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(54) Title: LIQUID FORMULATIONS WITH HIGH CONCENTRATION OF HUMAN GROWTH HORMONE (hgh) COMPRISING 1,2-PROLPYLENE GLYCOL

(57) Abstract: The present invention relates to liquid formulations of human growth hormone (hGH, somatropin) which are storage stable, show reduced or no crystallization on storage and are suitable for administration to the human or animal body. More particularly, the invention relates to liquid formulations of human growth hormone which are stable and exhibit minimal or no crystallization when stored at least for a time at temperature above refrigeration temperatures.

LIQUID FORMULATIONS WITH HIGH CONCENTRATION OF HUMAN GROWTH HORMONE (HGH) COMPRI ING 1,2-PROPYLENE GLYCOL

The present invention relates to liquid formulations of human growth hormone (hGH, somatropin) which are storage stable, show reduced or no crystallization on storage and are suitable for administration to the human or animal body. More particularly, the invention relates to liquid formulations of human growth hormone which are stable and exhibit minimal or no crystallization when stored at least for a time at temperatures above refrigeration temperatures.

Native hGH is a single polypeptide chain protein consisting of 191 amino acids. The protein is internally cross-linked by two disulphide bridges and in monomeric form exhibits a molecular weight of about 22kDa.

A major biological effect of hGH is to promote growth throughout a range of organs and tissues in the body. hGH is secreted in a pulsatile manner from the pituitary gland throughout life. The major biological effect of hGH is to promote growth. hGH responsive organs or tissues include the liver, intestine, kidneys, muscles, connective tissue and the skeleton. hGH deficiency can occur in all age groups. The consequences of hGH deficiency include reduction in bone density, shortness in stature in children, reduction in lean body mass and extracellular volume and increase in cardiovascular risk factors. Replacement therapy with recombinant hGH has proven safe and effective in reversing these effects, but requires repeated injections at regular intervals

For example, hypopituitary dwarfism is a condition which is readily treated by administering hGH to a subject suffering the condition. Prior to the production of large quantities of hGH by recombinant means only limited amounts of hGH could be prepared by laborious extraction of pituitary glands from human cadavers. This practice carried with it risks associated with infectious agents, eg the agent responsible for Creutzfeldt-Jakob disease (CJD), and that these agents might be passed to the patient receiving hGH. The isolation of the hGH gene and the construction of transformed host cells expressing recombinant hGH in cell culture has opened up not only a more reliable, safer and more cost effective treatment of hypopituitary dwarfism, but the possibility of using hGH for treatment of other diseases and conditions as well. Accordingly, in the context of the present invention, hGH preferably designates recombinant human growth hormone. However, it will readily appreciated that

also human growth hormone isolated from natural sources can in principle likewise be included in a pharmaceutical formulation of the present invention.

A long appreciated problem with aqueous liquid formulations of pharmaceutical proteins, not just hGH, is that of instability during storage over a period of time. hGH in aqueous solution is known to undergo a variety of degradative changes. In common with most other proteins, Somatropin (recombinant human growth hormone, rhGH) has three main potential routes of degradation, namely hydrolysis leading to deamidation of free amide groups, oxidation of sulphur containing amino acids, and physical change of aggregation, where two or more hGH molecules physically stick together, for example, resulting in the formation of opaque insolubles. There is also the possibility of a clipping of the peptide backbone as a result of hydrolysis. Additionally, a major problem is crystallization of hGH.

Early suggestions about how to solve the problems of instability noted above included freeze drying, but this of course meant that the resulting lyophilised product needed reconstitution immediately or shortly prior to administration. In the circumstances of routine self-administration by a patient at home, this normally means that the patient has the task of reconstituting the lyophilised preparation into an aqueous solution. This is inconvenient for the patient and carries with it a risk of improper reconstitution due to lack of care, lack of attention to detail and instructions, or simply misunderstanding on the part of the patient. Freeze drying of formulations also suffers from the disadvantage of being costly and time consuming from a manufacturing perspective.

Much effort is therefore expended in finding formulations which permit a simpler self-administration of hGH by patients. These efforts are focused on ways of providing sufficiently stable aqueous liquid hGH formulations in a ready to use form. Such liquid dosage forms offer increased convenience and hence better compliance compared to lyophilized dosage forms which have to be reconstituted and filled into a pen cartridge via an additional device.

However, care has to be taken that excipients which may be able to stabilize an aqueous formulation of hGH may carry some risk in administration to patients. Many compounds which may serve as stabilizers would not appear clinically acceptable and therefore would not enable a pharmaceutically acceptable formulation to be made. Furthermore,

pharmaceutical regulatory requirements dictate that any unnecessary additives / excipients, particularly synthetic additives / excipients, must be avoided in order to reduce risks to patients.

Conveniently, aqueous pharmaceutical formulations of hGH should be offered as multi-dosage formulations to the patient, who will administer such a formulation by means of an injector device. Such multi-dosage pharmaceutical formulations usually require an appropriate preservative to be present.

Common liquid formulations of hGH are known to contain the drug at a low concentration, e.g. about 3.33 mg / ml, which, however, upon administration may cause certain disadvantages for the patient.

In particular, a patient has to receive a relatively large volume of such a low-concentration formulation of hGH per injection, which may cause discomfort or even pain. For example, for children suffering from growth hormone deficiency (GHD) hGH may have to be administered at a dosage of about 0.1 IU / kg bodyweight / day. Accordingly, a patient having a bodyweight of 50 kg would have to receive about 5 IU hGH per day, which is contained in 500 µl of a liquid formulation comprising about 3.33 mg / ml hGH (1 IU hGH = 0.33 mg hGH). It will readily be appreciated that the application of a volume of less than 500 µl would be highly desired.

In the alternative, such a dosage could be administered in 2 or more injections of such a low-concentrated hGH formulation, each injection having a reduced volume. However, in terms of application safety, the use of more than one injection per dosage is not recommended.

Furthermore, depending on the treatment schedule and dosage, a patient may have to use more than one single injection of such a low-concentration hGH formulation in order to be able to provide the prescribed amount of hGH. This may apply for example to patients having growth deficiency related to the Turner-Syndrome, who because of their increased body weight may be in need of a high amount of hGH. In many instances it will not be possible to deliver the required amount of hGH to such patients with a single injection having a reasonable volume of a such low-concentrated hGH formulation.

Therefore, there is an ongoing need for a liquid pharmaceutical formulation containing hGH at a high concentration.

In the course of the present invention it has been noticed that crystals tend to form in known aqueous, liquid growth hormone formulations if the concentration of hGH is adjusted to higher values, e.g. to 5 mg/ml hGH or more, in such formulations. This does not only apply just when such formulations are stored at refrigeration temperatures, but also when they are stored above refrigeration temperatures, at least for a time. The presence of crystals in liquid hGH formulations is highly undesirable because prior to administration such formulations need to be agitated or swirled and there may be instances when crystals are small or unobserved and the formulation is caused to be administered without dissolving the crystals sufficiently first. There is also the obvious disadvantage in terms of the visual appearance of hGH formulations when crystals have formed during storage.

An object of the invention is therefore to provide a multi-dosage, aqueous liquid hGH formulation which is stable when stored for periods of time at refrigeration temperatures, e.g. for several months, or even for 1 or 2 years. Another object of the invention is to provide liquid hGH formulations which are stable when stored for at least a period of time above common refrigeration temperatures (e.g. above 2°C - 8°C) or even outside a refrigerator, e.g. for periods of several hours, days, or even weeks.

In the context of the present application, "stable" mainly means that the problem of crystal formation is essentially avoided; preferably this problem is avoided completely. Accordingly, pharmaceutical formulation of the present invention exhibit minimal or no crystallization upon storage as decribed above.

In addition to avoiding crystallization, a stable formulation should preferably show no or minimal aggregation of hGH upon storage. Likewise, a stable formulation preferably should not or only to a minimal extent undergo other degradation of hGH, e.g. by deamidation, oxidation and/or hydrolysis.

In the context of the present invention, it has been developed that 1,2-propylene glycol to be used in such a multi-dosage liquid formulation containing a high concentration of hGH is a

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