insulin preparations is associated with weight gain and a significant risk of hypoglycemia including severe, life-threatening hypoglycemic events.

**[0018]** Until recently, subcutaneous (SC) injection has been the only route of delivering insulin for self-administration by patients commercially available. However, SC insulin administration does not lead to optimal pharmacodynamics for the administered insulin. Absorption into the blood (even with rapid acting insulin analogues) does not mimic the prandial physiologic insulin secretion pattern of a rapid spike in serum insulin concentration. Subcutaneous injections are also rarely ideal in providing insulin to type 2 diabetics and may actually worsen insulin action because of delayed, variable and slow rate of absorption into the bloodstream. It has been shown, however, that if insulin is administered intravenously with a meal, early stage type 2 diabetics experience the shutdown of hepatic glucose release and exhibit increased physiologic glucose control. In addition their free fatty acids levels fall at a faster rate than without insulin therapy. While possibly effective in treating type 2 diabetes, intravenous administration of insulin is not a reasonable solution, as it is not safe or feasible for patients to intravenously administer insulin at every meal.

**[0019]** For a short period of time there was an inhalable insulin, EXUBERA® (Pfizer), which was marketed for the treatment of diabetes. This insulin preparation had a pharmacokinetic profile similar to the injectable rapid acting analogues and was used as a substitute for short acting insulin in the standard treatment paradigm. While this insulin preparation did allow patients using short acting insulins to avoid injections, it offered no other notable advantage which contributed to its commercial failure. Moreover, because its kinetic profile was so similar to subcutaneously administered regular and rapid-acting insulins, that after accounting for differences in bioavailability, its dosing and modes of administration could generally follow that of those subcutaneous insulins.

**[0020]** Though not yet commercially available, an ultrarapid acting insulin, insulin-fumaryl diketopiperazine (FDKP) has been under development. Growing experience with the use of this insulin formulation in human studies is showing that its unique kinetic profile can accommodate different dosing schemes and modes of administration as its use is applied to various situations and patient populations in order to achieve improved glycemic control. Such methods are the object of the present disclosure.

## SUMMARY ~~OF THE INVENTION~~

[0020a] One aspect of the present invention relates to the use of an ultrarapid acting insulin preparation in the manufacture of a medicament for treating a patient with diabetes type 2, wherein the patient is selected from a patient with diabetes type 2 currently being treated with a suppressor of hepatic glucose output and an insulin secretagogue; the patient is to be discontinued from the treatment with the insulin secretagogue; and wherein the medicament is to be routinely administered with at least one established meal.

**[0021]** Embodiments disclosed herein include methods useful for treating diabetes mellitus including both type 1 and type 2 using an ultrarapid acting insulin formulation. The disclosed methods relate to procedures for determining dosages, the use of standard dosages that are not adjusted from individual meal to meal, the use of split dosages wherein

inhaler cartridge for patient dosages of 6 U to 72 or 96 U. As explained below dosages can be more universally expressed in subcutaneous equivalent (subQ eq) units. In these units preferred dosages are in the range of 1-32 or more units, for example 3, 6, 9 ... or 4, 8, 12... subQ eq units. For example with an alternative inhaler system as described in U.S. Patent Application Nos. 12/484,125, 12/484,129, and 12/484,137, dosages of 3-4 subQ eq units are obtained with cartridges filled with 20-22 IU.

**[0024]** In an embodiment, the insulin dose comprises a dose sufficient to control glucose excursions. In another embodiment, the insulin reaches peak serum levels within about 15 minutes of administration. In another embodiment, the peak serum insulin level is at least 60 mU/L. In still another embodiment, the peak serum insulin concentration is at least 60, 100, or 120 mU/L above the pre-dosing insulin concentration baseline. In one aspect of this embodiment, the recipient has type 2 diabetes. In another embodiment, the insulin dose is sufficient to control blood glucose levels. In yet another embodiment, the insulin dose is sufficient to reduce or suppress glucose release from the liver. In one aspect of this embodiment, the suppression lasts several hours (see FIG. 5). In one aspect of this embodiment a nadir in endogenous glucose production is reached more quickly than following subcutaneous administration of regular insulin or a rapid-acting insulin analogue, preferably in ≤60 minutes, more preferably in ≤50 minutes, still more preferably in about 40 minutes. In still another embodiment the dose is sufficient to maximally suppress endogenous glucose production.

**[0025]** Additional embodiments provide methods for improved treatment of patients with diabetes comprising selecting a patient in need of improved glycemic control, discontinuing current treatment, and routinely administering an ultrarapid acting insulin with at least two meals each day.

**[0026]** In other embodiments, the need for improved glycemic control is determined from HbA1c levels. In one embodiment, the level of serum HbA1c is ≥8%. In yet other embodiments, the level of serum HbA1c is ≥7.5%, ≥7.0%, ≥6.5%, or ≥ 6.0%. In other embodiments, the need for improved glycemic control is determined from elevated mean amplitude of glucose excursions or elevated post prandial blood glucose levels. In yet another embodiment, the patient has evidence of elevated oxidative stress and the oxidative stress is measured by 8-iso PGF(2a) levels. Elevated oxidative stress is correlated with elevated mean amplitude of glucose excursions.

**[0027]** In one ~~aspect~~ of these embodiments, the patient is further in need of avoiding weight gain, and treatment with the ultrarapid acting insulin does not result in weight gain or as much weight gain as expected from another mode of treatment. In a related embodiment,