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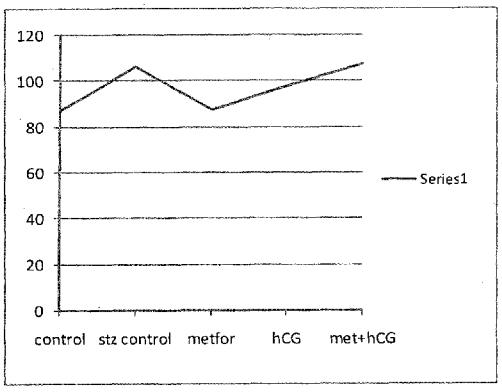
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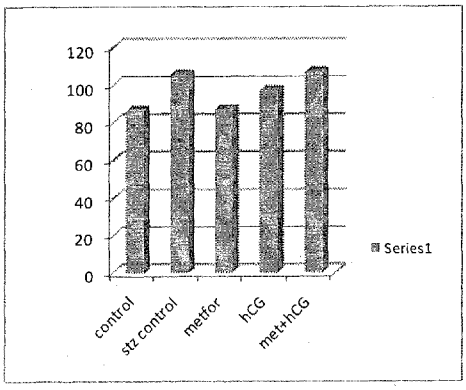
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(54) **Title**: HCG - NEWER TREATMENT MODALITY FOR TYPE 2 DIABETES MELLITUS (T2DM)





(57) **Abstract**: The present invention discloses a method of treating Type 2 Diabetes(T2DM) and associated co-morbid conditions of Metabolic syndrome (Met S), Insulin sensitivity and physiological testosterone deficient related complications using hCG which could either be used singly or in combination with anti -diabetic agent(s). The present invention further disclose a pharmaceutical combination of hCG with one or more anti diabetic agents thereof for treating Type 2 Diabetes(T2DM) and associated co-morbid conditions of Metabolic syndrome (Met S), Insulin sensitivity and physiological testosterone deficient related complications.

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

— *with amended claims and statement (Art. 19(1))*

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Date of publication of the amended claims and statement: 5 December 2013

AMENDED CLAIMS
received by the International Bureau on 26 August 2013 (26.08.13)

1. A method of treating Type 2 Diabetes(T2DM) and associated co-morbid conditions of Metabolic syndrome (Met S), Insulin sensitivity and physiological testosterone deficient related complications comprising administering to a subject in need thereof an effective amount of Human chorionic gonadotropin (hCG) in the range of 50 IU - 15000 IU either alone or in combination with one or more anti-diabetic agent(s).

2. The method of treating as claimed in claim 1, wherein said anti-diabetic agent(s) are selected from the group comprising biguanides such as metformin and /or its organic, inorganic salts; sulfonylureas selected from tolazamide, glipizide, glimepiride, glibenclamide, gliclazide tolbutamide; Alpha-glucosidase inhibitors like acarbose; members of the glitazone such as rosiglitazone, pioglitazone, a combination of pioglitazone and biguanides; miglitol-a glucosidase inhibitor, postprandial glucose inhibitors such as repaglinide, nateglinide; DPP -4 inhibitors like sitagliptin (or in combination form), vildagliptin(or in combination form), dutogliptin ,saxagliptin, linagliptin, gemigliptin and alogliptin.

3. The method of treating as claimed in claim 1, wherein said anti-diabetic agent is metformin.

4. The method of treating as claimed in claim 1, wherein treatment of Type 2 Diabetes Mellitus (T2DM) and associated co-morbid conditions of Metabolic syndrome (Met S), Insulin sensitivity and physiological testosterone deficient related complications comprises administering to a subject in need thereof an effective amount of Human chorionic gonadotropin (hCG) parentally.

5. The method of treating as claimed in claim 1, wherein treatment of Type 2 Diabetes Mellitus (T2DM) and associated co-morbid conditions of Metabolic syndrome (Met S), Insulin sensitivity and physiological testosterone deficient related complications comprises administering to a subject in need thereof an effective amount of Human chorionic gonadotropin (hCG) parentally in

combination with anti- diabetic agents orally, either sequentially, concurrently, simultaneously or alternatively.

6. The method of treating as claimed in claim1, wherein dosage of hCG is 500 IU either alone or in combination with metformin.

7. A pharmaceutical formulation for the treatment of Type 2 Diabetes(T2DM) and associated co-morbid conditions of Metabolic syndrome (Met S), Insulin sensitivity and physiological testosterone deficient related complications, wherein said formulation comprises Human chorionic gonadotropin (hCG) along with suitable pharmaceutical diluents and carriers.

8. The pharmaceutical formulation as claimed in claim 7, wherein the said formulation is administered subcutaneously or intramuscularly.

9. A pharmaceutical combination for the treatment of Type 2 Diabetes(T2DM) and associated co-morbid conditions of Metabolic syndrome (Met S), Insulin sensitivity and physiological testosterone deficient related complications, wherein said combination comprises Human chorionic gonadotropin (hCG) in combination with one or more anti-diabetic agent(s) excipients.

10. The pharmaceutical combination as claimed in claim 9, wherein said anti-diabetic agent(s) are selected from the group comprising biguanides such as metformin and /or its organic, inorganic salts; sulfonylureas selected from tolazamide, glipizide, glimepiride, glibenclamide, gliclazide tolbutamide; Alpha-glucosidase inhibitors like acarbose; members of the glitazone such as rosiglitazone, pioglitazone, a combination of pioglitazone and biguanides; miglitol-a glucosidase inhibitor, postprandial glucose inhibitors such as repaglinide, nateglinide; DPP -4 inhibitors like sitagliptin (or in combination form), vildagliptin (or in combination form), dutogliptin, saxagliptin, linagliptin, gemigliptin and alogliptin.

11. The pharmaceutical formulation as claimed in claim 1, wherein dosage of Human chorionic gonadotropin (hCG) is in the range of 50 IU - 15000 IU.

12. The pharmaceutical formulation as claimed in claim 11, wherein the dosage of hCG is 500 IU.

13. The pharmaceutical combination as claimed in claim 9, wherein the dosage of hCG is 500 IU in combination with metformin.

14. Use of pharmaceutical formulation comprising hCG in highly purified form in association with one or more anti diabetic agent(s) for treatment of Type 2 Diabetes(T2DM) and associated co-morbid conditions of Metabolic syndrome (Met S), Insulin sensitivity and physiological testosterone deficient related complications.

"Statement under article 19 (1) (Rule 46.4)"

Explanation:

We note from the ISR dated 25th June, 2013 that in examiner's opinion, the claims 1 to 15 are novel, have industrial applicability. The claims 1 to 15 lack inventive step.

The Applicant respectfully submits the justification for better understanding of the invention and to appreciate the inventive step of the current invention and also in the interest of expediting prosecution of the current application.

The Applicant submits that the claim 1 of the present invention is amended by merging claim- 6. Accordingly, there are in total 14 claims. Claims 2-5 remain same, original claims 7-15 are now renumbered as claims 6-14.

The amended claim 1 is reproduced below:

"A method of treating Type 2 diabetes (T2DM) and associated co-morbid conditions of Metabolic Syndrome (Met S), Insulin sensitivity and physiological testosterone deficient related complications comprising administering to a subject in need thereof an effective amount of Human chorionic gonadotropin (hCG) in the range of 50IU-15000IU either alone or in combination of one or more anti-diabetic agent(s)".

The Applicant specifically distinguishes the present invention vis-à-vis the cited prior arts as below:

1. **US2009156468 (Belluscio)**

Para [0034] and para [0035] as referred by Ld. Examiner of US'468 relates to the use of human chorionic gonadotropin oral or injectable for the treatment of Type 2 diabetes and associated co-morbid conditions of metabolic syndrome. However, US'468 does not disclose the treatment of Type 2 diabetes and associated co-morbid conditions of Metabolic syndrome (Met S), insulin sensitivity and physiological testosterone deficient related complications

using human chorionic gonadotropin (hCG) either alone or in combination with one or more anti-diabetic agents.

The instant invention is however aimed at addressing the co-morbid conditions of Met S, insulin sensitivity and physiological testosterone deficient related complications associated with T2DM using lower dose of hCG which could either be used singly or in combination with anti-diabetic agents which the cited document US'468 fails to disclose.

2. The article titled **"Increasing Insulin Resistance is associated with a decrease in Leydig Cell Testosterone Secretion in Men"** by Pitteloud et.al.

The cited document relates to the field of studying the effects of human chorionic gonadotropin (hCG) insulin resistance and low testosterone in men. The Examiner has cited pg. 2639, left column, third paragraph, fig .3 which show correlation of insulin sensitivity with Leydig cell function assessed by the T(testosterone) response to physiological stimulation with hCG.

Fig 3 depicts an increase in T (testosterone) levels are observed after administration of hCG, which is admitted in the specification of the current invention, however, there is no teaching in said article to provide an effective treatment of Type 2 diabetes and associated co-morbid conditions of Metabolic syndrome, insulin sensitivity and physiological testosterone deficient related complications using lower dose of hCG either alone or in combination of one or more anti-diabetic agent(s).

The present invention thus provides a value addition treatment intervention to the existing treatment algorithms for the management of co-morbid conditions, insulin resistance and Metabolic syndrome in Type 2 diabetes Mellitus using low doses of hCG that maintains baseline levels of ITT (intratesticular testosterone) in men with gonadotropin withdrawal from exogeno testosterone administration, improves endothelial cell function and helps in

maintaining glucose levels. It is therefore evident that the instant invention is inventive over the art.

3. An article titled **"Should patients with polycystic ovary syndrome be treated with metformin"** by Stadtmauer et.al.

The article focuses on treating polycystic ovary syndrome (PCOS) patients undergoing gonadotropin therapy with metformin for 6 weeks before commencing gonadotropin treatment at 850 mg twice daily that is continued until ovulation or day of hCG administration (pg. 3019, 4th para as cited by the examiner).

In PCOS, the high levels of androgens lead to chronic anovulation, menstrual disturbances and hirsuitism. The patients typically have elevated LH levels, and LH-FSH ratios as well as insulin resistance. Thus, the cited article is not relevant to the instant invention as LH levels are already high, hCG as a treatment modality, is not preferred.

4. **US2011/0034385 (Surola et.al)**

US'385 discloses supramolecular protein assembly, wherein the supramolecular protein assembly comprises the insoluble and aggregated oligomeric form of the protein for example insulin, glucagon, calcitonin, a peptide GNNQQNY, transthyretin (TTR), human growth hormone, blood clotting factors, albumin, human follicle stimulating hormone (FSH), human chorionic gonadotropin (HCG), Interleukin-1 Receptor Antagonist (IL-1RA), extendin-4 and erythropoietin from the group consisting of type 1 and type 2 diabetes mellitus and complications. Further, the supramolecular insulin assembly (SIA) as disclosed comprises insoluble and aggregated oligomeric form of insulin at SIA II, wherein SIA II consists of linear association of elongated clusters having pearl like arrangement of insulin monomer and supramolecular extendin-4 assembly (SEA).

From the foregoing, it is clear that the cited document holds no relevance to the instant invention.

5. **US2007/0299001 (Paradisi et. al)**

US'001 relates to process for preparation of recombinant human chorionic gonadotropin (hCG). Said recombinant human chorionic gonadotropin have specific bioactivity in the range of 23,000 to 28,000 IU/mg. US'001 does not disclose an effective treatment of Type 2 diabetes (T2DM) and associated co-morbid conditions of Metabolic Syndrome (Met S), Insulin sensitivity and physiological testosterone deficient related complications using human chorionic gonadotropin (hCG) in the range of 50IU-15000IU either alone or in combination of one or more anti-diabetic agent(s) and hence not relevant to the instant invention.

In view of the foregoing discussions, we dispute with the observation of lacking inventive step as opined by the Ld. Examiner.

Further, the Applicant has amended claim 1 of instant invention and submitted herewith.

In the light of the above rationale, we respectfully request the examiner to review and reassess the inventive step of the claims as claimed in the current application.

It is submitted that the above application is now in order to proceed for the publication, however, should the examiner, unexpectedly, have any further objections, the primary examiner is respectfully requested to communicate the same.