Duodopa for the treatment of Advanced Parkinson Disease

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Device Aided Therapies

Treatment options potentially available in Canada for aPD patients who have become difficult to manage adequately on oral Parkinson medications:

1. Deep Brain Stimulation (DBS) - primarily in the area of the subthalamic nucleus (STN))

2. DUODOPA / LCIG Treatment

3. In London: SCS
Rationale behind DUODOPA

Erratic gastric emptying:
- Delays oral levodopa absorption into the bloodstream, since levodopa is primarily absorbed in the small intestine\textsuperscript{1,2}
- Results in varying plasma levels, leading to motor fluctuations\textsuperscript{1,2}
- Constipation\textsuperscript{3}

Competitive inhibition from amino acids in food
- Large neutral amino acids can compete with levodopa for transfer across the intestinal mucosa\textsuperscript{4}

Rationale behind DUODOPA

**Continuous intestinal infusion**

Unique delivery system continuously administers DUODOPA at a constant rate directly into the jejunum

Provides stable levodopa concentrations within the therapeutic window

Bypasses the stomach to avoid the effects of slowed or delayed gastric emptying

Helps regain control of motor fluctuations, increasing “ON” time and reducing “OFF” time and dyskinesia

Pharmacokinetics

Differences in variability of plasma levodopa levels when administered orally versus via intestinal infusion

- Oral Levodopa-Carbidopa
- Levodopa-Carbidopa Intestinal Gel

Large variation in plasma levodopa levels
Smaller variation in plasma levodopa levels

Adapted from Figure 2 of Nyholm D et al. Clinical Neuropharmacology 2003; 26(3): 156-163
Duodopa Centres of Excellence in Canada

4.8M British Columbia
3.8M Alberta
1.0M SK
1.2M Manitoba
8.0M Quebec
13.1M Ontario
0.1M YK+NWT+NT

Vancouver
Kelowna
Edmonton
Calgary
Winnipeg
Toronto Western
London
ATC-Baycrest
Hamilton
Kingston
Ottawa
Mississauga

St. John’s
Halifax

CHUM – Montreal
McGill – Montreal
CHA - Quebec City
CHUQ -Levis
CHUS- Sherbooke
JGH – Montreal
Approved Health Canada Indication for Use

LCIG (levodopa-carbidopa intestinal gel) is indicated for the treatment of patients with advanced levodopa-responsive PD:

• Who do not have satisfactory control of severe, debilitating motor fluctuations and hyper-/dyskinesia despite optimized treatment with available combinations of Parkinson’s medicinal products, and

• For whom the benefits of this treatment may outweigh the risks associated with the insertion and long-term use of the percutaneous endoscopic gastrostomy-jejunostomy (PEG-J) tube required for administration

AbbVie PEG and J Tube Contraindications

AbbVie PEG Contraindications\(^1\)

- Lack of transillumination and positive needle aspiration test are an absolute contraindication for AbbVie PEG insertion
- Known or suspected intestinal obstruction
- Serious coagulation disorders
- Sepsis
- Active peritonitis
- Relative contraindications include ascites and neoplastic, inflammatory, and infiltrative diseases of the gastric and abdominal walls

AbbVie J Contraindications\(^2\)

- Known or suspected intestinal obstruction
- Sepsis
- Active peritonitis
- Relative contraindications include ascites and neoplastic, inflammatory, and infiltrative diseases of the gastric and abdominal walls

Clinical Studies

What data supports the use of Duodopa?
Clinical study efficacy and safety data

Pivotal trial design: DUODOPA vs oral levodopa/carbidopa IR\(^1,2\)

12-Week, randomized, double-blind, double-dummy, active-controlled, multicenter study†

<table>
<thead>
<tr>
<th>OUTPATIENT SCREENING</th>
<th>HOSPITALIZATION</th>
<th>TREATMENT PHASE- STABLE DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>(up to 28 days)</td>
<td>(±10 days)</td>
<td>(through Day 84)</td>
</tr>
</tbody>
</table>

- **Conversion** to oral levodopa/carbidopa IR while continuing adjunctive Parkinson’s therapies
- PEG-J procedure performed in all patients
- Double-blind therapies initiated and dose adjusted (through day 28)
- DUODOPA + Oral placebo (n=37; 35 completed)
- Placebo enteral suspension via pump + oral levodopa/carbidopa IR (n=34; 31 completed)

† Two identically designed phase III studies were performed. The two studies were combined prior to breaking the blind and a single analysis was conducted.

Clinical study efficacy and safety data

Pivotal trial design: DUODOPA vs oral levodopa/carbidopa IR

**Primary endpoint:** Comparison between DUODOPA vs oral levodopa/carbidopa IR in the change from baseline to week 12 in total daily mean “Off” time†

**Secondary endpoint:** Comparison between treatment groups in the change from baseline to week 12 in mean daily “On” time without troublesome dyskinesia

† Change in "Off" time was based on Parkinson’s Disease Diary® data collected using last observation carried forward. Mean number of off-hours collected on the home diary was calculated from information entered during the 3 days before each visit. "Off" time was normalized to a 16-hour awake period based on a typical person’s waking day and the daily infusion duration of 16 hours.

DUODOPA Product Monograph, AbbVie Corporation, 27 APRIL 2017
Clinical study efficacy and safety data

Pivotal trial: Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>LCIG (N=37)</th>
<th>LC-IR (N=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>63.7 (9.5)</td>
<td>65.1 (6.8)</td>
</tr>
<tr>
<td>Male, %</td>
<td>64.9</td>
<td>64.7</td>
</tr>
<tr>
<td>White, %</td>
<td>94.6</td>
<td>91.2</td>
</tr>
<tr>
<td>Mean Mini-Mental State Examination (SD)</td>
<td>28.7 (1.4)</td>
<td>28.9 (1.4)</td>
</tr>
<tr>
<td>Mean duration of PD, years (SD)</td>
<td>10.0 (4.6)</td>
<td>11.8 (5.6)</td>
</tr>
<tr>
<td>Mean daily “Off” time during 16-hour period†, hours (SD)</td>
<td>6.3 (1.7)</td>
<td>6.9 (2.1)</td>
</tr>
<tr>
<td>Mean “on” time without troublesome dyskinesia, hours (SD)a</td>
<td>8.7 (2.0)</td>
<td>8.0 (2.1)</td>
</tr>
<tr>
<td>Mean “on” time with troublesome dyskinesia, hours (SD)</td>
<td>1.0 (1.6)</td>
<td>1.1 (1.5)</td>
</tr>
</tbody>
</table>

† Collected in patient diary during 3 days prior to randomization and after 28 days of preexisting oral therapies’ dose optimization on outpatient basis.

a “On” time without troublesome dyskinesia=“On” time with non-troublesome dyskinesia + “On” time without dyskinesia.

**Clinical study efficacy and safety data**

**DUODOPA pivotal trial:** reduced “Off” time and increased “On” time without troublesome dyskinesia† vs oral levodopa/carbidopa IR

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**Change in mean daily “Off” time‡‡ (primary endpoint)**

- **DUODOPA + placebo capsules (n=35)**
  - Change in mean daily “Off” time: -4.04 hours
  - LS mean difference: -1.91
  - \( P=0.0015 \)

- **Placebo suspension + levodopa/carbidopa IR capsules (n=31)**
  - Change in mean daily “Off” time: -2.14 hours

**Change in mean daily “On” time without troublesome dyskinesia (secondary endpoint)**

- **DUODOPA + placebo capsules (n=35)**
  - Change in mean daily “On” time without troublesome dyskinesia: 4.11 hours
  - LS mean difference: 1.86
  - \( P=0.0059 \)

- **Placebo suspension + levodopa/carbidopa IR capsules (n=31)**
  - Change in mean daily “On” time without troublesome dyskinesia: 2.24 hours

† “On” time without troublesome dyskinesia = “On” time with non-troublesome dyskinesia + “On” time without dyskinesia

‡‡ “Off” time was normalized to a 16-hour awake period and the daily infusion duration of 16 hours.

LS=least squares.

Clinical study efficacy and safety data

**DUODOPA pivotal trial: Change in “Off” time**

Mean change in daily “Off” time during 16-hour infusion period:
From baseline to week 12

<table>
<thead>
<tr>
<th>Visit</th>
<th>DUODOPA, n</th>
<th>Levodopa/carbidopa IR, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>35</td>
<td>31</td>
</tr>
<tr>
<td>Week 2</td>
<td>33</td>
<td>27</td>
</tr>
<tr>
<td>Week 3</td>
<td>34</td>
<td>29</td>
</tr>
<tr>
<td>Week 4</td>
<td>35</td>
<td>31</td>
</tr>
<tr>
<td>Week 6</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>Week 8</td>
<td>35</td>
<td>28</td>
</tr>
<tr>
<td>Week 10</td>
<td>33</td>
<td>30</td>
</tr>
<tr>
<td>Week 12</td>
<td>35</td>
<td>31</td>
</tr>
</tbody>
</table>

* Primary endpoint = week 12

† Mixed-model repeated-measures analysis.
‡ Baseline values were collected 3 days prior to randomization and after 28 days of oral therapy standardization.

Clinical study efficacy and safety data

Initiation of Treatment-Emergent AEs >10% per Time Period: Majority of TEAEs were Procedure-Related

AbbVie data on file. S187.3.001 and S187.3.002. Table 14.3.1.2.8.1.
Longer follow up data

12 months of Duodopa shows same efficacy results
Clinical study efficacy and safety data

A phase III, open-label, single-arm, multicenter safety study conducted over 12 months\(^1,2,3\)

**OUTPATIENT SCREENING**
(up to 28 days)

Conversion to oral levodopa/carbidopa IR while continuing dose optimized adjunctive Parkinson’s therapies

**Baseline Assessments**

**INPATIENT PHASE**
(4 to 28 days)

NJ Test Period 2 – 14 days

PEG-J procedure 2 – 14 days

Duodopa monotherapy initiated and dose adjusted (through Day 28)

**LONG-TERM TREATMENT PHASE**
(through Day 378)

Duodopa (n=323)

Allowed adjunctive Parkinson’s therapies\(^\dagger\) could be restarted or initiated 28 days after PEG-J placement if needed

(n=272 completed the study)

\(^\dagger\) Including dopamine agonists, COMT inhibitors, selective MAO-B inhibitors, amantadine, and/or anticholinergics, but excluding apomorphine, levodopa/benserazide, and levodopa/carbidopa CR.

COMT=catechol-O-methyltransferase.

Clinical study efficacy and safety data

A phase III, open-label, single-arm, multicenter safety study conducted over 12 months – Patient disposition

1. Adapted with permission from Fernandez et al., Mov Disord 2014.
Clinical study efficacy and safety data

A phase III, open-label, single-arm, multicenter safety study conducted over 12 months – Mean daily “OFF” and “ON” times assessed by a Parkinson’s disease diary†‡

Mean ± SD daily “OFF” and “ON” times as assessed by a Parkinson’s disease diary. * p<0.05; ** p<0.01; *** p<0.001 versus baseline.
† Mixed-model repeated-measures analysis.
‡ Baseline values were collected 3 days prior to randomization and after 28 days of oral therapy standardization.

Clinical study efficacy and safety data

A phase III, open-label, single-arm, multicenter safety study conducted over 12 months – UPDRS†

Mean ± SD changes from baseline.

*** p<0.001 versus baseline, one-sample t test.

† Mixed-model repeated-measures analysis.

Clinical study efficacy and safety data

A phase III, open-label, single-arm, multicenter safety study conducted over 12 months – PDQ-39†

![PDQ-39 Summary Index Score graph]

† Mixed-model repeated-measures analysis

a Baseline value from screening

Clinical study efficacy and safety data

A phase III, open-label, single-arm, multicenter safety study conducted over 12 months – EQ-5D†

† Mixed-model repeated-measures analysis
Clinical study efficacy and safety data

A phase III, open-label, single-arm, multicenter safety study conducted over 12 months – Safety data

Adverse events and serious adverse events during PEG/J treatment period (n=324)

<table>
<thead>
<tr>
<th>MedDRA Preferred Term</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>298 (92.0)</td>
</tr>
<tr>
<td>AEs reported in ≥10%</td>
<td></td>
</tr>
<tr>
<td>Complication of device insertion</td>
<td>113 (34.9)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>101 (31.2)</td>
</tr>
<tr>
<td>Procedural pain</td>
<td>67 (20.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>54 (16.7)</td>
</tr>
<tr>
<td>Excessive granulation tissue</td>
<td>52 (16.0)</td>
</tr>
<tr>
<td>Postoperative wound infection</td>
<td>50 (15.4)</td>
</tr>
<tr>
<td>Fall</td>
<td>49 (15.1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>47 (14.5)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>44 (13.6)</td>
</tr>
<tr>
<td>Incision site erythema</td>
<td>42 (13.0)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>37 (11.4)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>105 (32.4)</td>
</tr>
<tr>
<td>SAEs reported in ≥1%</td>
<td></td>
</tr>
<tr>
<td>Complication of device insertion</td>
<td>21 (6.5)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10 (3.1)</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>9 (2.8)</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>9 (2.8)</td>
</tr>
<tr>
<td>PD&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8 (2.5)</td>
</tr>
<tr>
<td>Pneumoperitoneum</td>
<td>8 (2.5)</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>6 (1.9)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6 (1.9)</td>
</tr>
<tr>
<td>Device dislocation</td>
<td>5 (1.5)</td>
</tr>
<tr>
<td>Depression</td>
<td>4 (1.2)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Single event could be coded for >1 preferred term; <sup>b</sup> Events with this term were most often additionally coded to abdominal pain, abdominal discomfort, abdominal distension, flatulence, and pneumoperitoneum; <sup>c</sup> Patients requiring hospitalization or extended hospitalization resulting from PD.

### Clinical study efficacy and safety data

**Procedure- and device-associated adverse events in ≥5% of all patients who received DUODOPA via PEG-J**

<table>
<thead>
<tr>
<th>System organ class</th>
<th>PEG-J N=395</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MedDRA 14.0 preferred term</strong></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders:</td>
<td></td>
</tr>
<tr>
<td>• Abdominal pain</td>
<td>34.2%</td>
</tr>
<tr>
<td>• Pneumoperitoneum</td>
<td>6.1%</td>
</tr>
<tr>
<td>General disorders and administration site conditions:</td>
<td>39.5%</td>
</tr>
<tr>
<td>• Complication of device insertion†</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations:</td>
<td></td>
</tr>
<tr>
<td>• Postoperative wound infection</td>
<td>21%</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications:</td>
<td></td>
</tr>
<tr>
<td>• Procedural pain</td>
<td>25.3%</td>
</tr>
<tr>
<td>• Incision site erythema</td>
<td>17.5%</td>
</tr>
<tr>
<td>• Procedural site reaction</td>
<td>11.6%</td>
</tr>
<tr>
<td>• Post procedural discharge</td>
<td>10.9%</td>
</tr>
<tr>
<td>• Incision site pain</td>
<td>5.3%</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders:</td>
<td></td>
</tr>
<tr>
<td>• Excessive granulation issue</td>
<td>18.2%</td>
</tr>
</tbody>
</table>

† Complication of device insertion was a commonly reported adverse event for both the nasojejunal (NJ) and the PEG-J. This adverse event was co-reported with 1 or more of the following adverse events for the NJ: oropharyngeal pain, abdominal distension, abdominal pain, abdominal discomfort, pain, throat irritation, gastrointestinal injury, esophageal hemorrhage, anxiety, dysphagia, and vomiting. For the PEG-J, this adverse event was co-reported with 1 or more of the following adverse events abdominal pain, abdominal discomfort, abdominal distension, flatulence, or pneumoperitoneum. Other adverse events that were co-reported with complication of device insertion included, abdominal pain upper, duodenal ulcer, duodenal ulcer hemorrhage, erosive duodenitis, gastritis erosive, gastrointestinal hemorrhage, peritonitis, and small intestine ulcer.

Adapted from data within Table 1 of the DUODOPA PM.

Practical Duodopa Information

What does the device look like?
DUODOPA treatment characteristics

DUODOPA administration:

- DUODOPA is continuously administered over 16 hours. If medically justified, DUODOPA may be administered during the night.
- Daily doses include:
  - Morning Dose
  - Continuous Dose up to 16 hours per day
  - Extra Doses as needed
- Pump is disconnected at bedtime.
- Patients should be given prescriptions for a supply of levodopa/carbidopa tablets. Following the discontinuation of the daily DUODOPA infusion, patients should administer their routine night-time dosage of oral levodopa/carbidopa tablets.
DUODOPA treatment characteristics

**DUODOPA cassette:**

- DUODOPA is stable for 15 weeks (expiration date is written on the outer carton).
- DUODOPA should be stored in the refrigerator at 2°C - 8°C.
- The cassette should be kept in the outer carton in order to protect from light.
- Each box contains 7 cassettes.
- By the end of the storage time the gel might become slightly yellow. This does not affect the amount of the drug or the treatment.

DUODOPA treatment characteristics

DUODOPA delivery system

DUODOPA includes the following components:
A. CADD-Legacy® DUODOPA 1400 pump
B. DUODOPA cassette
C. AbbVie™ PEG tube
D. AbbVie™ jejunal tube

• Administration of DUODOPA requires placement of a PEG outer transabdominal tube and inner jejunal tube by percutaneous endoscopic gastrostomy.
• DUODOPA is infused into the small intestine via PEG-J using the CADD-Legacy® DUODOPA 1400 pump.