ANTI-IGF-1R HUMAN MONOCLONAL ANTIBODY FORMULATION

The present invention relates to an anti-IGF-1R human monoclonal antibody formulation, a process for the preparation and uses thereof.

In an aspect, the invention relates to an IGF-1R formulation comprising:

- about 1 to about 150 mg/mL huMab IGF-1R,
- about 0.001 to about 1% of at least one surfactant, and
- about 1 to about 100 mM of a buffer,
- at a pH of about 5.0 to about 7.0.

The IGF-IR (type 1 insulin-like growth factor receptor), has been implicated in promoting oncogenic transformation, growth, and survival of cancer cells. High levels of expression of IGF-IR have been reported in a broad range of human malignancies. In addition, high levels of IGF-I and IGF-II expression have been noted in tumors and associated stromal cells and may stimulate cancer cell growth in an autocrine or paracrine manner. Epidemiological studies have correlated upper quintile plasma levels of IGF-I with increased risk for prostate, colon, lung, and breast cancer. In addition to its role in proliferation of cancer cells, IGF-IR protects cells from apoptosis caused by growth factor deprivation, anchorage independence, or cytotoxic drug treatment.

One promising strategy to inhibit the function of IGF-IR in cancer cells is to apply human anti-IGF-IR antibodies that bind to the extracellular domains of IGF-IR and inhibit receptor activation. Such an antagonistic, fully human, monoclonal antibody, designated huMab IGF-1R, has been developed which binds specifically to the human insulin-like growth factor I receptor (IGF-IR) and inhibits signal transduction and the proliferation functions of the receptor in cancer cells.

The antibody comprised in the formulation of the invention has been first described in PCT patent application No. WO2005/005635 of which the Applicant is proprietor and the content of which, especially the claims is incorporated herein by reference. As described in WO2005/005635, said antibody is binding to IGF-IR and inhibiting the binding of IGF-I and IGF-II to IGF-IR, and is characterized in that it:

a) is of IgG1 isotype,

b) shows a ratio of IC_{50} values of inhibition of the binding of IGF-I to IGF-IR to the inhibition of binding of IGF-II to IGF-IR of 1:3 to 3:1,

c) inhibits for at least 80%, preferably at least 90%, at a concentration of 5 nM IGF-IR phosphorylation in a cellular phosphorylation assay using HT29 cells in a medium containing 0.5% heat inactivated fetal calf serum (FCS) when compared to such an assay without said antibody, and

d) shows no IGF-IR stimulating activity measured as pkB phosphorylation at a concentration of 10 μM in a cellular phosphorylation assay using 3T3 cells providing 400,000 to 600,000 molecules IGF-IR per cell in a medium containing 0.5% heat inactivated fetal calf serum (FCS) when compared to such an assay without said antibody.

Antibodies comprised in the formulation according to the invention show benefits for patients in need of antitumor therapy and provide reduction of tumor growth and a significant prolongation of the time to progression. The antibodies comprised in the formulation according to the invention have new and inventive properties causing a benefit for a patient suffering from a disease associated with an IGF deregulation, especially a tumor disease. The antibodies comprised in the formulation of the invention are characterized by the abovementioned properties. The properties are therefore especially specific binding to IGF-IR, inhibiting the binding of IGF-I and IGF-II to IGF-IR at the abovementioned ratio, being of IgG1 isotype, and not activating the IGF-IR signaling even in IGF-IR overexpressing cells at a 200-fold concentration of its IC_{50} value. Antibodies having no "IGF-I mimetic activity" provide a strong advantage when used as a therapeutic agent.

The term "anti-IGF-1R human monoclonal antibody" or "huMAb IGF-IR" denotes an antibody as described and claimed in WO2005/005635, the content of which, especially the claims, is incorporated herein by reference.

The term "antibody" encompasses the various forms of antibodies including but not being limited to whole antibodies, antibody fragments, human antibodies, humanized antibodies and genetically engineered antibodies as long as the characteristic properties according to the invention are retained.

"Antibody fragments" comprise a portion of a full length antibody, generally at least the antigen binding portion or the variable region thereof. Examples of antibody fragments include diabodies, single-chain antibody molecules, immunotoxins, and multispecific antibodies formed from antibody fragments. In addition, antibody

fragments comprise single chain polypeptides having the characteristics of a VH chain, namely being able to assemble together with a VL chain or of a VL chain binding to IGF-1R, namely being able to assemble together with a VH chain to a functional antigen binding pocket and thereby providing the property of inhibiting the binding of IGF-I and IGF-II to IGF-IR.

"Antibody fragments" also comprises such fragments which per se are not able to provide effector functions (ADCC/CDC) but provide this function in a manner according to the invention after being combined with appropriate antibody constant domain(s).

The terms "monoclonal antibody" or "monoclonal antibody composition" as used herein refer to a preparation of antibody molecules of a single amino acid composition. Accordingly, the term "human monoclonal antibody" refers to antibodies displaying a single binding specificity which have variable and constant regions derived from human germline immunoglobulin sequences. In one embodiment, the human monoclonal antibodies are produced by a hybridoma which includes a B cell obtained from a transgenic non-human animal, e.g. a transgenic mouse, having a genome comprising a human heavy chain transgene and a light human chain transgene fused to an immortalized cell.

The term "chimeric antibody" refers to a monoclonal antibody comprising a variable region, i.e., binding region, from one source or species and at least a portion of a constant region derived from a different source or species, usually prepared by recombinant DNA techniques. Chimeric antibodies comprising a murine variable region and a human constant region are especially preferred. Such murine/human chimeric antibodies are the product of expressed immunoglobulin genes comprising DNA segments encoding murine immunoglobulin variable regions and DNA segments encoding human immunoglobulin constant regions. Other forms of "chimeric antibodies" encompassed by the present invention are those in which the class or subclass has been modified or changed from that of the original antibody. Such "chimeric" antibodies are also referred to as "class-switched antibodies." Methods for producing chimeric antibodies involve conventional recombinant DNA and gene transfection techniques now well known in the art. See, e.g., Morrison, S.L., et al., Proc. Natl. Acad Sci. USA 81 (1984) 6851-6855; US Patent Nos. 5,202,238 and 5,204,244.

The term "humanized antibody" refers to antibodies in which the framework or "complementarity determining regions" (CDR) have been modified to comprise the CDR of an immunoglobulin of different specificity as compared to that of the parent

immunoglobulin. In a preferred embodiment, a murine CDR is grafted into the framework region of a human antibody to prepare the "humanized antibody." See, e.g., Riechmann, L., et al., Nature 332 (1988) 323-327; and Neuberger, M.S., et al., Nature 314 (1985) 268-270. Particularly preferred CDRs correspond to those representing sequences recognizing the antigens noted above for chimeric and bifunctional antibodies.

The term "human antibody", as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The variable heavy chain is preferably derived from germline sequence DP-50 (GenBank LO6618) and the variable light chain is preferably derived from germline sequence L6 (GenBank X01668). The constant regions of the antibody are constant regions of human IgG1 type. Such regions can be allotypic and are described by, e.g., Johnson, G., and Wu, T.T., Nucleic Acids Res. 28 (2000) 214-218 and the databases referenced therein and are useful as long as the properties of induction of ADCC and preferably CDC according to the invention are retained.

The term "recombinant human antibody", as used herein, is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies isolated from a host cell such as an SP2-0, NS0 or CHO cell or from an animal (e.g. a mouse) that is transgenic for human immunoglobulin genes or antibodies expressed using a recombinant expression vector transfected into a host cell. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences in a rearranged form. The recombinant human antibodies according to the invention have been subjected to in vivo somatic hypermutation. Thus, the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire in vivo.

As used herein, "binding" refers to antibody binding to IGF-IR with an affinity of about 10^{-13} to 10^{-8} M (K_D), preferably of about 10^{-13} to 10^{-9} M.

The term "nucleic acid molecule", as used herein, is intended to include DNA molecules and RNA molecules. A nucleic acid molecule may be single-stranded or double-stranded, but preferably is double-stranded DNA.

The "constant domains" are not involved directly in binding the antibody to an antigen but are involved in the effector functions (ADCC, complement binding, and CDC). The constant domain of an antibody according to the invention is of the IgG1

type. Human constant domains having these characteristics are described in detail by Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991), and by Brüggemann, M., et al., J. Exp. Med. 166 (1987) 1351-1361; Love, T.W., et al., Methods Enzymol. 178 (1989) 515-527. Examples are shown in SEQ ID NOS:5 to 8 in WO2005/005635. Other useful and preferred constant domains are the constant domains of the antibodies obtainable from the hybridoma cell lines deposited with DSMZ for this invention. The constant domains useful in the invention provide complement binding. ADCC and optionally CDC are provided by the combination of variable and constant domains.

The "variable region" (variable region of a light chain (VL), variable region of a heavy chain (VH)) as used herein denotes each of the pair of light and heavy chains which is involved directly in binding the antibody to the antigen. The domains of variable human light and heavy chains have the same general structure and each domain comprises four framework (FR) regions whose sequences are widely conserved, connected by three "hypervariable regions" (or complementarity determining regions, CDRs). The framework regions adopt a β-sheet conformation and the CDRs may form loops connecting the β-sheet structure. The CDRs in each chain are held in their three-dimensional structure by the framework regions and form together with the CDRs from the other chain the antigen binding site. The antibody heavy and light chain CDR3 regions play a particularly important role in the binding specificity/affinity of the antibodies according to the invention and therefore provide a further object of the invention.

The terms "hypervariable region" or "antigen-binding portion of an antibody" when used herein refer to the amino acid residues of an antibody which are responsible for antigen-binding. The hypervariable region comprises amino acid residues from the "complementarity determining regions" or "CDRs". "Framework" or "FR" regions are those variable domain regions other than the hypervariable region residues as herein defined. Therefore, the light and heavy chains of an antibody comprise from N- to C-terminus the domains FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. Especially, CDR3 of the heavy chain is the region which contributes most to antigen binding. CDR and FR regions are determined according to the standard definition of Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)) and/or those residues from a "hypervariable loop".

The term "binding to IGF-IR" as used herein means the binding of the antibody to IGF-IR in an in vitro assay, preferably in a binding assay in which the antibody is bound

to a surface and binding of IGF-IR is measured by Surface Plasmon Resonance (SPR). Binding means a binding affinity (K_D) of 10^{-8} M or less, preferably 10^{-13} to 10^{-9} M.

Binding to IGF-IR can be investigated by a BIAcore assay (Pharmacia Biosensor AB, Uppsala, Sweden). The affinity of the binding is defined by the terms ka (rate constant for the association of the antibody from the antibody/antigen complex), kd (dissociation constant), and K_D (kd/ka). The antibodies according to the invention show a K_D of 10^{-10} M or less.

The binding of IGF-I and IGF-II to IGF-IR is also inhibited by the antibodies according to the invention. The inhibition is measured as IC_{50} in an assay for binding of IGF-I/IGF-II to IGF-IR on tumor cells. Such an assay is described in Example 7. In such an assay, the amount of radiolabeled IGF-I or IGF-II or IGF-IR binding fragments thereof bound to the IGF-IR provided at the surface of said tumor cells (e.g. HT29) is measured without and with increasing concentrations of the antibody. The IC_{50} values of the antibodies according to the invention for the binding of IGF-I and IGF-II to IGF-IR are no more than 2 nM and the ratio of the IC_{50} values for binding of IGF-I/IGF-II to IGF-IR is about 1:3 to 3:1. IC_{50} values are measured as average or median values of at least three independent measurements. Single IC_{50} values may be out of the scope.

The term “inhibiting the binding of IGF-I and IGF-II to IGF-IR” as used herein refers to inhibiting the binding of I^{125}-labeled IGF-I or IGF-II to IGF-IR presented on the surface of HT29 (ATCC HTB-38) tumor cells in an in vitro assay. Inhibiting means an IC_{50} value of 2 nM or lower.

The term “surfactant” as used herein denotes a pharmaceutically acceptable surfactant. In the formulation of the invention, the amount of surfactant is described a percentage expressed in weight/volume. The most commonly used weight/volume unit is mg/mL. Suitable pharmaceutically acceptable surfactants comprise but are not limited to polyethylen-sorbitan-fatty acid esters, polyethylene-polypropylene glycols, polyoxyethylene-stearates and sodium dodecyl sulphates. Preferred polyethylen-sorbitan-are polyethylen(20)-sorbitan-esters (synonym to polysorbate 20, sold under the trademark Tween 20™) and polyoxyethylen(20)sorbitanmonooleat (synonym to polysorbate 80 sold under the trademark Tween 80™). Preferred polyethylene-polypropylene glycols are those sold under the names Pluronic®F68 or Poloxamer 188™. Preferred polyoxyethylene-stearates are those sold under the trademark Myrj™. Preferred Polyoxyethylene monolauryl ether are those sold under the trademark Brij™. When polyethylen-sorbitan-polyethylen(20)-sorbitan-esters (Tween 20™) and polyoxyethylen(20)sorbitanmonooleat (Tween 80™) are used they are generally used in

an amount of about 0.001 to about 1%, preferably of about 0.005 to about 0.1% and still preferably about 0.01% to about 0.02%w/v.

The term "buffer" as used herein denotes a pharmaceutically acceptable buffer. Suitable pharmaceutically acceptable buffer comprise but are not limited to histidine-buffers, citrate-buffers, succinate-buffers, acetate-buffers and phosphate-buffers. Preferred buffers comprise L-histidine or mixtures of L-histidine with L-histidine hydrochloride with isotonicity agents and pH adjustment with an acid or a base known in the art. The abovementioned histidine-buffers are generally used in an amount of about 1mM to about 100 mM, preferably of about 5 mM to about 50 mM and still more preferably of about 20 mM. Independently from the buffer used, the pH will be adjusted at a value comprising about 5.0 to about 7.0 and preferably about 5.5 to about 6.5 and still preferably about 6.0.

The term "isotonicity agents" as used herein denotes pharmaceutically acceptable isotonicity agents. Isotonicity agents are used to provide an isotonic formulation. An isotonic formulation is liquid or liquid reconstituted from a solid form, e.g. a lyophilized form and denotes a solution having the same tonicity as some other solution with which it is compared, such as physiologic salt solution and the blood serum. Suitable isotonicity agents comprise but are not limited to sodium chloride, potassium chloride, glucose, glycerine and any component from the group of amino acids, sugars and combinations thereof. Isotonicity agents are generally used in a total amount of about 5 mM to about 350 mM.

The term "liquid" as used herein in connection with the formulation according to the invention denotes a formulation which is liquid at a temperature of at least about 2 to about 8 °C.

The term "lyophilized" as used herein in connection with the formulation according to the invention denotes a formulation which is dried by freezing the formulation and subsequently subliming the ice from the frozen content by any freeze-drying methods known in the art, for example commercially available freeze-drying devices.

The term "amino acid" as used herein denotes an amino acid in an amount of about 1 to about 100 mg/mL comprising but not limited to arginine, glycine, ornithine, lysine, histidine, glutamic acid, asparagic acid, isoleucine, leucine, alanine, phenylalanine, tyrosine, tryptophane, methionine, serine, proline.

The term "sugar" as used herein denotes a pharmaceutically acceptable sugar used in an amount of about 25 mM to about 500 mM. Suitable sugars comprise but are not limited to trehalose, saccharose, lactose, glucose, mannose, maltose, galactose, fructose, sorbose, raffinose, glucosamine, N-Methylglucosamine (so-called "Meglumine"), galactosamine and neuraminic acid.

The term "stabilizer" refers to pharmaceutically acceptable stabilizers, like for example but not limited to amino acids and sugars as described in the above sections as well as commercially available cyclodextrins and dextrans of any kind and molecular weight as known in the art.

The term "antioxidant" denotes a pharmaceutically acceptable antioxidant.

As mentioned above, in an aspect, the invention relates to an IGF-1R formulation comprising:

- about 1 to about 150 mg/mL huMab IGF-1R,
- about 0.001 to about 1% of at least one surfactant, and
- about 1 to about 100 mM of a buffer,
- at a pH of about 5.0 to about 7.0.

The formulation according to the invention preferably comprises about 0.001 to about 1% of at least one surfactant.

In a certain embodiment the formulation according to the invention comprises:

- about 1 to about 150 mg/mL huMab IGF-1R,
- about 0.005 to about 0.05 % of at least one surfactant, and
- about 1 to about 100 mM of a buffer,
- at a pH of about 5.0 to about 7.0.

The formulation according to the invention can be in a liquid form, in a lyophilized form or in a liquid form reconstituted from a lyophilized form.

In a certain embodiment the formulation according to the invention is a lyophilized formulation. The lyophilized formulation according to the invention has the advantage of an improved stability with regard to the formation of particulates and aggregates of higher molecular weight that is usually difficult to be achieved with liquid formulations at the same concentration of the described anti-IGF-1R human monoclonal antibody.

The formulation according to the invention can be administered by intravenous (i.v.), subcutaneous (s.c.) or any other parental administration means such as those known in the pharmaceutical art.

The formulation of the invention can further comprise one or more isotonicity agents in an amount of about 5 mM to about 350 mM. Suitable isotonicity agents can be selected from the group consisting of sodium chloride (NaCl), potassium chloride, sugars comprising glucose, glycerin, amino acids, and combinations thereof.

The formulation of the invention can further comprise a sugar in an amount of about 25 mM to about 500 mM. Suitable sugars can be selected from the group consisting of trehalose, saccharose, lactose, glucose, mannose, maltose, galactose, fructose, sorbose, raffinose, glucosamine, N-Methylglucosamine, galactosamine, neuraminic acid and combinations thereof.

The formulation of the invention can further comprise one or more of the following ingredients: antioxidants, ascorbic acid, Glutathion, preservatives, e.g., m-cresol, phenol, benzylalcohol, methylparaben, propylparaben, chlorbutanol, thiomersal, benzalkoniumchloride, cyclodextrine, e.g. hydroxypropyl-β-cyclodextrine, sulfobutylethyl-β-cyclodextrin, β-Cyclodextrin, polyethylenglycole, e.g. PEG 3000, 3350, 4000, 6000, albumine, human serum albumin (HSA), bovines serum albumin (BSA), polyhydric alcohol, glycerol, ethanol, mannitol, salts, acetate salts (e.g. sodium acetate), magnesiumchloride, calciumchloride, tromethamine, EDTA, (e.g. Na-EDTA).

The formulation of the invention can further comprise one or more stabilizers as defined hereinabove and ingredients also known in the art as "lyoprotectants" such as sugars, sugar alcohols, amino acids and dextrans as known in the art.

In a certain embodiment, the formulation of the invention comprises the following formulations, either in the liquid, lyophilized or liquid reconstituted from lyophilized forms:

- about 1 to about 150 mg/mL huMab IGF-1R,
- 0.01% Tween 20 w/v,
- 20 mM L-histidine,
- 140 mM NaCl,
- at pH 6.0.

The formulation according to the invention also comprises the following specific formulations:

- 25 mg/mL huMab IGF-1R,
- 0.01% polysorbate 20,
- 20 mM L-histidine,
- 140 mM NaCl,
- at pH 6.0.

or

- 25 mg/mL huMab IGF-1R,
- 0.03% polysorbate 20,
- 20 mM L-histidine,
- 140 mM NaCl,
- at pH 6.0.

or

- 25 mg/mL huMab IGF-1R,
- 0.05% polysorbate 20,
- 20 mM L-histidine,
- 140 mM NaCl,
- at pH 6.0.

or

- 10 mg/mL huMab IGF-1R,
- 0.01% polysorbate 20,
- 20 mM L-histidine,
- 140 mM NaCl,
- at pH 6.0.

or

- 10 mg/mL huMab IGF-1R,
- 0.03% polysorbate 20,

- 20 mM L-histidine,
- 140 mM NaCl,
- at pH 6.0.

or

- 10 mg/mL huMab IGF-1R,
- 0.05% polysorbate 20,
- 20 mM L-histidine,
- 140 mM NaCl,
- at pH 6.0.

or

- 25 mg/mL huMab IGF-1R,
- 20 mM L-histidine,
- 140 mM NaCl,
- at pH 5.5.

or

- 25 mg/mL huMab IGF-1R,
- 0.01% polysorbate 20,
- 20 mM L-histidine,
- 250 mM trehalose dihydrate,
- at pH 5.5.

or

- 25 mg/mL huMab IGF-1R,
- 20 mM L-histidine,
- 250 mM trehalose dihydrate,
- at pH 6.0.

or

- 25 mg/mL huMab IGF-1R,
- 0.01% polysorbate 20,
- 20 mM L-histidine,

- 250 mM trehalose dihydrate,
- at pH 6.0.

or

- 25 mg/mL huMab IGF-1R,
- 20 mM L-histidine,
- 250 mM trehalose dihydrate,
- 0.05% polysorbate 20,
- at pH 6.0.

or

- 25 mg/mL huMab IGF-1R,
- 20 mM L-histidine,
- 60 mM trehalose dihydrate,
- 0.01% polysorbate 20,
- at pH 6.0.

or

- 25 mg/mL huMab IGF-1R,
- 20 mM Succinate,
- 250 mM trehalose dihydrate,
- 0.01% polysorbate 20,
- at pH 5.5.

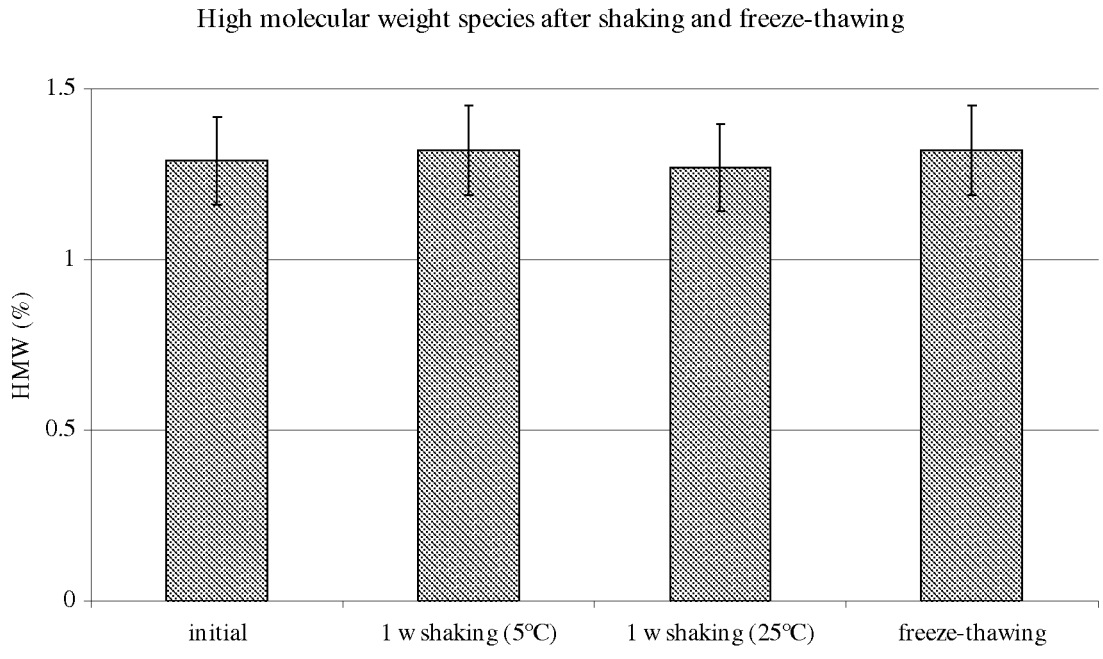
or

- 25 mg/mL huMab IGF-1R,
- 20 mM L-histidine,
- 60 mM trehalose dihydrate,
- 0.01% polysorbate 20,
- at pH 6.0.

In a preferred embodiment of the formulation according to the invention, the formulation is in a lyophilized form and comprises after reconstitution with the appropriate amount of water for injection:

- 25 mg/mL huMab IGF-1R,
- 0.01% polysorbate 20,
- 20 mM L-histidine,
- 250 mM trehalose dihydrate,
- at pH 5.5.

This formulation shows a good stability upon storage for approx 6 months at 2-8°C and 25°C with high molecular weight species less than 1.5% and without the formation of visible and sub-visible particles. Shaking and multiple freezing-thawing steps were applied to the liquid formulation to simulate physical stress conditions that potentially occur during manufacturing, e.g., by pressure filtration and filling, lyophilization and finish operations. This formulation was found to be stable after one week shaking at 5°C and 25°C. Formation of visible and sub-visible particles could not be detected and no significant increase in the fraction of high molecular weight species indicating the formation of soluble aggregates was observed.



EXAMPLES

Liquid and lyophilized drug product formulations for intravenous administration according to the invention were developed as follows:

Preparation of liquid formulations

Solutions of approx. 10 and 25 mg/mL huMab IGF-1R in the production buffer (approx. 10 mM histidine buffer with approx 150 mM NaCl) were dialysed against large volumes of water and of the respective buffer salt systems for the final formulation (see table with the exact composition of the formulations). If necessary, protein concentration was increased by filtration using commercially available centrifugal filter devices) prior to dialysis and then adjusted to the desired protein concentration by dilution with dialysis buffer. Sugars and salt for stabilizing the protein and for tonicity adjustment were added to the dialysis buffer as required. Surfactant was added to the formulations after dialysis as 2 to 40-fold stock solutions. Alternatively, buffer exchange and concentration was performed using a commercially available tangential flow filtration device, e.g., ÄKTA CF (GE Healthcare) with a Sartorius Hydrosart membrane (30'000Da molecular weight cut-off). Ingredients such as sugars, salts or surfactants were added after the buffer exchange by using appropriate quantities of concentrated stock solutions. All formulations were sterile filtered through 0.22 µm low protein binding filters and aseptically aliquoted into sterile 6 mL glass vials closed with Teflon-coated rubber stoppers and alucrimp caps. These formulations were stored at different temperatures for different intervals of time and removed for analysis at the timepoints indicated in the individual paragraphs by 1) UV spectrophotometry, 2) Size Exclusion Chromatography (SEC) and 3) light obscuration to determine the turbidity of the solution. Further, analysis for visible particles was performed for each sample using a Seidenader V90-T instrument. Occurrence of subvisible particles was assessed by a HIAC Royco device.

Preparation of lyophilized formulations

Solutions of 25 mg/mL huMab IGF-1R were prepared as described above for liquid formulations. All formulations were sterile filtered through 0.22 µm low protein binding filters and aseptically aliquoted into sterile glass vials. The vials were partly closed with Teflon-coated rubber stoppers suitable for the use in lyphilization processes and transferred to the drying chamber of the lyophilizer. Any lyophilization method known in the art is intended to be within the scope of the invention. For example, the lyophilization process used for this study included the cooling of the formulation from room temperature to approx 5°C (pre-cooling) followed by a freezing at -40°C (Freeze I) at a ramping rate of about 1°C/min to 5°C/min. The first drying step can be applied at a ramping rate of 0.3 to 0.5°C / min from -40°C to -30°C and then hold at -30°C for at least

50 hours at a chamber pressure of approx. 75 to 80 mTorr. A second drying step can take place at a ramping rate of 0.1 to 0.3°C / min from -30°C to 25°C and hold at 25°C for at least 5 hours at a chamber pressure of about 50 to 80 mTorr. huMab IGF-1R formulations which were dried using the described lyophilization processes were found to have conveniently quick reconstitution times of about < 5 min. Lyophilization was carried out in a LyoStar II Freeze-dryer (FTS Systems, Stone Ridge, NY, USA and Usifroid Orion, Maurepas, France). All lyophilized cakes in this study had a residual water content of approximately 0.1 to 5.0% as determined by Karl-Fischer method. The lyophilized vials were stored at different temperatures for different intervals of time. The lyophilized formulations were reconstituted with the respective volume of water for injection (WFI) prior to analysis by 1) UV sprectrophotometry, 2) determination of the reconstitution time, 3) Size Exclusion Chromatography (SEC) and 4) light obscuration to determine the turbidity of the solution. Further, analysis for visible particles was performed for each sample using a Seidenader V90-T instrument (Seidenader, Marktschwaben, Germany). Occurrence of subvisible particles was assessed by a HIAC Royco device.

Size Exclusion Chromatography (SEC) was performed to detect soluble high molecular weight species (aggregates) and low molecular weight hydrolysis products in the formulations. The method used a Merck Hitachi 7000 HPLC instrument or a Waters Alliance 2795 with UV detector (detection wavelength λ(280 nm) Both instruments were equipped with a TSK G3000 SWXL column; the method used 0.2M K_2HPO_4 / 0.25M KCL, pH 7.0 as mobile phase. Flow rate was 0.5 mL/min (isocratic), run time 30 min at 25°C column temperature. The UV spectroscopy for the determination of the protein concentration was performed after diluting the samples to 0.5 mg/mL antibody concentration on an Uvikon 932 (Kontron Instruments) at a wavelength of 278 nm and on a Varian Cary Bio UV spectrophotometer at 280 nm respectively. For the determination of the turbidity, light obscuration was measured in FTU (turbidity units) using a HACH 2100AN turbidimeter at room temperature.

Compositions of liquid huMAb IGF-1R drug product formulations according to this invention and stability data after 3 months storage at 2-8°C

Formulation A is a liquid formulation with the composition 25 mg/mL huMab IGF-1R, 20 mM L-histidine, 140 mM NaCl, 0.01% polysorbate 20, at pH 6.0.

Timepoint	Protein concentration	High molecular weight species (%)	Turbidity in FTU (turbidity)
initial	24.47	0.82	9.94
4 weeks	22.35	1.0	10.3
8 weeks	23.02	1.31	9.83
12 weeks	23.59	1.46	9.22

Formulation B is a liquid formulation with the composition 25 mg/mL huMab IGF-1R, 20 mM L-histidine, 140 mM NaCl, 0.03% polysorbate 20, at pH 6.0.

Timepoint	Protein concentration	High molecular weight species (%)	Turbidity in FTU
initial	24.98	0.84	9.79
4 weeks	23.58	1.01	9.97
8 weeks	25.43	1.37	10.5
12 weeks	23.68	1.49	10.3

Formulation C is a liquid formulation with the composition 25 mg/mL huMab IGF-1R, 20 mM L-histidine, 140 mM NaCl, 0.05% polysorbate 20, at pH 6.0.

Timepoint	Protein concentration	High molecular weight species (%)	Turbidity in FTU
initial	24.42	0.85	10.1
4 weeks	21.57	1.02	10.5
8 weeks	25.0	1.36	10.6
12 weeks	23.97	1.51	10.2

Formulation D is a liquid formulation with the composition 10 mg/mL huMab IGF-1R, 20 mM L-histidine, 140 mM NaCl, 0.01% polysorbate 20, at pH 6.0

Timepoint	Protein concentration	High molecular weight species (%)	Turbidity in FTU
initial	9.87	0.63	4.42

4 weeks	9.61	0.75	4.44
8 weeks	9.72	0.97	4.53
12 weeks	9.63	1.11	4.24

Formulation E is a liquid formulation with the composition 10 mg/mL huMab IGF-1R, 20 mM L-histidine, 140 mM NaCl, 0.03% polysorbate 20, at pH 6.0.

Timepoint	Protein concentration	High molecular weight species (%)	Turbidity in FTU
initial	9.98	0.69	4.26
4 weeks	9.68	0.79	4.72
8 weeks	9.68	1.05	4.54
12 weeks	9.62	1.59	4.26

Formulation F is a liquid formulation with the composition 10 mg/mL huMab IGF-1R, 20 mM L-histidine, 140 mM NaCl, 0.05% polysorbate 20, at pH 6.0

Timepoint	Protein concentration	High molecular weight species (%)	Turbidity in FTU
initial	9.81	0.67	4.45
4 weeks	9.69	0.83	4.36
8 weeks	9.62	1.19	5.01
12 weeks	9.18	1.45	4.44

Formulation G is a liquid formulation with the composition 10 mg/mL huMab IGF-1R, 20 mM L-histidine, 140 mM NaCl, at pH 5.5.

Timepoint	Protein concentration	High molecular weight species (%)	Turbidity in FTU
initial	24.7	0.8	4.9
4 weeks	24.6	1.0	3.9
8 weeks	n.d.	n.d.	n.d.
12 weeks	24.8	0.8	6.1

Formulation H is a liquid formulation with the composition 25 mg/mL huMab IGF-1R, 20 mM L-histidine, 250 mM trehalose dihydrate, 0.01% polysorbate 20, at pH 5.5

Timepoint	Protein	High molecular weight	Turbidity

	concentration	species (%)	in FTU
initial	27.1	1.29	3.58
4 weeks	26.9	1.27	3.74
8 weeks	29.33	1.43	5.03
12 weeks	26.44	1.38	4.10

Formulation I is a liquid formulation with the composition 25 mg/mL huMab IGF-1R, 20 mM L-histidine, 250 mM trehalose dihydrate, at pH 6.0

Formulation J is a liquid formulation with the composition 25 mg/mL huMab IGF-1R, 20 mM L-histidine, 250 mM trehalose dihydrate, 0.01% polysorbate 20, at pH 6.0

Formulation K is a liquid formulation with the composition 25 mg/mL huMab IGF-1R, 20 mM L-histidine, 250 mM trehalose dihydrate, 0.05% polysorbate 20, at pH 6.0

Formulation L is a liquid formulation with the composition 25 mg/mL huMab IGF-1R, 20 mM L-histidine, 60 mM trehalose dihydrate, 0.01% polysorbate 20, at pH 6.0

Formulation M is a liquid formulation with the composition 25 mg/mL huMab IGF-1R, 20 mM succinate, 250 mM trehalose dihydrate, 0.01% polysorbate 20, at pH 5.5

Timepoint	Protein concentration	High molecular weight species (%)	Turbidity in FTU
initial	26.13	1.49	7.06
4 weeks	27.93	1.46	7.25
8 weeks	26.59	1.62	8.20
12 weeks	26.89	1.62	7.10

Compositions of lyophilized huMAb IGF-1R drug product formulations according to this invention and stability data after 3 months storage at 2-8°C

Formulation N is a lyophilized formulation with the composition of the reconstituted solution of 25 mg/mL huMab IGF-1R, 20 mM L-histidine, 60 mM trehalose dihydrate, 0.01% polysorbate 20, at pH 6.0

Timepoint	Protein concentration	High molecular weight species (%)	Turbidity in FTU
initial	27.40	1.37	3.99
4 weeks	27.89	1.36	4.20
8 weeks	27.93	1.43	5.04
12 weeks	27.34	1.38	4.31

Formulation O is a lyophilized formulation with the composition of the reconstituted solution of 25 mg/mL huMab IGF-1R, 20 mM L-histidine, 60 mM sucrose, 0.01% polysorbate 20, at pH 6.0

Timepoint	Protein concentration	High molecular weight species (%)	Turbidity in FTU
initial	24.77	0.93	5.77
4 weeks	24.81	0.93	6.79
8 weeks	24.11	0.88	5.38
12 weeks	24.32	1.03	3.93

Formulation P is a lyophilized formulation with the composition of the reconstituted solution of 25 mg/mL huMab IGF-1R, 20 mM succinate, 250 mM trehalose dihydrate, 0.01% polysorbate 20, at pH 5.5

Timepoint	Protein concentration	High molecular weight species (%)	Turbidity in FTU
initial	26.9	1.45	7.17
4 weeks	27.71	1.55	7.44
8 weeks	26.59	1.43	7.13
12 weeks	26.89	1.36	7.07

Formulation Q is a lyophilized formulation with the composition of the reconstituted solution of 25 mg/mL huMab IGF-1R, 20 mM L-histidine, 250 mM trehalose dihydrate, 0.01% polysorbate 20, at pH 5.5

Timepoint	Protein concentration	High molecular weight species (%)	Turbidity in FTU
initial	27.11	1.33	3.59
4 weeks	28.28	1.22	3.49
8 weeks	27.81	1.30	4.65
12 weeks	28.22	1.18	4.04

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Claims

1. A formulation comprising:
- about 1 to about 150 mg/mL huMab IGF-1R,
- about 0.001 to about 1% of at least one surfactant, and
- about 1 to about 100 mM of a buffer,
- at a pH of about 5.0 to about 7.0.

2. The formulation according to claim 1, which comprises about 0.001 to about 1% of at least one surfactant.

3. The formulation according to claim 1, which is in a liquid form, in a lyophilized form or in a liquid form reconstituted from a lyophilized form.

4. The formulation according to any one of claim 1 or 3, which can be administered by intravenous (i.v.) or subcutaneous (s.c.) or any other parental administration.

5. The formulation according to any one of claims 1 to 4, which further comprises one or more isotonicity agents in an amount of about 5 mM to about 350 mM.

6. The formulation according to claim 5, wherein the isotonicity agents are selected from the group consisting of sodium chloride (NaCl), potassium chloride, sugars comprising glucose, glycerin, amino acids, and combinations thereof.

7. The formulation according to any one of claims 1 to 6 which further comprises a sugar in an amount of about 25 mM to about 500 mM.

8. The formulation according to claim 7, wherein the sugars are selected from the group consisting trehalose, saccharose, lactose, glucose, mannose, maltose, galactose, fructose, sorbose, raffinose, glucosamine, N-Methylglucosamine ("Meglumine"), galactosamine, neuraminic acid.

9. The formulation according to any one of claims 1 to 8, which further comprises one or more ingredients selected from the group consisting of pharmaceutically acceptable: antioxidants, ascorbic acid, Glutathion, preservatives, in particular, m-cresol, phenol, benzylalcohol, methylparaben, propylparaben, chlorbutanol, thimersal, benzalkoniumchloride, cyclodextrine, in particlar hydroxypropyl-β-cyclodextrine, sulfobutylethyl-β-cyclodextrin, β-Cyclodextrin, polyethylenglycole, in particular PEG 3000, 3350, 4000 or 6000, albumine, Humanes Serum Albumin (HSA), bovines serum

albumin (BSA), polyhydric alcohol, glycerol, ethanol, mannitol, salts, acetate salts in particular sodium acetate, magnesiumchloride, calciumchloride, tromethamine, EDTA, in particular Na-EDTA.

10. The formulation according to any one of claims 1 to 9, wherein it comprises:

- about 1 to about 150 mg/mL huMab IGF-1R,
- 0.01% Tween 20 w/v,
- 20 mM L-histidine,
- 140 mM NaCl,
- at pH 6.0.

11. The formulation according to any one of claims 1 to 9, wherein it is:

- 25 mg/mL huMab IGF-1R,
- 0.01% polysorbate 20,
- 20 mM L-histidine,
- 140 mM NaCl,
- at pH 6.0;

or

- 25 mg/mL huMab IGF-1R,
- 0.03% polysorbate 20,
- 20 mM L-histidine,
- 140 mM NaCl,
- at pH 6.0;

or

- 25 mg/mL huMab IGF-1R,
- 0.05% polysorbate 20,
- 20 mM L-histidine,
- 140 mM NaCl,
- at pH 6.0;

or

- 10 mg/mL huMab IGF-1R,
- 0.01% polysorbate 20,
- 20 mM L-histidine,
- 140 mM NaCl,
- at pH 6.0;

or

- 10 mg/mL huMab IGF-1R,
- 0.03% polysorbate 20,
- 20 mM L-histidine,
- 140 mM NaCl,
- at pH 6.0;

or

- 10 mg/mL huMab IGF-1R,
- 0.05% polysorbate 20,
- 20 mM L-histidine,
- 140 mM NaCl,
- at pH 6.0;

or

- 25 mg/mL huMab IGF-1R,
- 20 mM L-histidine,
- 140 mM NaCl,
- at pH 5.5;

or

- 25 mg/mL huMab IGF-1R,
- 0.01% polysorbate 20,
- 20 mM L-histidine,
- 250 mM trehalose dihydrate,
- at pH 5.5;

or

- 25 mg/mL huMab IGF-1R,
- 20 mM L-histidine,
- 250 mM trehalose dihydrate,
- at pH 6.0;.

or

- 25 mg/mL huMab IGF-1R,
- 0.01% polysorbate 20,
- 20 mM L-histidine,
- 250 mM trehalose dihydrate,
- at pH 6.0;

or

- 25 mg/mL huMab IGF-1R,
- 20 mM L-histidine,
- 250 mM trehalose dihydrate,
- 0.05% polysorbate 20,
- at pH 6.0;

or

- 25 mg/mL huMab IGF-1R,
- 20 mM L-histidine,
- 60 mM trehalose dihydrate,
- 0.01% polysorbate 20,
- at pH 6.0;

or

- 25 mg/mL huMab IGF-1R,
- 20 mM Succinate,
- 250 mM trehalose dihydrate,
- 0.01% polysorbate 20,
- at pH 5.5;

or

- 25 mg/mL huMab IGF-1R,
- 20 mM L-histidine,
- 60 mM trehalose dihydrate,
- 0.01% polysorbate 20,
- at pH 6.0.

12. Use of a formulation according to any one of claims 1 to 11 for the preparation of a medicament useful for treating diseases modulated by the IGF-IR receptor.

13. The use according to claim 12, wherein the disease is selected from the group consisting of breast cancer, colorectal cancer, non-small cell lung cancer (NSCLC) and prostate cancer.

14. The invention as described hereinabove.

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