ANTI-PROLACTIN RECEPTOR ANTIBODY FORMULATIONS

This application is being filed on 28 August 2013, as a PCT International patent application, and claims priority to U.S. Provisional Patent Application No. 61/695,949, filed August 31, 2012, and U.S. Patent Application No. 13/842,906, filed March 15, 2013, the disclosures of which are hereby incorporated by reference herein in their entirety.

BACKGROUND

The present disclosure relates generally to a wide concentration range of anti-prolactin receptor antibody formulations that are substantially isosmotic and of low viscosity, including formulations that are useful for subcutaneous and general injection administration.

Prolactin (PRL) is a polypeptide hormone composed of 199 amino acids. PRL belongs to the growth hormone (GH), placental lactogen (PL) family of polypeptide hormones and is synthesized in lactotroph cells of the pituitary and in several extrapituitary tissues such as lymphocytes, mammary epithelial cells, the myometrium, and the prostate. Two different promoters regulate pituitary and extrapituitary PRL synthesis (*BioEssays* 28:1051-1055 (2006)).

PRL binds to the PRL receptor (PRLR), a single transmembrane receptor belonging to the class 1 cytokine receptor superfamily (*Endocrine Reviews* 19:225-268 (1998)). PRLR exists in three different isoforms, the short, the long, and the intermediate form that can be distinguished by the length of their cytoplasmic tails. Upon ligand binding, a sequential process leads to PRLR activation. PRL interacts via its binding site 1 with one PRLR molecule and then attracts via its binding site 2 a second receptor molecule leading to an active dimer of PRLRs.

PRLR dimerization leads to the predominant activation of the JAK/STAT (Janus Kinase/Signal transducers and activators of transcription) pathway. Upon receptor dimerization, JAKs (predominantly JAK2) associated with the receptor, transphosphorylate and activate each other. In addition the PRLR is also phosphorylated and can bind to SH2-domain containing proteins such as STATs.

Receptor bound STATs are subsequently phosphorylated, dissociate from the receptor and translocate to the nucleus where they stimulate transcription of target genes. In addition, activation of the Ras-Raf-MAPK pathway and activation of the cytoplasmic src kinase by PRLRs have been described (for review *Endocrine Reviews* 19: 225-268 (1998)).

The role of PRLR-mediated signalling has been investigated in the context of the benign disease endometriosis. In one study the expression pattern of the PRLR in endometriotic samples and eutopic endometrium from endometriosis patients was analysed (*Acta Obstet Gynecol Scand* 81:5-10, 2002) during the mid-late proliferative phase of the menstrual cycle. It was demonstrated that the PRLR mRNA was present in the eutopic endometrium in 79% of the analysed endometriosis patients, whereas it was absent in the endometriotic lesions in 86% of the endometriosis patients. These data suggested a possible differential regulation of PRLR expression between normal and endometriotic tissue. However, from these expression data it cannot be concluded that inhibition of the PRLR might represent a suitable endometriosis therapy – especially since the PRLR was not found to be expressed in the endometriotic lesions (*Acta Obstet Gynecol Scand* 81:5-10 (2002)).

Antibodies that are directed against prolactin receptor (PRLR), including anti-PRLR monoclonal antibodies (aPRLR mAbs), are being developed in an effort to block PRLR function. One such aPRLR mAb is an IgG2 anti-PRLR mAb that is being developed for the non-hormonal treatment of endometriosis patients.

Antibodies may be administrated to patients via intravenous, intramuscular, and/or subcutaneous injection. To ensure patient compliance, it is desirable that intramuscular and subcutaneous injection dosage forms be isotonic and include small injection volumes (<2 ml per injection site). To reduce injection volume, and to provide an effective dose, antibodies are often administered with a wide concentration range, from 1 mg/ml to 150 mg/mL, including high concentrations within the range of 20 mg/ml to 150 mg/ml.

While both liquid and lyophilized dosage forms are used for currently marketed antibody drug products, lyophilized forms are more frequently used for

antibody drug products having high protein concentrations. A high concentration antibody formulation may present many challenges in formulation development, especially for liquid formulation. For formulations in which the antibody concentration is near its apparent solubility limit, phase separation can occur through precipitation, gelation, and/or crystallization. At high protein concentration, the stability of an antibody can become problematic due to the formation of soluble and insoluble protein-protein aggregates. Highly concentrated antibody formulations are frequently highly viscous, which presents difficulties for processing, such as ultrafiltration and sterile filtration, and for injection of the dosage solution. And at high antibody concentrations, which are desirable for formulations intended for intramuscular or subcutaneous administration, proportionally high concentrations of stabilizers, such as sucrose and sodium chloride, are required to achieve long-term protein stability. The resulting hypertonic solutions often cause injection pain due to tissue damage. Therefore, it is often desirable to balance the amount of stabilizers for stability and osmolality of the high protein concentration formulation.

SUMMARY

The present disclosure provides liquid and lyophilized anti-PRLR antibody formulations with a wide range of anti-PRLR antibody concentrations, which are substantially isotonic and low viscosity and that contain substantially no salt other than an organic salt or an inorganic salt that is used to buffer the formulation.

The anti-PRLR antibody formulations presented herein contain from about 0 mM to about 70 mM histidine; from about 50 ppm to about 300 ppm of a non-ionic surfactant such as, for example, polysorbate (Tween®) 80 and/or polysorbate (Tween®) 20; from about 34 mM to about 292 mM of a sugar or sugar alcohol such as, for example, mannitol, dextrose, glucose, trehalose, and/or sucrose; from about 0 mM to about 50 mM arginine; from about 0 mM to about 50 mM lysine; from about 0 mM to about 270 mM glycine or alanine; from about 0 mM to about 10 mM methionine; and from about 1 mg/ml to about 150 mg/ml of an anti-PRLR antibody, including an aPRLR-specific IgG2 monoclonal antibody (mAb) at a pH from about pH 5.0 to about pH 6.5.

Each of the presently disclosed antibody formulations contains substantially no salt other than an organic salt or an inorganic salt that is used to buffer the formulation. This permits the addition of alternative stabilizers to maintain the isosmoticity of the formulation (*i.e.*, osmolality ranging from about 240 mmol/kg to about 380 mmol/kg), which thereby promotes a higher degree of patient compliance.

Each of the presently disclosed antibody formulations has a low viscosity ranging from about 1 to about 8 mPa-S at 22°C-23°C, which promotes ease of processing such as, for example, improved ultrafiltration and sterile filtration as well as injection of the antibody formulation through a syringe needle during administration.

The formulations disclosed herein stabilize antibodies, in particular anti-PRLR antibodies including anti-PRLR IgG2 antibodies, at high protein concentrations in liquid form or in lyophilized form.

DESCRIPTION OF VARIOUS EMBODIMENTS

As described above, the present disclosure provides anti-PRLR antibody formulations that stabilize the anti-PRLR antibody in a wide range of concentrations in liquid form or in lyophilized form at intended storage conditions. The formulations described herein include one or more pharmaceutically acceptable excipients or stabilizers, and are contained in buffered media at a suitable pH and are substantially isosmotic with physiological fluids. For systemic administration, injection is one possible route of administration, including intramuscular, intravenous, intraperitoneal, and subcutaneous for injection.

Because of their low viscosity, the presently disclosed anti-PRLR antibody formulations can be conveniently processed via, for example, ultrafiltration and sterile filtration and can be administered to a patient via injection, including both intravenous and subcutaneous injection. Moreover, because they are substantially isosmotic, the presently disclosed anti-PRLR antibody formulations reduce tissue damage or other adverse physiologic effects and thereby achieving favorable patient tolerance and increased patient compliance.

The formulations described herein are characterized by the substantial absence of added salt other than an organic salt or an inorganic salt that is used to buffer the formulation, which provides the flexibility for increasing the concentrations of other stabilizers, such as sucrose, while maintaining the osmolality of the formulation for improved *in vivo* tolerability and, consequently, increased patient compliance. Moreover, the low viscosity of the presently described formulations permits convenient processing, including ultrafiltration and sterile filtration, and injection of the drug product solution through the needle.

For the purpose of interpreting this specification, the following definitions will apply. In the event that any definition set forth below conflicts with the usage of that word in any other document, including any document incorporated herein by reference, the definition set forth below shall always control for purposes of interpreting this specification and its associated claims unless a contrary meaning is clearly intended (for example in the document where the term is originally used).

Whenever appropriate, terms used in the singular also will include the plural and vice versa. The use of "a" herein means "one or more" unless stated otherwise or where the use of "one or more" is clearly inappropriate. The use of "or" means "and/or" unless stated otherwise. The use of "comprise," "comprises," "comprising," "include," "includes," and "including" are interchangeable and not intended to be limiting. The term "such as" also is not intended to be limiting. For example, the term "including" shall mean "including, but not limited to." Furthermore, where the description of one or more embodiments uses the term "comprising," those skilled in the art would understand that, in some specific instances, the embodiment or embodiments can be alternatively described using the language "consisting essentially of" and/or "consisting of."

As used herein, the term "viscosity" refers to the resistance of a liquid formulation to flow, such as when injected through a syringe needle during administration to a patient. Viscosity measurements can be done by a cone and plate technique with a Peltier element set at a defined temperature, such as 22°C-23°C as described herein. Typically, a well-defined shear stress gradient is applied to the liquid formulation and the resulting shear rate is measured. The viscosity is the ratio

of the shear stress to the shear rate. As used herein, viscosity is expressed in units of mPa-S at 22°C-23°C wherein 1 mPa-S = 1 cP. The high concentration, low viscosity, substantially isosmotic formulations disclosed herein are typically characterized by having a viscosity ranging from 1 to 8 mPa-S at 22 °C-23°C.

As used herein, the term "osmolality" refers to a measure of solute concentration, defined as the number of mmole of solute per kg of solution. A desired level of osmolality can be achieved by the addition of one or more stabilizer such as a sugar or a sugar alcohol including mannitol, dextrose, glucose, trehalose, and/or sucrose. Additional stabilizers that are suitable for providing osmolality are described in references such as the handbook of Pharmaceutical Excipients (Fourth Edition, Royal Pharmaceutical Society of Great Britain, Science & Practice Publishers) or Remingtons: The Science and Practice of Pharmacy (Nineteenth Edition, Mack Publishing Company).

As used herein, the term "about" refers to +/- 10% of the unit value provided. As used herein, the term "substantially" refers to the qualitative condition of exhibiting a total or approximate degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, achieve or avoid an absolute result because of the many variables that affect testing, production, and storage of biological and chemical compositions and materials, and because of the inherent error in the instruments and equipment used in the testing, production, and storage of biological and chemical compositions and materials. The term substantially is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

As used herein, the terms "isosmotic" and "isotonic" are used interchangeably with the terms "substantially isosmotic," and "substantially isotonic" and refer to formulations characterized by having an osmotic pressure that is the same as or at least substantially equivalent to the osmotic pressure of another solution, which is achieved by formulations wherein the total concentration of solutes, including both permeable and impermeable solutes, in the formulation are the same as or at least substantially equivalent to the total number of solutes in another solution. Thus, while it will be

appreciated by those of skill in the art that "isosmotic" and "isotonic" formulations that are used for *in vivo* administration generally have an osmolality ranging from about 270 mmol/kg to about 310 mmol/kg, in the context of the high concentration, low viscosity formulations of the present disclosure, the terms "isosmotic," "isotonic," "substantially isosmotic," and "substantially isotonic" are used interchangeably to refer to formulations having an osmolality ranging from about 240 mmol/kg to about 380 mmol/kg, or from about 270 mmol/kg to about 370 mmol/kg, or from about 300 mmol/kg to about 330 mmol/kg.

The presently disclosed high concentration, low viscosity, substantially isosmotic anti-PRLR antibody formulations contain from about 0 mM to about 70 mM histidine; from about 50 ppm to about 300 ppm of a non-ionic surfactant such as, for example, polysorbate (Tween®) 80 and/or polysorbate (Tween®) 20; from about 34 mM to about 292 mM of a sugar or sugar alcohol, such as, for example, mannitol, dextrose, glucose, trehalose, and/or sucrose; from about 0 mM to about 50 mM arginine; from about 0 mM to about 50 mM lysine; from about 0 mM to about 270 mM glycine or alanine; from about 0 mM to about 10 mM methionine; and from about 1 mg/ml to about 150 mg/ml of an anti-PRLR antibody at a pH from about pH 5.0 to about pH 6.5. The formulations disclosed herein exhibit a viscosity ranging from about 1 to about 8 mPa-S at 22°C-23°C and osmolality ranging from about 240 to about 380 mmol/kg.

In these formulations, histidine is a buffer agent, which can be used to maintain the formulation pH from about pH 5.0 to about pH 6.5, or from about pH 5.5 to about pH 6.0, such as about pH 5.0, about pH 5.5, about pH 6.0, or about pH 6.5.

Sugars or sugar alcohol, such as mannitol, dextrose, glucose, trehalose, and/or sucrose, are used separately or in combination both as cryo-protectants and a stabilizer the anti-PRLR antibody in liquid formulations as well as during lyophilization.

Non-ionic surfactants such as polysorbates, including polysorbate 20 and polysorbate 80; polyoxamers, including poloxamer 184 and 188; pluronic® polyols; and other ethylene/polypropylene block polymers, stabilize the anti-PRLR antibody

during processing and storage by reducing interfacial interaction and prevent antibody from adsorption.

Arginine is a protein solubilizer and also a stabilizer that reduces antibody and other protein aggregation, such as anti-PRLR antibody aggregation, and other possible degradation. Methionine is an antioxidant that prevents antibody oxidation during processing and storage.

Sugars and inorganic salts are commonly used as protein stabilizers; however, both sugars and inorganic salts are also effective tonicity agents. If a formulation requires a high concentration of one or more sugars to stabilize an anti-PRLR antibody, the inorganic salt concentration should be zero or kept very low in order to maintain the formulation's osmolality such that injection pain is reduced upon administration.

As used herein, the term "salt" refers to inorganic salts, which include sodium chloride (NaCl), sodium sulfate (Na_2SO_4), sodium thiocyanate (NaSCN), magnesium chloride (MgCl), magnesium sulfate ($MgSO_4$), ammonium thiocyanate (NH_4SCN), ammonium sulfate ($(NH_4)_2SO_4$), ammonium chloride (NH_4Cl), calcium chloride ($CaCl_2$), calcium sulfate ($CaSO_4$), zinc chloride ($ZnCl_2$) and the like, or combinations thereof. The anti-PRLR antibody formulations disclosed herein are characterized by a substantial absence of added salt and are, therefore, referred to herein as salt-free antibody formulations. It will be understood by those of skill in the art that the presence of inorganic salts within the presently disclosed formulations that are introduced by pH adjustment are not considered to be added salts. Such inorganic salts when introduced by pH adjustments, if present in a formulation according to the present disclosure, should not exceed a concentration of about 2 mM.

As used herein, the term "surfactant" includes non-ionic surfactants including, without limitation, polysorbates, such as polysorbate 20 or 80, and the polyoxamers, such as poloxamer 184 or 188, pluronic® polyols, and other ethylene/polypropylene block polymers. Amounts of surfactants effective to provide stable high concentration anti-PRLR antibody formulations are usually in the

range of 50 ppm to 300 ppm. The use of non-ionic surfactants permits the formulations to be exposed to shear and surface stresses without causing denaturation of the anti-PRLR antibody, and also reduce the adsorption on the surfaces during processing and storage. The formulations disclosed herein include, without limitation, formulations having one or more non-ionic surfactant(s) including, for example, one or more polysorbate(s), such as polysorbate 20 or 80; one or more polyoxamers, such as poloxamer 184 or 188; pluronic® polyols; and/or one or more ethylene/polypropylene block polymer(s). Exemplified herein are formulations having a polysorbate, such as polysorbate 20 (Tween® 20) or polysorbate 80 (Tween® 80).

As used herein, the term "antibody" refers to a class of proteins that are generally known as immunoglobulins. Antibodies include full-length monoclonal antibodies (mAb), such as IgG2 monoclonal antibodies, which include immunoglobulin Fc regions. The term antibody also includes bispecific antibodies, diabodies, single-chain molecules, and antibody fragments such as Fab, $F(ab')_2$, and Fv.

As used herein, the term "anti-PRLR antibody" refers to an antibody having binding specificity against the human PRLR protein as well as fragments and variants of the human PRLR protein. Anti-PRLR antibodies presented herein can be IgG2 antibodies and include anti-PRLR IgG2 monoclonal antibodies, such as chimeric, humanized, and fully-human anti-PRLR IgG2 monoclonal antibodies. Anti-PRLR monoclonal antibodies, including full-length antibodies and antigen binding fragments and variants thereof, that are suitable for use in the formulations disclosed herein are presented in PCT Patent Publication NOs. WO/2011/069799, WO/2011/069798, WO/2011/069797, WO/2011/069796, WO/2011/069795, and WO/2011/069794, each of which are incorporated by reference herein in their entirety.

"Monoclonal antibodies" are characterized by having specificity for a single antigenic determinant. Monoclonal antibodies can, for example, be made by the hybridoma method described by Kohler and Milstein, *Nature* 256:495 (1975) or by recombinant DNA methods such as those described in U.S. Patent No. 4,816,567.

Monoclonal antibodies can also be isolated from phage display libraries using the techniques such as those described in Clackson *et al.*, *Nature* 352:624-628 (1991) and Marks *et al.*, *J. Mol. Biol.* 222:581-597 (1991).

Monoclonal antibodies include "chimeric monoclonal antibodies" wherein a portion of a heavy and/or light chain includes sequences from antibodies derived from one species, while the remainder of the antibody, including the Fc region, includes sequences from antibodies derived from a second species, and the second species may be human. See, e.g., U.S. Patent No. 4,816,567 and Morrison *et al.*, *Proc. Natl. Acad. Sci. USA* 81:6851-6855 (1984).

Monoclonal antibodies also include "humanized monoclonal antibodies" wherein one or more complementarity determining region (CDR) from a heavy and/or light chain sequence from antibodies derived from one species replace one or more CDR from a heavy and/or light chain sequence from antibodies derived from a second species, and the second species may be human. The process of "humanization" is usually applied to monoclonal antibodies developed for administration to humans. See, *e.g.*, Riechmann *et al.*, *Nature* 332(6162):323-27 (1988) and Queen *et al.*, *Proc. Natl. Acad. Sci. USA* 86(24):10029-33 (1989).

Monoclonal antibodies also include "fully-human monoclonal antibodies" wherein the entire heavy and light chain sequences are derived from human antibody sequences. Fully-human monoclonal antibodies can be generated by phage display technologies and can be isolated from mice that have been genetically engineered to express the human antibody repertoire. See, *e.g.*, McCafferty *et al.*, *Nature* 348(6301):552-554 (1990), Marks *et al.*, *J. Mol. Biol.* 222(3):581-597 (1991), and Carmen and Jermutus, *Brief Funct. Genomic Proteomic* 1(2):189-203 (2002).

As used herein, the term "Pharmaceutically effective amount" of an anti-PRLR antibody formulation refers to an amount of the formulation that provides therapeutic effect in an administration regimen. The high concentration anti-PRLR antibody formulations disclosed herein typically include an anti-PRLR antibody at a concentration ranging from about 1 mg/ml to about 150 mg/ml, or from about 2 mg/ml to about 120 mg/ml, or from about 5 mg/ml to about 100 mg/ml, or from

about 7.5 mg/ml to about 60 mg/ml. Within some aspects the concentration of anti-PRLR antibody within these formulations is about 2 mg/ml, or about 7.5 mg/ml, or about 20 mg/ml, or about 50 mg/ml, or about 60 mg/ml. Such formulations are typically administered in a volume of less than about 2 ml, or about 1.5 ml, or about 1 ml, or about 0.5 ml per injection site for subcutaneous injection.

Within certain aspects, the anti-PRLR antibody formulation contains about 30 mM histidine, about 100 ppm polysorbate 80, about 292 mM sucrose, about 20 mg/ml anti-PRLR antibody at a pH ranging from about pH 5.0 to about pH 6.5. Within related aspects, the anti-PRLR antibody formulation also contains from about 10 mM to about 50 mM arginine.

Within other aspects, the anti-PRLR antibody formulation contains about 10 mM histidine, about 80 ppm polysorbate 80, about 234 mM sucrose, about 60 mg/ml anti-PRLR antibody at a pH ranging from about pH 5.0 to about pH 6.5. Within related aspects, the anti-PRLR antibody formulation also contains from about 30 mM to about 50 mM arginine.

Within other aspects, the anti-PRLR antibody formulation contains about 10 mM histidine, about 75 ppm polysorbate 80, about 234 sucrose, about 60 mg/ml anti-PRLR antibody at a pH ranging from about pH 5.0 to about pH 6.5. Within related aspects, the anti-PRLR antibody formulation also contains from about 30 mM to about 50 mM arginine.

Within other aspects, the anti-PRLR antibody formulation contains about 10 mM histidine, about 75 ppm polysorbate 80, about 88 mM sucrose, about 133 mM glycine, about 60 mg/ml anti-PRLR antibody at a pH ranging from about pH 5.0 to about pH 6.5. Within related aspects, the anti-PRLR antibody formulation also contains from about 10 mM to about 50 mM arginine.

Within other aspects, the anti-PRLR antibody formulation contains about 10 mM histidine, about 75 ppm polysorbate 20, about 88 mM sucrose, about 133 mM glycine, about 60 mg/ml anti-PRLR antibody at a pH ranging from about pH 5.0 to

about pH 6.5. Within related aspects, the anti-PRLR antibody formulation also contains from about 10 mM to about 50 mM arginine.

Within other aspects, the anti-PRLR antibody formulation contains about 10 mM histidine, about 200 ppm polysorbate 20, about 88 mM sucrose, about 133 mM glycine, about 60 mg/ml anti-PRLR antibody at a pH ranging from about pH 5.0 to about pH 6.5. Within related aspects, the anti-PRLR antibody formulation also contains from about 10 mM to about 50 mM arginine.

Within other aspects, the anti-PRLR antibody formulation contains about 70 mM histidine, about 80 ppm polysorbate 80, about 200 mM sucrose, about 60 mg/ml anti-PRLR antibody at a pH ranging from about pH 5.0 to about pH 6.5. Within related aspects, the anti-PRLR antibody formulation also contains from about 10 mM to about 50 mM arginine.

Within other aspects, the anti-PRLR antibody formulation contains about 10 mM histidine, about 80 ppm polysorbate 80, about 292 mM sucrose, about 10 mM arginine, about 60 mg/ml anti-PRLR antibody at a pH ranging from about pH 5.0 to about pH 6.5. Within related aspects, the anti-PRLR antibody formulation also contains from about 0 mM to about 10 mM methionine.

Within other aspects, the anti-PRLR antibody formulation contains about 70 mM histidine, about 80 ppm polysorbate 80, about 176 mM sucrose, about 133 mM glycine, about 30 mM lysine, about 60 mg/ml anti-PRLR antibody at a pH ranging from about pH 5.0 to about pH 6.5.

Within other aspects, the anti-PRLR antibody formulation contains about 10 mM histidine, about 75 ppm about polysorbate 80, about 234 mM sucrose, about 30 mM arginine, about 60 mg/ml anti-PRLR antibody at a pH ranging from about pH 5.0 to about pH 6.5. Within related aspects, the anti-PRLR antibody formulation also contains from about 0 mM to 10 mM methionine.

Within other aspects, the anti-PRLR antibody formulation contains about 10 mM histidine, about 80 ppm about polysorbate 80, about 234 mM sucrose, about 20 mM arginine, about 150 mg/ml anti-PRLR antibody at a pH ranging from about pH

5.0 to about pH 6.5. Within related aspects, the anti-PRLR antibody formulation also contains from about 0 mM to 10 mM methionine.

Within other aspects, the anti-PRLR antibody formulation contains about 10 mM histidine, about 80 ppm about polysorbate 80, about 205 mM sucrose, about 20 mM arginine, about 60 mg/ml anti-PRLR antibody at a pH ranging from about pH 5.0 to about pH 6.5. Within related aspects, the anti-PRLR antibody formulation also contains from about 0 mM to 10 mM methionine.

Within other aspects, the anti-PRLR antibody formulation contains about 10 mM histidine, about 80 ppm about polysorbate 80, about 205 mM sucrose, about 20 mM arginine, about 2 mg/ml anti-PRLR antibody at a pH ranging from about pH 5.0 to about pH 6.5. Within related aspects, the anti-PRLR antibody formulation also contains from about 0 mM to 10 mM methionine.

Within other aspects, the anti-PRLR antibody formulation contains about 10 mM histidine, about 80 ppm about polysorbate 80, about 205 sucrose, about 20 mM arginine, about 1 mg/ml anti-PRLR antibody at a pH ranging from about pH 5.0 to about pH 6.5. Within related aspects, the anti-PRLR antibody formulation also contains from about 0 mM to 10 mM methionine.

Within other aspects, the anti-PRLR antibody formulation contains about 10 mM histidine, about 75 ppm about polysorbate 80, about 205 trehalose, about 20 mM arginine, about 2 mg/ml anti-PRLR antibody at a pH ranging from about pH 5.0 to about pH 6.5. Within related aspects, the anti-PRLR antibody formulation also contains from about 0 mM to 10 mM methionine.Within other aspects, the anti-PRLR antibody formulation contains about 10 mM histidine, about 75 ppm about polysorbate 80, about 205 trehalose, about 20 mM arginine, about 60 mg/ml anti-PRLR antibody at a pH ranging from about pH 5.0 to about pH 6.5. Within related aspects, the anti-PRLR antibody formulation also contains from about 0 mM to 10 mM methionine.

Within other aspects, the anti-PRLR antibody formulation contains about 10 mM histidine, about 234 mM sucrose, about 80 ppm polysorbate 80, about 30 mM

arginine, about 5 mM methionine, about 7.5 mg/ml anti-PRLR antibody at a pH ranging from about pH 5.0 to about pH 6.5, such as pH 5.5.

Within other aspects, the anti-PRLR antibody formulation contains about 10 mM histidine, about 234 mM sucrose, about 80 ppm polysorbate 80, about 30 mM arginine, about 5 mM methionine, about 60 mg/mL anti-PRLR antibody at a pH ranging from about pH 5.0 to about pH 6.5, such as pH 5.5.

Within other aspects, the anti-PRLR antibody formulation contains about 10 mM histidine, about 234 mM sucrose, about 75 ppm Tween 80, about 30 mM arginine, about 10 mM methionine, about 60 mg/mL anti-PRLR antibody at a pH ranging from about pH 5.0 to about pH 6.5, such as pH 5.5.

Within other aspects, the anti-PRLR antibody formulation contains about 10 mM histidine, about 263 mM sucrose, about 80 ppm polysorbate 80, about 60 mg/mL anti-PRLR antibody at a pH ranging from about pH 5.0 to about pH 6.5, such as pH 6.0.

Thus, the present disclosure provides anti-PRLR mAb formulations, including anti-PRLR IgG2 mAb formulations, wherein the anit-PRLR mAb is soluble at high protein concentrations. The anti-PRLR mAb in the formulations disclosed herein remain soluble at concentrations of between about 1 mg/ml to about 150 mg/ml and remain stable under isosmotic storage conditions and exhibit reduced viscosity as compared to currently available antibody formulations.

The anti-PRLR antibody having a light chain comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 7 is an IgG2 antibody that blocks prolactin receptor (PRLR). Anti-PRLR antibodies can prevent the onset or progression of endometriosis by blocking PRLR, thereby overcoming deficiencies in endometrial pathways. The high concentration, salt free anti-PRLR antibody formulations presented herein can be administrated to the patients via intravenous injection or subcutaneous injection or other injection routes.

As part of the present disclosure, stability of anti-PRLR antibodies is affected by excipients. The stability of anti-PRLR antibody increases with the decrease of NaCl concentrations in the pH range defined. In addition, positively charged amino acids, such as arginine and lysine, can improve the stability anti-PRLR antibody and that pH greatly affects anti-PRLR antibody aggregation. The aggregation of antibody solutions increases with increases in pH. The optimal pH for stabilizing the anti-PRLR antibodies presented herein ranges from about pH 5.0 to about pH 6.5 or from about pH 5.5 to about pH 6.0 such as about pH 5.0, about pH 5.5, about pH 6.0, or about pH 6.5.

Provided herein are anti-PRLR antibody formulations wherein the anti-PRLR antibodies include IgG2 antibodies, including human IgG2 monoclonal anti-PRLR antibodies having a light chain sequence and a heavy chain sequence presented in one or more of PCT Patent Publication NOs. WO/2011/069799, WO/2011/069798, WO/2011/069797, WO/2011/069796, WO/2011/069795, and WO/2011/069794.

Antibodies that may be suitably employed in the anti-PRLR antibody formulations described herein are exemplified by the Mat3-hIgG2 antibody presented in Table 1, which was obtained from the BioInvent Phage Display library (Lund, Sweden) and subsequently germlined and sequence-optimized for affinity, activity, species cross-reactivity, and manufacturability.

The Fab part comprises a lambda light chain (VL: DPL3 germline; CL: Mcg-/Kern-/Oz- isotype) and a heavy chain VH DP47-germline framework region. The antibody was reformatted into a human IgG2 of the IgG2m (n-) heavychain allotype lacking the C-terminal lysine. A potential deamidation site is present in CDR3 at amino acid position 98 of the light chain and was left unchanged in this antibody. The standard N-glycosylation site of IgG2 is present at N294 of the heavy chain.

Table 1

Heavy and Light Chain Sequences of Exemplary Human Anti-PRLR IgG2 Monoclonal Antibody Mat3-hIgG2

Sequence Identifier	Portion of Antibody Chain	Amino Acid Sequence (NH_3-COOH)
SEQ ID NO: 1	Light Chain, Full-length	QSVLTQPPSA SGTPGQRVTI SCTGSSSNIG AGYVVHWYQQ LPGTAPKLLI YRNNQRPSGV PDRFSGSKSG TSASLAISGL RSEDEADYYC AAWDDSLNGW LFGGGTKLTV LGQPKAAPSV TLFPPSSEEL QANKATLVCL ISDFYPGAVT VAWKADSSPV KAGVETTTPS KQSNNKYAAS SYLSLTPEQW KSHRSYSCQV THEGSTVEKT VAPTECS
SEQ ID NO: 2	Light Chain, Variable Domain	QSVLTQPPSA SGTPGQRVTI SCTGSSSNIG AGYVVHWYQQ LPGTAPKLLI YRNNQRPSGV PDRFSGSKSG TSASLAISGL RSEDEADYYC AAWDDSLNGW LFGGGTKLTV LGQ
SEQ ID NO: 3	Light Chain, Variable Domain, CDR1	SCTGSSSNIG AGYVVH
SEQ ID NO: 4	Light Chain, Variable Domain, CDR2	RNNQRPS
SEQ ID NO: 5	Light Chain, Variable Domain, CDR3	CAAWDDSLNG WL
SEQ ID NO: 6	Light Chain, Constant Domain	PKAAPSVTLF PPSSEELQAN KATLVCLISD FYPGAVTVAW KADSSPVKAG VETTTPSKQS NNKYAASSYL SLTPEQWKSH RSYSCQVTHE GSTVEKTVAP TECS
SEQ ID NO: 7	Heavy Chain, Full-length	EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYWMHWVRQA PGKGLEWVSD IARLSSYTNY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGL DARRMDYWGQ GTLVTVSSAS TKGPSVFPLA PCSRSTSEST AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSNFGTQTYT CNVDHKPSNT KVDKTVERKC CVECPPCPAP PVAGPSVFLF PPKPKDTLMI SRTPEVTCVV VDVSHEDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTFRVV SVLTVVHQDW LNGKEYKCKV SNKGLPAPIE KTISKTKGQP

		REPQVYTLPP SREEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPMLDSDGS FFLYSKLTVD KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPG
SEQ ID NO: 8	Heavy Chain, Variable Domain	EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYWMHWVRQA PGKGLEWVSD IARLSSYTNY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARGL DARRMDYWGQ GTLVTVSS
SEQ ID NO: 9	Heavy Chain, Variable Domain, CDR1	FSSYWMHW
SEQ ID NO: 10	Heavy Chain, Variable Domain, CDR2	SDIARLSSYT NYADSVKGR
SEQ ID NO: 11	Heavy Chain, Variable Domain, CDR3	ARGLDARRMD Y
SEQ ID NO: 12	Heavy Chain, Constant Domain	ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSNFGTQT YTCNVDHKPS NTKVDKTVER KCCVECPPCP APPVAGPSVF LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTFR VVSVLTVVHQ DWLNGKEYKC KVSNKGLPAP IEKTISKTKG QPREPQVYTL PPSREEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPMLDSD GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPG

Thus, the present disclosure provides anti-PRLR mAb formulations, including anti-PRLR IgG2 mAb formulations, wherein the anti-PRLR mAb is soluble at high protein concentrations. Typically, the anti-PRLR mAb in the formulations disclosed herein remain soluble at concentrations from about 1 mg/ml to about 150 mg/ml and remain stable under isosmotic storage conditions and exhibit reduced viscosity as compared to currently available antibody formulations.

The anti-PRLR antibody having a light chain sequence and a heavy chain sequence presented in the Sequence Listing attached hereto and in one or more of PCT Patent Publication NOs. WO/2011/069799 (U.S. 2013/0129739),

WO/2011/069798 (U.S. 2013/0022606), WO/2011/069797 (U.S. 2012/0315276), WO/2011/069796 (U.S. 2013/0171147), WO/2011/069795, and WO/2011/069794 (U.S. 2012/0321632) can be an IgG2 antibody that blocks a prolactin receptor activity. Anti-PRLR antibodies can prevent the onset or progression of endometriosis by blocking PRLR, thereby overcoming deficiencies in endometrial pathways. The wide protein concentration range, including high concentration anti-PRLR antibody formulations presented herein can be administrated to the patients via intravenous injection intramuscular injection or subcutaneous injection.

The present disclosure also provides methods for the non-hormonal treatment of endometriosis in a patient, comprising the administration to the patient of a therapeutically effective amount of one or more formulations described herein. For example, provided are methods for the non-hormonal treatment of endometriosis in a patient, comprising the administration to the patient of a therapeutically effective amount of an anti-prolactin receptor antibody (aPRLR Ab) formulation including an aPRLR-specific IgG2 monoclonal antibody (mAb) formulation that contains from about 0 mM to about 70 mM histidine; from about 50 ppm to about 300 ppm polysorbate (Tween®) 80 and/or polysorbate (Tween®) 20; from about 34 mM to about 292 mM sucrose; from about 0 mM to about 50 mM arginine, from about 0 mM to about 50 mM lysine, from about 0 mM to about 270 mM glycine or alanine, from about 0 mM to about 10 mM methionine, and from about 1 mg/ml to about 150 mg/ml of an anti-PRLR antibody at a pH ranging from about pH 5.0 to about pH 6.5. Within at least one aspect of these methods, the anti-PRLR antibody formulation can be administered intravenously. Within other aspects of these methods, the anti-PRLR antibody formulation can be administered subcutaneously. Within other aspects of these methods, the anti-PRLR antibody formulation can be administered intramuscularly.

According to certain aspects of these methods for the non-hormonal treatment of endometriosis in a patient, the anti-PRLR antibody is a human anti-PRLR IgG2 monoclonal antibody such as, for example, a human anti-PRLR IgG2 monoclonal antibody that contains a light chain sequence and a heavy chain sequence presented in one or more of PCT Patent Publication NOs. WO/2011/069799,

WO/2011/069798, WO/2011/069797, WO/2011/069796, WO/2011/069795, and WO/2011/069794.

Aspects of the present disclosure may be further understood in light of the following examples, which should not be construed as limiting the scope of the present teachings in any way.

EXAMPLES

Example 1

Effect of NaCl Concentration and pH on the Turbidity of Antibody Solutions

This Example discloses the effect of salt (NaCl) concentration and pH on the aggregation of solutions containing an anti-PRLR human monoclonal antibody that contains a light chain sequence and a heavy chain sequence presented in one or more of PCT Patent Publication Nos. WO/2011/069799, WO/2011/069798, WO/2011/069797, WO/2011/069796, WO/2011/069795, and WO/2011/069794. The turbidity of solutions is assessed by visual observation to quickly evaluate the effects of salt concentrations and pH on aPRLR mAb solutions. No precipitation is observed after 2 months at 5°C and 25 °C with the formulation in absence of salt at pH 5.5-6.5.

Solutions without sodium chloride at pH 5.0 to 6.5 are recommended for the presently disclosed anti-PRLR antibody formulations.

Without being bound by theory, it is believed that the decreased stability in terms of turbidity or aggregation of the anti-PRLR mAb formulations with high NaCl concentration results from the neutralization of positive charges on the anti-PRLR mAb arginine side-chains. The phase behavior of aPRLR mAb at different pH with the impact of monovalent salt (NaCl) explains why the stable, soluble, non-salt, and substantial isosmolality aPRLR mAb formulations are achieved.

At a pH below the PI, such as pH 5-6.5, an anti-PRLR antibody has a net positive charge. The repulsion of the positive charges on such an anti-PRLR antibody surface likely prevents protein-protein association between individual molecules and, thereby, significantly increases solubility. It is hypothesized that the

anion (Cl^-) of salt binds to the guanidinium group on arginine side-chains on an anti-PRLR antibody surface to neutralize the positive charges, which enhances protein-protein interactions and, hence, causes lower solubility and solution turbidity. By shifting the pH to 5.0-6.5, the non-salt formulations that are described herein are developed to achieve increased antibody solubility and stability. In absence of salt, the concentration of other stabilizers, such as sucrose, can be increased to >150 mM and <300 mM without compromising osmolality.

Example 2
Anti-PRLR Antibody Formulations

Substantially isosmotic high concentration anti-PRLR Ab formulations are prepared without NaCl. These formulations employ high sucrose concentrations to help stabilize the anti-PRLR Ab.

Frozen anti-PRLR antibody is thawed and formulated according to formulations presented in Table 2. The formulations are prepared and are sterile filtered with a 0.22 μm filter and sterile filled in glass tubing vials and stoppered with rubber stoppers.

In the absence of NaCl, and in the presence of sucrose or trehalose 34 mM to 292 mM and polysobate 80 (50-300 ppm), and at pH 5.0-6.5, the positive charged amino acids, such as arginine (10-50 mM), can effectively inhibit aPRLR Ab from aggregation.

Table 2
Anti-PRLR Antibody Formulations

1 mg/ml aPRLR Ab		
1 mg/ml aPRLR Ab 10 mM histidine 205 mM sucrose 75 ppm polysorbate 80 20 mM arginine 10 mM methionine pH 5.5		
2 mg/ml aPRLR Ab		
2 mg/ml aPRLR Ab 10 mM histidine 234 mM sucrose 75 ppm polysorbate 80 30 mM arginine 10 mM methionine pH 5.5	2 mg/ml aPRLR Ab 10 mM histidine 234 mM sucrose 75 ppm polysorbate 80 30 mM arginine 10 mM methionine pH 5.0	
7.5 mg/ml aPRLR Ab		
7.5 mg/ml aPRLR Ab 10 mM histidine 234 mM sucrose 80 ppm polysorbate 80 30 mM arginine 5 mM methionine pH 5.5		
20 mg/ml aPRLR Ab		
20 mg/ml aPRLR Ab 30 mM histidine 292 mM sucrose 60 ppm polysorbate 80 pH 5.0	20 mg/ml aPRLR Ab 30 mM histidine 292 mM sucrose 60 ppm polysorbate 80 pH 5.5	20 mg/ml aPRLR Ab 30 mM histidine 10% sucrose 60 ppm polysorbate 80 pH 6.5
20 mg/ml aPRLR Ab 30 mM histidine 292 mM sucrose 60 ppm polysorbate 80 50 mM arginine pH 6.0		
50 mg/ml aPRLR Ab		
50 mg/ml aPRLR Ab 10 mM histidine 234 mM sucrose 75 ppm polysorbate 80 50 mM arginine pH at 6	50 mg/ml aPRLR Ab 10 mM histidine 234 mM sucrose 75 ppm polysorbate 80 30 mM arginine pH 5.5	
60 mg/ml aPRLR Ab		
60 mg/ml aPRLR Ab 10 mM histidine 234 mM sucrose 75 ppm polysorbate 80 pH 5.5	60 mg/ml aPRLR Ab 10 mM histidine 88 mM sucrose 200 ppm polysorbate 20 30 mM arginine 133 mM glycine pH at 5.5	60 mg/ml aPRLR Ab 10 mM histidine 205 mM sucrose 75 ppm polysorbate 80 20 mM arginine 10 mM methionine pH 6.5

60 mg/ml aPRLR Ab 10 mM histidine 234 mM sucrose 75 ppm polysorbate 80 30 mM arginine pH 5.5	60 mg/ml aPRLR Ab 10 mM histidine 88 mM sucrose 75 ppm polysorbate 80 10 mM arginine 133 mM glycine pH 5.5	60 mg/ml aPRLR Ab 10 mM histidine 205 mM trehalose 75 ppm polysorbate 80 20 mM arginine 10 mM methionine pH 5.5
60 mg/ml aPRLR Ab 10 mM histidine 234 mM sucrose 75 ppm polysorbate 80 30 mM arginine pH 6	60 mg/ml aPRLR Ab 10 mM histidine 292 mM sucrose 75 ppm polysorbate 80 10 mM arginine 10 mM methionine 133 mM glycine pH 5.5	60 mg/ml aPRLR Ab 10 mM histidine 205 mM trehalose 75 ppm polysorbate 80 20 mM arginine 10 mM methionine pH 5.5
60 mg/ml aPRLR Ab 10 mM histidine 88 mM sucrose 75 ppm polysorbate 80 30 mM arginine 133 mM glycine pH 5.5	60 mg/ml aPRLR Ab 10 mM histidine 388 mM sucrose 75 ppm polysorbate 80 30 mM lysine 133 mM glycine pH 5.5	60 mg/mL aPRLR Ab 10 mM histidine 234 mM sucrose 80 ppm polysorbate 80 30 mM arginine 5 mM methionine pH 5.5
60 mg/ml aPRLR Ab 10 mM histidine 88 mM sucrose 75 ppm polysorbate 20 30 mM arginine 133 mM glycine pH 5.5	60 mg/ml aPRLR Ab 10 mM histidine 234 mM sucrose 75 ppm polysorbate 80 30 mM arginine 10 mM methionine pH 5.5	60 mg/mL aPRLR Ab 10 mM histidine 234 mM sucrose 75 ppm polysorbate 80 30 mM arginine 10 mM methionine pH 5.5
60 mg/mL aPRLR Ab 70 mM histidine 200 mM sucrose 80 ppm polysorbate 80 pH 6.0	60 mg/mL aPRLR Ab 10 mM histidine 263 mM sucrose 80 ppm polysorbate 80 pH 6.0	60 mg/mL aPRLR Ab 70 mM histidine 176 mM sucrose 75 ppm polysorbate 80 30 mM lysine pH 6.0
150 mg/ml aPRLR Ab		
150 mg/ml aPRLR Ab 10 mM histidine 234 mM sucrose 75 ppm polysorbate 80 30 mM arginine 10 mM methionine pH 5.5		

Representative anti-PRLR mAb formulations were analyzed by HPLC-SEC for protein aggregation and degradation, LC-MS for aPRLR structural changes (glycation and oxidation), viscometer for viscosity measurement, and osmolality instrument for osmolality measurement. The results for the HPLC-SEC analysis of protein aggregation are presented in Table 3, the results for the nephlometry analysis of turbidity are presented in Table 4, the results for the LC-MS analysis of aPRLR structural changes are presented in Table 5, and the results for the analysis of viscosity and osmolality are presented in Table 6.

Table 3

HPLC-SEC Average Rate of Aggregation Formation (%/day)

Formulation Composition		5°C	25°C
Anti-PRLR	60 mg/mL		
Histidine	10 mM		
Sucrose	234 mM		
Polysorbate 80	75 ppm	0.000 [1]	0.005 [1]
pH	5.5		
Arginine	30 mM		
Methionine	10 mM		
Anti-PRLR	60 mg/mL		
Histidine	10 mM		
Sucrose	263 mM	0.013 [2]	0.022 [2]
Polysorbate 80	80 ppm		
pH	6.0		

[1] The calculation was based on 100 days value.

[2] The calculation was based on 90 days value.

Table 4

LC-MS Results of the Formulations after Shaking at 100 rpm at Room Temperature

Formulation Composition		Intact Mass	Mass of LC and HC
Anti-PRLR	60 mg/mL		
Histidine	10 mM		
Sucrose	234 mM		
Polysorbate 80	75 ppm	Comparable to RS [1]	Comparable to RS [1]
pH	5.5		
Arginine	30 mM		
Methionine	10 mM		
Anti-PRLR	60 mg/mL		
Histidine	10 mM		
Sucrose	263 mM		
Polysorbate 80	80 ppm	Comparable to RS [2]	Comparable to RS [2]
pH	6.0		

[1] After the formulation was shaken at 100 rpm at room temperature for 14 days.

[2] After the formulation was shaken at 100 rpm at room temperature for 21 days.

LC = Light Chain; HC = Heavy Chain; RS = Reference Standard.

Table 5

Average Rate of Turbidity change (by Nephelometry) After Shaking at 100 rpm at Room Temperature

Formulation Composition		FNU/day
Anti-PRLR	60 mg/mL	0.643 [1]
Histidine	10 mM	
Sucrose	234 mM	
Polysorbate 80	75 ppm	
pH	5.5	
Arginine	30 mM	
Methionine	10 mM	
Anti-PRLR	60 mg/mL	0.013 [2]
Histidine	10 mM	
Sucrose	263 mM	
Polysorbate 80	80 ppm	
pH	6.0	

[1] After the formulation was shaken at 100 rpm at room temperature for 14 days.

[2] After the formulation was shaken at 100 rpm at room temperature for 21 days.

Table 6

Viscosity and Osmolality of Anti-PRLR Ab Formulations

Formulation Composition		Viscosity (mPa-S) at 22.0°C-23.0°C	Osmolality (mmol/kg)
Anti-PRLR	60 mg/mL	1.83	342
Histidine	10 mM		
Sucrose	234 mM		
Polysorbate 80	80 ppm		
pH	5.5		
Arginine	30 mM		
Methionine	5 mM		
Anti-PRLR	60 mg/mL	2.37	345
Histidine	10 mM		
Sucrose	234 mM		
Polysorbate 80	75 ppm		
pH	5.5		
Arginine	30 mM		
Methionine	10 mM		
Anti-PRLR	60 mg/mL	2.17	299
Histidine	10 mM		
Sucrose	263 mM		
Polysorbate 80	80 ppm		
pH	6.0		

CLAIMS

What is claimed is:

1. An anti-PRLR antibody formulation, comprising:
   a. 0 mM to 70 mM histidine;
   b. 50 ppm to 300 ppm of a non-ionic surfactant;
   c. 34 mM to 292 mM of a sugar selected from mannitol, dextrose, glucose, trehalose, and sucrose;
   d. 0 mM to 50 mM arginine;
   e. 0 mM to 50 mM lysine;
   f. 0 mM to 270 mM glycine or alanine;
   g. 0 mM to 10 mM methionine; and
   h. 1 mg/ml to 150 mg/ml of an anti-PRLR antibody;

wherein said anti-PRLR antibody formulation has a pH ranging from pH 5.0 to pH 6.5.

2. The anti-PRLR antibody formulation of claim 1 wherein said anti-PRLR formulation contains substantially no inorganic salt other than an organic salt or an inorganic salt that buffers said formulation.

3. The anti-PRLR antibody formulation of claim 1 wherein said anti-PRLR formulation contains substantially no inorganic salt selected from the group consisting of sodium chloride (NaCl), sodium sulfate (Na_2SO_4), sodium thiocyanate (NaSCN), magnesium chloride (MgCl), magnesium sulfate ($MgSO_4$), ammonium thiocyanate (NH_4SCN), ammonium sulfate ($(NH_4)_2SO_4$), ammonium chloride (NH_4Cl), calcium chloride ($CaCl_2$), calcium sulfate ($CaSO_4$), and zinc chloride ($ZnCl_2$).

4. The anti-PRLR antibody formulation of claim 1 wherein said formulation has a viscosity ranging from 1 to 8 mPa-S at 22°C-23°C.

5. The anti-PRLR antibody formulation of claim 1 wherein said formulation has and osmolality ranging from 240 to 380 mmol/kg.

6. The anti-PRLR antibody formulation of any of claim 1 wherein said non-ionic surfactant is a polysorbate selected from polysorbate 20 and polysorbate 80.

7. The anti-PRLR antibody formulation of claim 1 wherein said sugar is sucrose or trehalose.

8. The anti-PRLR antibody formulation of claim 1 comprising between 10 mM and 50 mM arginine.

9. The anti-PRLR antibody formulation of claim 1, comprising:

a. 30 mM histidine,

b. 100 ppm polysorbate 80,

c. 292 mM sucrose, and

d. 20 mg/ml anti-PRLR antibody;

wherein said anti-PRLR antibody formulation has a pH ranging from pH 5.0 to pH 6.5.

10. The anti-PRLR antibody formulation of claim 1, comprising:

a. 10 mM histidine,

b. 80 ppm polysorbate 80,

c. 234 mM sucrose,

d. 60 mg/ml anti-PRLR antibody;

wherein said anti-PRLR antibody formulation has a pH ranging from pH 5.0 to pH 6.0.

11. The anti-PRLR antibody formulation of claim 1, comprising:

a. 10 mM histidine,

b. 75 ppm polysorbate 80,

c. 234 mM sucrose, and

d. 60 mg/ml anti-PRLR antibody;

wherein said anti-PRLR antibody formulation has a pH ranging from pH 5.0 to pH 6.5.

12. The anti-PRLR antibody formulation of claim 1, comprising:

a. 10 mM histidine,

b. 75 ppm polysorbate 80,

c. 88 mM sucrose,

d. 270 mM glycine, and

e. 60 mg/ml anti-PRLR antibody;

wherein said anti-PRLR antibody formulation has a pH ranging from pH 5.0 to pH 6.5.

13. The anti-PRLR antibody formulation of claim 1, comprising:

a. 10 mM histidine,

b. 75 ppm polysorbate 20,

c. 88 mM sucrose,

d. 133 mM glycine, and

e. 60 mg/ml anti-PRLR antibody;

wherein said anti-PRLR antibody formulation has a pH ranging from pH 5.0 to pH 6.5.

14. The anti-PRLR antibody formulation of claim 1, comprising:

a. 10 mM histidine,

b. 200 ppm polysorbate 20,

c. 88 mM sucrose,

d. 133 mM glycine, and

e. 60 mg/ml anti-PRLR antibody;

wherein said anti-PRLR antibody formulation has a pH ranging from pH 5.0 to pH 6.5.

15. The anti-PRLR antibody formulation of claim 1, comprising:

a. 70 mM histidine,

b. 80 ppm polysorbate 80,

c. 200 mM sucrose, and

d. 60 mg/ml anti-PRLR antibody;

wherein said anti-PRLR antibody formulation has a pH ranging from pH 5.0 to pH 6.5.

16. The anti-PRLR antibody formulation of claim 1, comprising:

a. 10 mM histidine,

b. 75 ppm polysorbate 80,

c. 292 mM sucrose,

d. 10 mM arginine, and

e. 60 mg/ml anti-PRLR antibody;

wherein said anti-PRLR antibody formulation has a pH ranging from pH 5.0 to pH 6.5.

17. The anti-PRLR antibody formulation of claim 1, comprising:

a. 70 mM histidine,

b. 75 ppm polysorbate 80,

c. 176 mM sucrose,

d. 30 mM lysine, and

e. 60 mg/ml anti-PRLR antibody;

wherein said anti-PRLR antibody formulation has a pH ranging from pH 5.0 to pH 6.5.

18. The anti-PRLR antibody formulation of claim 1, comprising:

a. 10mM histidine,

b. 75 ppm polysorbate 80,

c. 234 mM sucrose,

d. 30mM arginine, and

e. 10mM methionine, and

f. 60 mg/ml anti-PRLR antibody;

wherein said anti-PRLR antibody formulation has a pH ranging from pH 5.0 to pH 6.5.

19. The anti-PRLR antibody formulation of claim 1, comprising:

a. 10mM histidine,

b. 75 ppm polysorbate 80,

c. 234 mM sucrose,

d. 30mM arginine, and

e. 10mM methionine, and

f. 2 mg/ml anti-PRLR antibody;

wherein said anti-PRLR antibody formulation has a pH ranging from pH 5.0 to pH 6.5.

20. The anti-PRLR antibody formulation of claim 1, comprising:

a. 10 mM histidine,

b. 75 ppm polysorbate 80,

c. 234 mM sucrose,

d. 20 mM arginine, and

e. 10 mM methionine, and

f. 150 mg/ml anti-PRLR antibody;

wherein said anti-PRLR antibody formulation has a pH ranging from pH 5.0 to pH 6.5.

21. The anti-PRLR antibody formulation of claim 1, comprising:

a. 10 mM histidine,

b. 75 ppm polysorbate 80,

c. 205 mM sucrose,

d. 20 mM arginine,

e. 10 mM methionine, and

f. 1 mg/ml anti-PRLR antibody;

wherein said anti-PRLR antibody formulation has a pH ranging from pH 5.0 to pH 6.5.

22. The anti-PRLR antibody formulation of claim 1, comprising:

a. 10 mM histidine,

b. 80ppm polysorbate 80,

c. 205 mM sucrose,

d. 20 mM arginine, and

e. 10 mM methionine, and

f. 60 mg/ml anti-PRLR antibody;

wherein said anti-PRLR antibody formulation has a pH ranging from pH 5.0 to pH 6.5.

23. The anti-PRLR antibody formulation of claim 1, comprising:

a. 10 mM histidine,

b. 75 ppm polysorbate 80,

c. 205 mM trehlose,

d. 20 mM arginine, and

e. 10 mM methionine, and

f. 60 mg/ml anti-PRLR antibody;

wherein said anti-PRLR antibody formulation has a pH ranging from pH 5.0 to pH 6.5.

24. The anti-PRLR antibody formulation of claim 1, comprising:

a. 10 mM histidine,

b. 75 ppm polysorbate 80,

c. 205 mM trehalose,

d. 30 mM arginine,

e. 10 mM methionine, and

f. 2 mg/ml anti-PRLR antibody;

wherein said anti-PRLR antibody formulation has a pH ranging from pH 5.0 to pH 6.5.

25. The anti-PRLR antibody formulation of claim 1, comprising:

a. 10 mM histidine,
b. 234 mM sucrose,
c. 80 ppm polysorbate 80,
d. 30 mM arginine,
e. 5 mM methionine, and
f. 7.5 mg/ml anti-PRLR antibody;

wherein said anti-PRLR antibody formulation has a pH ranging from pH 5.0 to pH 6.5.

26. The anti-PRLR antibody formulation of claim 1, comprising:
a. 10 mM histidine,
b. 234 mM sucrose,
c. 80 ppm polysorbate 80,
d. 30 mM arginine,
e. 5 mM methionine, and
f. 60 mg/mL anti-PRLR antibody;

wherein said anti-PRLR antibody formulation has a pH ranging from pH 5.0 to pH 6.5.

27. The anti-PRLR antibody formulation of claim 1, comprising:
a. 10 mM histidine,
b. 234 mM sucrose,
c. 75 ppm polysorbate 80,
d. 30 mM arginine,
e. 10 mM methionine, and
f. 60 mg/mL anti-PRLR antibody;

wherein said anti-PRLR antibody formulation has a pH ranging from pH 5.0 to pH 6.5.

28. The anti-PRLR antibody formulation of claim 1, comprising:
a. 10 mM histidine,
b. 263 mM sucrose,

c. 80 ppm polysorbate 80, and

d. 60 mg/mL anti-PRLR antibody;

wherein said anti-PRLR antibody formulation has a pH ranging from pH 5.0 to pH 6.5.

29. The anti-PRLR antibody formulation of claim 1 wherein said anti-PRLR antibody is a human IgG2 monoclonal antibody.

30. The anti-PRLR antibody formulation of claim 29 wherein said human IgG2 monoclonal antibody comprises a light chain sequence and a heavy chain sequence presented in one or more of PCT Patent Publication NOs. WO/2011/069799, WO/2011/069798, WO/2011/069797, WO/2011/069796, WO/2011/069795, and WO/2011/069794.

31. The anti-PRLR antibody formulation of claim 29 wherein said human IgG2 monoclonal antibody comprises a light chain sequence of SEQ ID NO: 1 and a heavy chain sequence of SEQ ID NO: 7.

32. A method for the non-hormonal treatment of endometriosis in a patient, said method comprising administering to said patient a therapeutically effective amount of an anti-PRLR antibody formulation comprising between 0 mM and 70 mM histidine, between 50 ppm and 200 ppm polysorbate 80 or polysorbate 20, between 34 mM and 292 mM sucrose or trehalose, between 0 mM and 50 mM arginine, between 0 mM and 50 mM lysine, between 0 mM and 270 mM glycine or alanine, between 0 mM and 10 mM methionine, and between 1 mg/ml and 150 mg/ml of a protein or antibody at a pH of between pH 5.0 and pH 6.5, wherein said anti-PRLR antibody formulation contains substantially no inorganic salt.

33. The method of claim 32 wherein said anti-PRLR antibody formulation is administered intravenously, subcutaneously, or intramuscularly.

34. The method of claim 33 wherein said anti-PRLR antibody is a human IgG2
monoclonal antibody.

35. The method of claim 34 wherein said human IgG2 monoclonal antibody comprises a light chain sequence and a heavy chain sequence presented in one or more of PCT Patent Publication NOs. WO/2011/069799, WO/2011/069798, WO/2011/069797, WO/2011/069796, WO/2011/069795, and WO/2011/069794.

36. The method of claim 34 wherein said human IgG2 monoclonal antibody comprises a light chain sequence of SEQ ID NO: 1 and a heavy chain sequence of SEQ ID NO: 7.