soluble hyaluronidase glycoprotein facilitating administration of other molecules), including sialated and pegylated forms of a recombinant sHASEGP to enhance stability and serum pharmacokinetics over naturally occurring slaughterhouse enzymes. Further described are suitable formulations of a substantially purified recombinant sHASEGP / rHuPH20, co-administration included. sHASEGPs are to dissolve vitreous aggregates or "floaters", which are generally macroscopic opaque aggregates of vitreous fibers, the administration of sHASEGP to the vitreous body can be used to promote disaggregation.

D4: anti-CD20 antibody, no hyaluronidase

D5: anti-CD20 antibody, no hyaluronidase

D6: Depolymerization of the viscoelastic component of the interstitial matrix in animal models with a highly purified recombinant human hyaluronidase enzyme (rHuPH20) increased the dispersion of locally injected drugs, across

a broad range of molecular weights without tissue distortion. rHuPH20 increased infusion rates and the pattern and extent of appearance of locally injected drugs in systemic blood. Exemplified is pegylated cytokine (1.5 mug/kg) was injected intravenously (IV) intradermally (ID) or intradermally with 100 Units rHuPH20 (ID+rHuPH20). Absolute bioavailability increased from 61% to 108% ($P<0.001$) and Cmax increased from 61,782 to 121,750 CPM/g ($P<0.0003$). (D) rHuPH20 decreases Tmax, increases Cmax and bioavailability of a therapeutic monoclonal antibody. Tested were the effects of rHuPH20 on bioavailability of a 31 kDa pegylated cytokine, PEG-Interferon alfa-2b, and a 149 kDa monoclonal antibody, infliximab. Monoclonal antibodies exemplified are infliximab (under item 2.9) and adalimumab (under item 3.6). IgG1 (10 mg/kg) were injected intravenously (IV) intradermally (ID) or intradermally with 100 Units rHuPH20 (ID+rHuPH20). By depolymerizing hyaluronan, rHuPH20 rapidly reduces its viscosity, changing the interstitial glycosaminoglycans from a gel-like phase to a fluid liquid phase, thereby making increased bulk fluid flow possible through the collagen fibers.

D7: [0182] Exemplary anti-CD20 ABM formulations are cited, describing liquid multidose formulation comprising 40 mg/ml rituximab, 25 mM acetate, 150 mM trehalose, 0.9% benzyl alcohol, 0.02% polysorbate 20 at pH 5.0 that has a minimum shelf life of two years storage at 2-8 C. Another anti-CD20 formulation of interest comprises 10 mg/ml rituximab in 9.0 mg/ml sodium chloride, 7.35 mg/ml sodium citrate dihydrate, 0.7 mg/ml polysorbate 80, and Sterile Water for Injection, pH 6.5. In the present invention, RITUXAN® will be substituted by an ABM of the present invention; for subcutaneous administration

- 2 After deletion of the optional feature and after limitation to the particular route of administration to subcutaneous injection, claim 1 meets the criteria of Article 33(1) PCT.
- 3 The present application does not meet the criteria of Article 33(1) PCT, because the subject matter of claims 3 and 11/12 and related subject-matter does not involve an inventive step in the sense of Article 33(3)PCT. In fact it would appear that a person skilled in this art confronted with the problem of looking for further pharmaceutical formulations comprising active anti-CD20-antibody in a highly concentrated stable formulation, avoiding aggregation and/or generation of further immunogenicity, being designed for subcutaneous administration,

would in principle have been able to conclude in an obvious manner from D3/D6, that addition of those facilitators of rapidly reducing viscosity by changing interstitial glycosaminoglycans from a gel-like phase to a fluid liquid phase (as rhuPH20 or Hylenex®) to the known pharmaceutical formulations of anti-CD20 antibodies (D4, D5, D7) would result in a reduced viscosity, since such a combination has already been cited in one document, either in D1 (*anti-CD20 antibody, like Rituximab, with hyaluronidase, such as Hylenex®*), or in D2 (*CD20/Anti-CD3 DVD-Ig, with hyaluronidase, such as Hylenex®*) or in D3 (*humanized anti-CD20 antibody like HuMabCD20, with soluble hyaluronidase glycoprotein sHASEGP / rhuPH20*). In principle also from D6 no reason is available, why the skilled person in this art should abstain from a combination of hyaluronidase with an other monoclonal antibody then the ones as described in D6 (*infliximab (under item 2.9) and adalimumab (under item 3.6)*), as for example with the anti-CD20 antibody as already mentioned in D1-D3 in a similar context. In fact, D6 already describes the mode of functioning of rhuPH20 in a detailed manner, by highlighting that

- co-injection of rHuPH20 hyaluronidase enhances the dispersion of molecules up to 200nm in diameter, by highlighting further that
- co-injection of rHuPH20 increases the infusion rates and permits injection of large volumes without tissue distortion, by illustrating that
- biopharmaceuticals such as monoclonal antibodies can be formulated as highly concentrated solutions and administered subcutaneously (like adalimumab or infliximab),
- by facilitation of the interstitial gel-like glycosaminoglycans to a fluid liquid phase,
- by managing that changes to the tissue are transient and non-inflammatory.

Therefore, this information and explanation of the mode of action as provided in D6 could in principle encourage the skilled person to effect such a combination.

However, the extent of the results achieved in respect of long term stability of high dose co-formulation of a CD20 antibody including a hyaluronidase enzyme over periods of 26 up to 96 weeks with CD20 antibody formulations at e.g. 50, 100 and 120 mg/ml at 2-8°C are considered to be surprising.

- 4 The description needs to be adapted to the set of claims in their restricted scope (Article 6 PCT). Claim 27 being free of particular technical features is considered to be sufficiently clear in the light of Article 6 PCT, it merely considered to be redundant.
- 5 Claims 21 to 26 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. Patentability, in particular novelty and inventive step, of the set of claims has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition. The patentability can be dependent upon the formulation of the claims.
- 6 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1, D2, D4-D6 are not mentioned in the description, nor is this document identified therein.

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Basel, December 07, 2011

Applicant: F. Hoffmann-La Roche AG
Application No.: PCT/EP2010/063271

Case: 26362 WO

This is in reply to the Communication pursuant to PCT Rule 66.2(a)(ii) dated November 22, 2011 in connection with the above-captioned International Patent Application.

Claim Amendments:

To facilitate prosecution, Applicant further amended claim 1 by inserting technical feature "for subcutaneous administration" from previous claim 17 and by omitting the term "optionally comprising" from technical feature e). Therefore, the formulation as claimed is for subcutaneous administration and no longer comprises the hyaluronidase enzyme as an optional feature. Claim 17 was omitted. The remaining claims were renumbered.

The unclaimed subject-matter is, however, maintained and might be subject to divisional applications at PCT national/regional phase.

Comments with respect of the lack of patentability objections*Novelty*

Applicant respectfully disagrees with the lack of novelty objections under Art. 33(2) PCT raised in the Written Opinion of the International Searching Authority.

None of the cited documents discloses the subject-matter of claim 1:

1. *A highly concentrated, stable pharmaceutical formulation for subcutaneous administration of a pharmaceutically active anti-CD20 antibody comprising:*

a. *about 50 to 350 mg/ml anti-CD20 antibody;*

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- b. *about 1 to 100 mM of a buffering agent providing a pH of 5.5 ± 2.0 ;*
- c. *about 1 to 500 mM of a stabilizer or a mixture of two or more stabilizers;*
- d. *about 0.01 to 0.1 % of a nonionic surfactant; and*
- e. *about 1'000 to 16'000 U/ml of a hyaluronidase enzyme, preferably about 2'000 U/ml or 12'000 U/ml.*

D1 relates to completely different type of proteins from antibodies, i.e. IL-12p40 binding proteins, in particular hIL12 or hIL-23.

D2 relates to binding proteins comprising a polypeptide chain, wherein said polypeptide chain comprises VD1-(X1)_n-VD2-C-(X2)_n (a first and second variable domain, a constant domain an amino acid or polypeptide and a Fc region).

D3 discloses soluble neutral active Hyaluronidase Glycoproteins (sHASEGPs).

D4 discloses specific, low dose type II anti-CD20 antibody formulations.

None of the prior art documents discloses the highly concentrated formulations of an anti-CD20 antibody as specified above.

Therefore, it is respectfully submitted that all present claims are novel over prior art.

Inventive Step

The cited prior art, whether taken alone or in combination, does not render the subject-matter as claimed obvious.

Surprisingly, the inventors invented highly concentrated, highly stable formulations of the CD20 antibodies as claimed and as evidenced in the examples of the specification.

D5 relates to stable aqueous formulations comprising a therapeutically effective amount of an antibody not subjected to prior lyophilization.

D6 relates to depolymerization of the interstitial matrix with rHuPH20 and tests of PEG-interferon alfa-2b and infliximab.

D7 relates to antibody binding molecules of specified sequences.

Neither D1-D7, whether alone or in combination, render the claimed subject-matter obvious.

The person skilled in the art is first confronted with the problem of inventing a stable high dose CD20 antibody formulation. None of the prior art documents teach the skilled

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person the invention of a stable high dose CD20 antibody formulation beyond 40 mg/ml protein concentration.

The invention of a stable high dose formulation of a CD20 antibody without a hyaluronidase enzyme is not rendered obvious by the cited prior art and alone meets the requirement for inventive step.

Furthermore, the co-formulation of a CD20 antibody with a hyaluronidase enzyme for a subcutaneous administration as claimed in the attached claim set clearly is not obvious from the cited art. The person skilled in the art would expect a co-formulation of a high dose CD20 antibody with a second protein, i.e. with a hyaluronidase enzyme at high concentrations to have poor long term stability data.

In contrast, the examples of the present invention impressively demonstrate long term stability for the high dose co-formulation a CD20 antibody including a hyaluronidase enzyme over periods of 26 up to 96 weeks with CD20 antibody formulations at e.g. 50, 100 and 120 mg/ml at 2 – 8°C. In support of the patentability of the claimed invention it is emphasized that the formulations in accordance of the invention show very high stability over prolonged period of time, e.g. several weeks at 2 – 8°C. In fact it has meanwhile been found that rituximab co-formulations in accordance with the invention remain stable upon storage in liquid form at 2 – 8°C for more than 24 months.

Applicants respectfully request to reconsider the objections under Article 33(1) PCT. Therefore, inventive step should be acknowledged.

Remark regarding the requirements under Rule 5.1(a)(ii) PCT

Applicants wish to point out that the cited document D3 (WO 2006/091871) is cited in the specification on page 1, line 21 of the specification as published. Document D7 (WO2005/044859) is cited on page 10, line 7.

It is, however requested that amendment of the description with background art is deferred to PCT national stage.

Final Remarks

Applicants respectfully request that the above comments and amendments are duly considered and that a favorable IPER is issued.

Amendments made at the present stage of the patent application are not to be interpreted as acknowledgement of the validity of any objection, nor as acknowledgement to any citation against the application is material to the patentability of the subject-matter claimed. Therefore, the cancellation, abandonment or amendment of any claim or any amendment in the description does not amount to abandonment of any subject matter in the application and upon any such cancellation, abandonment or amendment the right to

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pursue future divisional applications in respect of any subject-matter based on the application as filed after entry of the National Phase is maintained, irrespective of whether the subject-matter was in the claims of this application as filed.

Representative:



Dr. Thomas Klein

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Enclosures: - as mentioned -

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Claims

1. A highly concentrated, stable pharmaceutical formulation for subcutaneous administration of a pharmaceutically active anti-CD20 antibody comprising:

- a. about 50 to 350 mg/ml anti-CD20 antibody;
- 5 b. about 1 to 100 mM of a buffering agent providing a pH of 5.5 ± 2.0 ;
- c. about 1 to 500 mM of a stabilizer or a mixture of two or more stabilizers;
- d. about 0.01 to 0.1 % of a nonionic surfactant; and
- e. about 1'000 to 16'000 U/ml of a hyaluronidase enzyme, preferably about 2'000 U/ml or 12'000 U/ml.

10 2. A highly concentrated, stable pharmaceutical anti-CD20 antibody formulation according to claim 1, wherein the anti-CD20 antibody concentration is 100 to 150 mg/ml, preferably 120 ± 20 mg/ml.

3. A highly concentrated, stable pharmaceutical anti-CD20 antibody formulation according to any one of claims 1 to 2, wherein the buffering agent is at a concentration of 1 to 50 mM.

15 4. A highly concentrated, stable pharmaceutical anti-CD20 antibody formulation according to any one of claims 1 to 3, wherein the buffering agent provides a pH of 5.5 to 6.5, preferably selected from the group consisting of 5.5, 6.0, 6.1 and 6.5.

5. A highly concentrated, stable pharmaceutical anti-CD20 antibody formulation according to any one of claims 1 to 4, wherein the buffering agent is a histidine buffer.

20 6. A highly concentrated, stable pharmaceutical anti-CD20 antibody formulation according to any one of claims 1 to 5, wherein the stabilizer is a saccharide, such as e.g. α, α -trehalose dihydrate or sucrose.

7. A highly concentrated, stable pharmaceutical anti-CD20 antibody formulation according to any one of claims 1 to 6, wherein the stabilizer at a concentration of 15 to 250 mM.

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8. A highly concentrated, stable pharmaceutical anti-CD20 antibody formulation according to claim 6 or 7, wherein methionine is used as a second stabilizer.

9. A highly concentrated, stable pharmaceutical anti-CD20 antibody formulation according to claim 8, wherein methionine is present in a concentration of 5 to 25 mM.

5 10. A highly concentrated, stable pharmaceutical anti-CD20 antibody formulation according to any one of claims 1 to 9, wherein the nonionic surfactant is a polysorbate, preferably selected from the group consisting of polysorbate 20, polysorbate 80, and polyethylene-polypropylene copolymer.

10 11. A highly concentrated, stable pharmaceutical anti-CD20 antibody formulation according to claim 10, wherein the concentration of the polysorbate is 0.02 % (w/v) to 0.08 % (w/v).

12. A highly concentrated, stable pharmaceutical anti-CD20 antibody formulation according to any one of claims 1 to 11, wherein the hyaluronidase enzyme is rHuPH20.

13. A highly concentrated, stable pharmaceutical anti-CD20 antibody formulation according to any one of claims 1 to 12, wherein the anti-CD20 antibody is Rituximab.

15 14. A highly concentrated, stable pharmaceutical anti-CD20 antibody formulation according to any one of claims 1 to 12, wherein the anti-CD20 antibody is Ocrelizumab.

15. A highly concentrated, stable pharmaceutical anti-CD20 antibody formulation according to any one of claims 1 to 12, wherein the anti-CD20 antibody is HuMab<CD20>.

20 16. The highly concentrated, stable pharmaceutical anti-CD20 antibody formulation according to any one of claims 1 to 15 which is stable upon freezing and thawing.

17. The highly concentrated, stable pharmaceutical anti-CD20 antibody formulation according to any one of claims 1 to 16 in liquid form.

18. The highly concentrated, stable pharmaceutical anti-CD20 antibody formulation according to any one of claims 1 to 17 in lyophilized form.

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19. The use of a formulation according to any one of claims 1 to 18 for the preparation of a medicament useful for treating a disease or disorder amenable to treatment with an anti-CD20 antibody, preferably cancer or a non-malignant disease in a subject comprising administering the formulation described herein to a subject in an amount effective to treat the said disease or disorder.

5 20. The use according to claim 19 wherein the formulation is co-administered concomitantly or sequentially with chemotherapy.

21. The use according to claim 19 or 20 wherein a fixed dose of 1200 mg to about 2200 mg of the anti-CD20 antibody is administered to the subject in need thereof.

22. The use according to claim 19 or 20 wherein a fixed dose of about 1200 mg to about
10 1800 mg of the anti-CD20 antibody is administered to the subject in need thereof.

23. The use according to claim 19 or 20 wherein a fixed dose of 1600 mg to about 2200 mg of the anti-CD20 antibody is administered to the subject in need thereof.

24. A method of treating a disease or disorder which is amenable to treatment with an anti-CD20 antibody such as cancer or a non-malignant disease in a subject comprising administering a
15 formulation according to any one of claims 1 to 23 to a subject in an amount effective to treat the said disease or disorder.

25. The method according to claim 24 wherein the formulation is co-administered concomitantly or sequentially with a chemotherapeutic agent.

26. The invention as herein before described.

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