such carpidopa formulations that can be administered more easily to patients, especially as compared to current invasive modes such as duodenal administration.

SUMMARY ~~OF THE INVENTION~~

It has now been found in accordance with the present ~~invention~~ disclosure that an arginine salt of carbidopa can form a stable, liquid formulation, suitable for e.g., continuous subcutaneous, transdermal, intradermal, intravenous and/or intraduodenal administration, at a physiologically acceptable pH. Such disclosed compositions are capable of substantially continuously administering carbidopa to a patient.

It has been further found that substantially continuously administering a dopa decarboxylase inhibitor such as carbidopa, together with discrete (e.g. oral) co-administration of levodopa, may stimulate L-dopa substantially continuously and thus e.g., extend the effectiveness of a levodopa oral dosing regimen and/or reduce the daily dosage of levodopa, while effectively treating a movement and/or neurological disorder such as Parkinson's disease.

The present disclosure ~~invention~~ relates~~, in one aspect,~~ to an arginine salt of an active agent selected from carbidopa and levodopa that are suitable for e.g., continuous subcutaneous, trandermal, intradermal, intravenous, oral, or intraduodenal administration.

In a first aspect of the present disclosure, there is provided a pharmaceutically acceptable liquid composition comprising arginine and carbidopa, wherein the composition comprises 1% to 6% by weight carbidopa; has a pH of 8 to 9.5 at 25°C; and is stable at 25°C for 48 hours or more.

In a second aspect of the present disclosure, there is provided a kit comprising: a) a first composition suitable for continuous administration comprising the liquid composition of the first aspect; and b) a second composition suitable for oral administration comprising levodopa or a pharmaceutically acceptable salt or ester thereof.

In a third aspect of the present disclosure, there is provided the kit of the second aspect, for use in treating a neurological disorder selected from: restless leg syndrome, Parkinson's disease, secondary parkinsonism, Huntington's disease, Parkinson's like syndrome, progressive supranuclear palsy (PSP), multiple system atrophy (MSA), or amyotrophic lateral sclerosis (ALS).

In a fourth aspect of the present disclosure, there is provided the arginine salt of carbidopa.

In a fifth aspect of the present disclosure, there is provided a pharmaceutically acceptable liquid composition comprising the arginine salt of carbidopa of the fifth aspect, and optionally a pharmaceutically acceptable excipient.

Also contemplated herein are pharmaceutically acceptable liquid (e.g., liquid at room temperature) or gel formulations or compositions that include an arginine salt of carbidopa, e.g., include carbidopa and arginine, that may be suitable for substantially continuous administration to a patient e.g. with or without use of, for example, a transdermal patch or subcutaneous pump (e.g. an insulin-like pump). Such contemplated liquid compositions may include at least 1%, at least 4%, at least 6% or more by weight carbidopa, (e.g. about 2% to about 6% by weight carbidopa) and therefore may facilitate administration of smaller amounts of a pharmacologically acceptable formulation to achieve efficacy as compared to a carbidopa formulation that is only capable of having less than 1% by weight carbidopa. In another embodiment, contemplated herein is a liquid or gel composition that includes a molar ratio of about 1.0:0.5 to about 1: to about 2.5, e.g., 1: 1.0-1.2 molar ratio of carbidopa:basic amino acid, e.g. carbidopa:arginine. A liquid composition that includes carbidopa and arginine, as contemplated herein, may have a

physiologically acceptable pH, e.g. a pH of about 6.5 to 9.5, e.g., about 7 to about 9, or about 8 to about 9, at 25 °C.

In yet another embodiment, contemplated herein is a pharmaceutically acceptable liquid or gel composition that includes a molar ratio of about 1.0:0.5 to about 1:2, e.g., about 1:1.8 molar ratio of levodopa:arginine. For example, provided herein is a liquid composition that may include at least about 4% by weight, or at least 5%, at least about 6% (e.g. about 3% to about 7%) or more by weight levodopa. A liquid composition having levodopa and a basic amino acid, as contemplated herein, may have a pH of about 8 to 10, e.g., about 8.5 to about 9.5, at 25°C.

Exemplary liquid compositions contemplated herein may be liquid solutions, e.g. may be a substantially homogenous mixture that includes carbidopa and arginine, and may include water, or alternatively may be substantially non-aqueous. In other embodiments, contemplated compositions may also include one or more pharmaceutically acceptable excipients such as N-methylpyrrolidone (NMP), polyvinylpyrrolidone (PVP), propylene glycol, antioxidants, or combinations thereof.

In some embodiments, the pharmaceutically acceptable liquid composition of the ~~invention~~ present disclosure may comprise additional active agents such as entacapone or tolcapone.

Also provided herein is a kit comprising: a) a first composition suitable for continuous administration comprising the liquid or gel formulation of the present disclosure ~~invention~~ comprising an arginine salt of carbidopa; b) a second composition suitable for oral administration comprising levodopa or a pharmaceutically acceptable salt or ester thereof; and c) optionally instructions administration of the first formulation in conjunction with the second formulation.

The first composition in the kit for continuous administration of the arginine salt of carbidopa may be formulated for transdermal, intradermal, subcutaneous, intravenous, or intraduodenal administration such as by using an infusion pump.

The second composition in the kit, i.e., the levodopa composition may comprise levodopa, a pharmaceutically acceptable salt of levodopa., preferably an arginine salt thereof as disclosed herein, or may be a composition that includes levodopa and further comprises one or more decarboxylase inhibitors such as carbidopa and/or benserazide, or one or more catechol-O-methyl transferase (COMT) inhibitors such as entacapone and/or tolcapone, or one or more MAO-A or MOA-B inhibitors such as selegiline and/or rasagiline, or combination thereof.

CLAIMS

1. A pharmaceutically acceptable liquid composition comprising arginine and carbidopa, wherein the composition comprises 1% ~~or 2%~~ to 6% by weight carbidopa; ~~the liquid composition~~ has a pH of ~~6.5~~8 to 9.5 at 25°C; and ~~the liquid composition~~ is stable at 25°C for 48 hours or more.

2. The pharmaceutically acceptable liquid composition of claim 1, wherein the composition comprises at least 1% or 2% or 4% or 6% by weight carbidopa.

3. The pharmaceutically acceptable liquid composition of claims 1 or 2, wherein the carbidopa and the arginine have a molar ratio selected from 1:~~0.5~~1 to 1:2.5 ~~or 1:1 to 1:1.2~~.

~~4. The pharmaceutically acceptable liquid composition of claim 1, further comprising levodopa.~~

~~5. The pharmaceutically acceptable liquid composition of claim 4, wherein the levodopa and the arginine have a molar ratio of 1:1.5 to 1:2.5.~~

~~6. The pharmaceutically acceptable liquid composition of claim 4, comprising carbidopa, levodopa and arginine, wherein the levodopa and the arginine have a molar ratio of 1:1.5 to 1:2.5; the liquid composition comprise 2% by weight carbidopa; and the pH of the liquid composition is 8.5 to 9.5 at 25°C.~~

~~7. The pharmaceutically acceptable liquid composition of claim 4, comprising 1% by weight carbidopa, and further comprising levodopa and arginine, wherein the levodopa and the arginine have a molar ratio of 1:1.5 to 1:2.5; and the pH of the liquid composition is 8.5 to 9.5 at 25°C.~~

~~4~~8. The pharmaceutically acceptable liquid composition of claim 1, further comprising a pharmaceutically acceptable excipient preferably selected from N-methylpyrrolidone, polyvinylpyrrolidone, propylene glycol, antioxidants, or combinations thereof.

59. The pharmaceutically acceptable liquid composition of claim 1, further comprising water.

610. The pharmaceutically acceptable liquid composition of claim 1, further comprising entacapone or tolcapone.

711. The pharmaceutically acceptable liquid composition of claim 1, comprising 2% to 6% by weight carbidopa, and arginine, wherein the pH of the liquid composition is 8 to 9 at 25°C~~, wherein the carbidopa and the arginine have a molar ratio of 1:0.5 to 1:2.5, and wherein the liquid composition is stable at 25°C for 48 hours or more~~.

~~12. The pharmaceutically acceptable liquid composition of claim 11, comprising at least 4% by weight levodopa.~~

8~~13~~. A kit comprising: a) a first composition suitable for continuous administration comprising the liquid composition of any one of claims 1 to 7~~12~~; and b) a second composition suitable for oral administration comprising levodopa or a pharmaceutically acceptable salt or ester thereof.

9~~14~~. The kit of claim 8~~13~~, wherein said first composition for continuous administration is for transdermal, intradermal, subcutaneous, intravenous, or intraduodenal administration.

10~~15~~. The kit of claim 9~~14~~, wherein said continuous administration comprises using an infusion pump.

11~~16~~. The kit of claim 8~~13~~, wherein the second composition further comprises carbidopa, benserazide, entacapone, tolcapone, or a combination thereof.

12~~17~~. The kit of claim 8~~13~~, wherein the second composition comprises a pharmaceutically acceptable salt of levodopa.

13~~18~~. The kit of claim 12~~17~~, wherein the second composition comprises ~~an~~ the arginine salt of levodopa.

14~~19~~. The kit of any one of claims 8 to 13, ~~to 18~~ for use in treating a neurological disorder selected from: restless leg syndrome, Parkinson's disease, secondary parkinsonism, Huntington's disease, Parkinson's like syndrome, progressive supranuclear palsy (PSP), multiple system atrophy (MSA), or amyotrophic lateral sclerosis (ALS).

15~~20~~. The kit according to claim 14~~19~~, for use in treating or ameliorating Parkinson's disease.

16~~21~~. The arginine salt of carbidopa.

17~~22~~. A pharmaceutically acceptable liquid composition comprising the arginine salt of carbidopa of claim 16~~21~~, and optionally a pharmaceutically acceptable excipient.