

London New Drugs Group APC/DTC Briefing Document

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Duodopa

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Summary

- Levodopa/carbidopa intestinal gel (Duodopa™) is indicated for the treatment of advanced levodopa responsive Parkinson's disease with severe motor fluctuations and dyskinesia.
- Parkinson's disease is a chronic, progressive, neuro-degenerative disorder which affects movement, cognitive function, emotion, and autonomic function. In the UK, 1 in 500 (about 120,000) people have the condition, with about 10,000 new cases being diagnosed each year.
- To minimise fluctuations in dopamine plasma concentrations (due to erratic gastric emptying) and reduce motor complications, continuous dopaminergic stimulation (CDS) is currently used to mimic the physiological stimulation of the striatal dopamine receptors by providing continuous dopamine supplementation.
- Duodopa™ is a gel containing a combination of levodopa and carbidopa (ratio 4:1) for continuous intestinal administration. Each Duodopa™ cassette comprises 100mls of intestinal gel which contains 2000mg of levodopa and 500mg of carbidopa and should contain enough levodopa for one day's treatment.
- For long-term administration, the gel should be administered directly into the proximal jejunum via a permanent percutaneous endoscopic gastrostomy (PEG) tube.
- The DIREQT study is the main clinical trial to compare the safety and efficacy of Duodopa™ with conventional treatment. In this single blinded, cross over study, 24 patients were randomised to receive conventional treatment for three weeks and intra-duodenal administration of Duodopa™ for three weeks. Moderate to severe off state was reduced significantly in all patients during treatment with infusion. Moderate to severe dyskinesia was uncommon. Additionally the UPDRS, PDQ39 and electronic diary parameters documenting quality of life showed improvement during treatment with Duodopa.
- The estimated maintenance costs for one year's treatment to be £28,000 which includes the total cost of Duodopa and the cost of 4 follow up neurology appointments in the first year.
- Duodopa is only suitable for patients with very advanced Parkinson's disease. Patients suitable for Duodopa™ will either have failed to respond satisfactorily to, or failed to tolerate, all existing available pharmacological therapies including apomorphine administered via injection or pump.

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Levodopa/carbidopa intestinal gel (Duodopa™) is indicated for the treatment of advanced levodopa responsive Parkinson's disease with severe motor fluctuations and dyskinesia.¹

This briefing document aims to evaluate the information currently available on levodopa/carbidopa intestinal gel (Duodopa™) and view its place in the treatment of Parkinson's disease.

Background

Parkinson's disease is a chronic, progressive, neuro-degenerative disorder which affects movement, cognitive function, emotion, and autonomic function and is associated with substantial morbidity.² The main clinical features are akinesia, bradykinesia, rigidity, and tremor and are caused by progressive deterioration of dopaminergic neurones in the brain.²

Parkinson's disease is the second most common cause of chronic neurological disability in the UK.^{3,4} It is predominately a condition of the elderly and is uncommon in people younger than 30, after that the risk of developing it increases with age.^{3,4}

The prevalence of Parkinson's disease is approximately 1:1000 in the general population, rising to 1:100 over the age of 65 and 1:50 over the age of 80. In the UK, 1 in 500 (about 120,000) people have the condition, with about 10,000 new cases being diagnosed each year.^{3,4}

Treatment of Parkinson's disease involves stimulation of dopaminergic neurones by supplementation with levodopa or dopamine agonists such as bromocriptine. Other dopamine agonists include ropinirole, cabergoline, lisuride (lysuride), pergolide, pramipexole and apomorphine. Apomorphine is used in very advanced

Parkinson's disease.^{2,3}

Levodopa is the most common treatment.^{2,3} It is converted by the enzyme dopa-decarboxylase to dopamine, which relieves the symptoms of Parkinson's disease. It is always administered with a dopa-decarboxylase inhibitor, such as carbidopa, which does not cross the blood brain barrier and prevents the extra cerebral decarboxylation of levodopa without interfering with decarboxylation in the brain.

Levodopa absorption occurs in the proximal small intestine. It is metabolised extensively in the stomach and small intestine. Delayed or erratic gastric emptying may result in fluctuations in levodopa plasma concentrations which can lead to motor complications.⁵

The motility of the stomach varies in the fed and fasting states and gastric emptying may also be delayed in Parkinson's disease patients, particularly in those with motor fluctuations. Levodopa may also delay gastric emptying. In addition, levodopa has a short half life which can result in end of dose symptom control deterioration.⁵ The response duration to each dose also shortens as the disease progresses which results in motor complications.

Motor complications involve fluctuations in motor performance and drug induced involuntary movements (dyskinesias). Dyskinesias are initially mild and associated with good mobility. However, as the disease progresses and becomes advanced the on-off phenomenon appears. When this occurs, a patient who is mobile or 'on', suddenly changes to immobility or 'off'.

Continuous dopaminergic stimulation (CDS) is used to mimic the physiological stimulation of the striatal dopamine receptors by providing continuous dopamine supplementation. This minimises fluctuations in plasma concentrations and as a result can reduce motor com-

plications.⁵

CDS is currently attempted by use of small frequent doses of oral levodopa, sustained release levodopa preparations or the use of adjunctive therapy such as entacapone. In advanced stages of the disease apomorphine injections or continuous subcutaneous apomorphine infusions are also used.⁵

New formulations such as Duodopa™ intestinal gel and the ritogotine transdermal patch (Neupro™) are alternative methods of achieving continuous dopaminergic stimulation.^{5,6}

Levodopa/carbidopa intestinal gel (Duodopa)™

Duodopa™ is a gel containing a combination of levodopa and carbidopa (ratio 4:1) for continuous intestinal administration. The gel is contained within a cassette that is inserted into a pump for administration. Each Duodopa™ cassette comprises 100mls of intestinal gel which contains 2000mg of levodopa and 500mg of carbidopa and should contain enough levodopa for one day's treatment. The cassette should only be used with the CADD-legacy Duodopa™ pump; and they are designed for single use only. They should not be used for longer than one day (up to 16 hours) even if some of the medicinal product remains. An open cassette cannot be reused.¹

For long-term administration, the gel should be administered directly into the proximal jejunum via a permanent percutaneous endoscopic gastrostomy (PEG) tube. A temporary nasoduodenal tube should be used to ascertain if the patient responds favourably to this method of treatment and to adjust the dose before permanent treatment is started.¹

The total dose per day of Duodopa™ is composed of three individually adjusted doses:

- **The morning dose:** The morning bolus dose is administered by the pump to rapidly (within 10-30 minutes) achieve the therapeutic dose level. The dose should be based on the patient's previous morning intake of levodopa plus the volume to fill the tubing. The total morning dose is usually 5-10mls, corresponding to 100-200mg of levodopa. The total morning dose should not exceed 15mls (300mg levodopa).¹
- **Continuous maintenance dose:** The continuous maintenance dose is adjusted individually in steps of 2mg/hour (0.1ml/hour). The dose should be calculated according to the patient's previous daily intake of levodopa and should be kept in the range of 1-10mls per hour (20-200mg levodopa/hour) and is usually 2-6mls/hour (40-120mg levodopa/hour). In exceptional cases a higher dose may be needed. When supplementary medications are discontinued, the Duodopa™ dose should be adjusted.¹
- **Extra bolus doses:** To be given as required if the patient becomes hypokinetic during the day. The extra dose should be adjusted individually, normally 0.5-2.0ml. In rare cases a higher dose may be necessary. If more than 5 extra bolus doses are required per day, the maintenance dose should be increased.¹

After the initial dose setting, fine adjustments of the morning bolus dose, the maintenance dose and extra bolus dose should be carried out over a few weeks.¹

If medically justified Duodopa™ may be administered during the night.¹

Clinical Evidence

Successful intra-duodenal administration of levodopa was first described in

1986, however the delivery systems used were impractical and bulky.^{5,7} A small pharmacokinetic study in 2003, involving 12 patients showed that an intra-duodenal infusion of levodopa plus carbidopa resulted in lower variability in plasma levodopa levels compared with placebo. It concluded that continuous intra-duodenal levodopa infusion was an alternative treatment for advanced Parkinson's disease.⁸

The DIREQT study (Duodopa™ infusion: randomised efficacy and quality of life study) is the main clinical trial to compare the safety and efficacy of Duodopa™ with conventional treatment.⁹

In this single blinded, cross over study, 24 patients were initially randomised into 2 groups. Group 1 received conventional treatment for three weeks, followed by intra-duodenal administration of Duodopa™ for three weeks. Group 2 received the treatments in the opposite order.

Naso-jejunal tubes were used to avoid unnecessary surgery. Dose adjustments for individual optimisation

occurred during the first week of each treatment period and were allowed throughout the study, except during the video recording days. The patients were allowed to use rescue medication throughout the study if needed.

One video recording day took place during weeks 2 and 3 of each treatment period. Patients were video recorded for 1 to 2 minutes every 30 minutes from 9am to 5pm completing the following tasks; finger tapping, alternating hand movements, rising from a chair and walking. The recordings were subsequently assessed by two independent neurologists. Dummy nasal tubes were used during the video-taping of the patients on conventional treatment to ensure blinding. A treatment response scale (TRS) was used for assessment of clinical response, ranging from -3 (severe off) to +3 (on with severe dyskinesias) where 0 is on without any dyskinesias.

The primary efficacy variable was the percentage of ratings from the TRS within the interval -1 to +1, a clinically desirable functional on state accepting mild parkinsonism or mild dyskinesia

Table 1: Percentage of ratings in different motor states on treatment response scale

Efficacy variables		Conventional	Intra-duodenal
Clinically desirable state: functional 'on' state: -1 to +1	Mean ± SD	74.2 ± 24.6	90.7 ± 19.2;
	Median	81.3	100
	Range	18 - 100	37-100
	p value	Not stated	p<0.01
Severe 'off' state: -3 to -2	Mean ± SD	19.2 ± 17.9	1.8 ± 5.0
	Median	15.4	0
	Range	0-51	0-22
	p value	Not stated	<0.01
'On' with severe dyskinesias +2 to +3	Mean ± SD	6.3 ± 14.6	7.5 ± 17.3;
	Median	0	0
	Range	0-49	0-63
	p value	Not stated	p=1

Table 2: UPDRS ratings at baseline and at the end of each treatment

Efficacy variables		Baseline	Conventional	Intraduodenal infusion
UPDRS part I: Mentation, behaviour and mood	Mean	Not stated	2.8	2
	Median	3.25	2.5	2
	Range	0-9	0-6	0-6
	p-value	Not stated	Not stated	0.046
UPDRS part II: Daily living	Mean	Not stated	15.3	11.1
	Median	11.75	14	11
	Range	9-27	6-25	6-20
	p-value	Not stated	Not stated	<0.01
UPDRS part III: Motor assessment	Mean	Not stated	24	17.1
	Median	31.0	22.5	14.5
	Range	12-61	0-46	5-36
	p-value	Not stated	Not stated	0.06
UPDRS part IV: Complications due to medical treatment	Mean	Not stated	8.8	6.7
	Median	9.75	8.5	7
	Range	3-12	3-13	2-13
	p-value	Not stated	Not stated	0.02
UPDRS total score	Mean	Not stated	50.9	36.8
	Median	62.75	53	35
	Range	36-92	14-80	19-63
	p-value	Not stated	Not stated	0.02

and percentage of ratings within the -3 to -2 and +2 to +3.

Moderate to severe off state was reduced in all patients during treatment with infusion. Moderate to severe dyskinesia was uncommon in both treatment arms.

The median difference of ratings in the desired, functional on interval (-1 to +1) on the TRS between the infusion and conventional treatments was 14% (range -15% to 63%; n=18, p<0.01). Two patients showed a negative difference (i.e. less ratings in the functional 'on' state with infusion) and had a significant decrease in the off state and an increased number of ratings in +2 (moderate dyskinesia). Median percentage of ratings in +3 was 0% (range 0% to

3%) for both treatments. Five patients had >98% of ratings within the functional on interval (-1 to +1) with conventional treatment. Table 1 provides a summary of these results.

Secondary efficacy variables included

- The percentage of ratings measured 0-1 within the unified Parkinson's disease rating scale (UPDRS).
- Evaluation of self assessment questionnaire scores at baseline and at the end of each treatment arm using the Parkinson's disease questionnaire (PDQ-39) and 15D quality of life instrument.

The UPDRS scale was used for patient assessment at baseline and at the end of each treatment arm and for

Table 3: Percentage of UPDRS items and dyskinesia ratings within score 0-1

Efficacy variables		Conventional	Intra-duodenal infusion
Finger tapping (UPDRS item 23)	Mean	53	75.2
	Median	65.1	91.2
	Range	0-98	3-100
	p-value	Not stated	<0.01
Alternating hand movements (UPDRS item 25)	Mean	49.1	67.1
	Median	58.8	70.6
	Range	1-97	8-98
	p-value	Not stated	0.01
Rising from chair (UPDRS item 27)	Mean	91.3	99.2
	Median	98.5	100
	Range	62-100	85-100
	p-value	Not stated	<0.01
Gait (UPDRS item 29)	Mean	26-100	34-100
	Median	90.4	100
	Range	80.5	94.3
	p-value	Not stated	<0.01
Bradykinesia (UPDRS item 31)	Mean	67.5	87.3
	Median	72.1	90.6
	Range	0-100	50-100
	p-value	Not stated	0.01
Dyskinesia rating	Mean	94	91.2
	Median	100	100
	Range	47-100	32-100
	p-value	Not stated	0.23

the following activities on the video sessions: finger tapping, rapid alternating movements of the hands, arising from chair, gait and bradykinesia. The greater the severity of the symptom and disease, the higher the UPDRS score.

The median percentages of scores within 0 to 1 (no or mild symptoms) of the five UPDRS items assessed from the video tapes were all signifi-

cantly increased with infusion compared with conventional treatment. Video assessment of dyskinesias revealed no differences between treatments.

The total median UPDRS score at the end of each treatment arm was 53 with conventional treatment and 35 with infusion. Infusion provided lower median scores in all parts of UPDRS. Average UPDRS assessment results

are summarised in tables 2 and 3. In addition, patients' completed a self assessment questionnaire during the course of the study. A handheld computer prompted the patients to answer a series of 7 questions about their abilities and quality of life at 8am, midday, 4.00pm and 8.00pm. Two additional morning questions were asked at 8am relating to the previous nights sleep. Table 4 includes details of the self assessment questions.

Each question had 5 alternative responses, ranging from 1; severe disability (i.e. not able to walk, 'off', dyskinesic, hyperkinetic, difficulties with chores, dystonia, very depressed, and not at all satisfied) to 5; no disability (i.e. fully able to walk etc, not depressed, completely satisfied). Increased scores indicated an improvement.

The scores for each patient were averaged over the 14 day baseline and during the 12 days of each treatment period and assessed using the PDQ 39 and 15D quality of life questionnaires.

The median scores for seven out of the eight dimensions of the PDQ-39 assessment were significantly better with the infusion. The remaining dimension social support was unchanged. Median total scores of the 15D QoL instrument was increased from 0.72 to 0.78 with infusion,

showing a higher quality of life with the infusion. Six of the electronic diary daily questions were improved on infusion; dyskinesia was reported to be unchanged.

Eighteen patients completed the study. Three patients withdrew their consent because they could not tolerate either the naso-duodenal tube or the pump, 1 patient withdrew their consent after the infusion period because they were extremely satisfied with the infusion and did not want to return to conventional therapy, 1 patient was removed from the study because of severe insomnia and 1 patient was excluded because they continued to take conventional medication whilst in the infusion phase.

Adverse effects occurred in 16 patients during conventional treatment and 17 patients during the infusion and were mostly mild. The most common adverse events were dyskinesia, constipation, depression, insomnia and somnolence. Dystonia, palpitation, anxiety, dizziness, headache, agitation and diarrhoea were also reported in both treatment groups. Anorexia, confusion and non specific accident were only reported in the infusion group.

Adverse Effects

Duodopa™ has the same adverse effect profile as generic levodopa and carbidopa, full details of which can be found in the SPC.¹

Table 4: Self assessment quality of life questions

- | |
|--|
| <ol style="list-style-type: none"> 1. Have you had any problems walking 100 metres in last 4 hours? 2. Have you been "off" (stiff, slow or shaking) during the last 4 hours? 3. Have you been hyperkinetic in the last 4 hours? 4. Have you had any difficulties with your daily chores in the last 4 hours? 5. Have you had any muscular cramps or spasms in the last 4 hours? 6. Have you felt depressed in the last 4 hours? 7. Have you been satisfied in your overall functioning in the last 4 hours? <p>Additional morning questions</p> <ol style="list-style-type: none"> 1. How did you sleep last night? 2. Could you turn over in bed last night? |
|--|

Complications with the Duodopa™ device are very common (>1/10) and include-

- Dislocation of the intestinal tube backwards into the stomach
- Occlusion or kinking of the tube. Occlusions can be remedied by flushing the tube with tap water; kinking may need re adjustment of the tube. If the tube completely fails then the patient must be treated with oral levodopa/carbidopa until the problem is solved.
- Abdominal pain, infection and leakage of gastric fluid may occur shortly after surgery.
- Local infections around the stoma may occur.

Precautions

Duodopa™ has the same contraindications, precautions and special warnings as generic levodopa/carbidopa, full details of which can be found in the SPC.¹

The following precautions and special warnings are specific for Duodopa™.

- When switching to Duodopa™, the dose may need to be adjusted downwards in order to avoid levodopa induced dyskinesias.
- Previous surgery in the upper part of the abdomen may lead to difficulty in performing the gastrostomy or jejunostomy.
- Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during extended therapy with Duodopa™.
- Reduced ability to handle the system as pump and tube connections can lead to complications. In such instances a caregiver (e.g. nurse, assistant nurse or close relative) should assist the patient.
- A sudden or gradual worsening of bradykinesia may indicate an ob-

struction in the device and should be investigated.

The effect of administration of antacids on Duodopa™ and bioavailability of levodopa has not been studied.¹

Special Populations

Renal/Hepatic impairment

No dose adjustment is necessary.¹

Children and adolescents

The safety in patients under 18 years of age has not been established.¹

Pregnancy and breast-feeding

There is insufficient data about the use of levodopa/carbidopa in pregnant women. The potential human risk is not known. Duodopa™ should not be used during pregnancy unless the benefits to the mother outweigh the risk to the foetus.¹ Levodopa is excreted in the breast milk in significant quantities. There is evidence that lactation is suppressed during treatment with levodopa. The safety of levodopa and carbidopa in the infant is not known. Women should not breast feed while using Duodopa™.¹

Place in Therapy

Duodopa™ may be of significant benefit in a small number of patients with very advanced Parkinson's disease,¹⁰

Patients suitable for Duodopa™ will either have failed to respond satisfactorily to, or failed to tolerate, all existing available pharmacological therapies including apomorphine administered via injection or pump. They are also likely to be unsuitable for or to have refused surgical options including deep brain stimulation.

They must show a positive clinical response to continuous levodopa therapy via a temporary naso-gastric tube prior to insertion of PEG tube. They must also be capable of managing the pump etc or have a carer able to operate the pump.

Economic Considerations

	Usual dose	Cost per 28 days treatment
Sinemet CR	Maintenance dose 3-8 tablets daily in four divided doses (600mg-1600mg levodopa per day)	£45.00
Madopar 125	1-10 capsules (100-1000mg levodopa) per day in divided doses	£44.00
Ropinirole	1.5-3mg TDS	£141
Apomorphine subcutaneous injections	3–30 mg daily in divided doses	£743
Apomorphine infusion	Initially 1 mg/hour daily increased according to response (not more often than every 4 hours) in max. steps of 500 micrograms/hour, to usual rate of 1–4 mg/hour) for 16 hours a day	£819
Duodopa™	1 cassette per day	£2156

Basic NHS prices. Drug Tariff/MIMS August 2006

Doses shown are for general comparison and do not imply therapeutic equivalence. Calculations are based on the maximum dose stated above.

The cost of the CADD pump tube and all materials required for Duodopa™ administration is included in the cassette price. It is anticipated by the manufacturers, that a 9 day inpatient stay will be required for treatment initiation. The cost for this has been estimated by Solvay as £3,823 (standard in-patient tariff cost). The cost of the Duodopa™ used during the initiation period will be paid for by Solvay.¹¹

Solvay have estimated the maintenance costs for one years treatment to be £28,000 which includes the total cost of Duodopa™ and the cost of 4 follow up neurology appointments in the first year.¹¹

It is expected, based on current incidence figures, that there will be approximately 1.1 patients requiring Duodopa™ treatment per 100,000 of the population per year with an anticipated cost burden of £37,470 per year. However this is expected to rise to 6.8 patients per 100,000 population by 2015, with a cost burden of £199,937.¹¹

Discussion points

- **Does the trial provide sufficient evidence?** This study was not double blinded or placebo controlled. There is evidence that substantial dopamine release in the striatum of parkinsonian patients can result from the placebo effect.¹² The study also allowed the use of rescue medication in both treatment arms even on assessment days but limited information is provided regarding the extent of rescue medication and additional support required in each treatment group and therefore it is very difficult to judge from this study how accurate the results are in terms of efficacy.¹³ Individual optimisation of therapy was conducted with out third party verification. In complex patients it can be very difficult to obtain adequate optimisation. If patients were inadequately optimised in the conventional treatment group, the trial results would be biased towards Duodopa™ ensuring its superiority. It is difficult to judge the robustness of the optimisation procedures from the information provided and conclude how effective Duodopa™ actually is and whether it provides any advantages over conventional treatment in order to justify its cost.¹³
- **Is the short term effectiveness maintained in the long term? Does the dose of Duodopa™ increase over time in order to maintain the same therapeutic effect? What is the maximum dose? Do patients find the administration system convenient over a long period of time? Are there any long term adverse effects relating to the formulation?** The need for treatment modification after follow up is to be expected from the natural progression of Parkinson's disease but it also may occur due to a reduction in the initial placebo effect seen in some patients.¹³ The DIREQT study was a small short term study over six weeks. It does not provide any information on sustainability of long term motor function and the changes with dose over time. It also does not provide any information relating to the long term adverse effects of the Duodopa™ system. The study authors' report that long-term follow up is underway and will be reported separately. A previous follow up study of 28 individually treated very advanced Parkinson's patients showed that whilst most patients still showed improvement from baseline, a gradual deterioration had occurred.¹⁴ Of these, 6 patients had returned to oral therapy, 2 patients had discontinued treatment due to decreasing effect; both having evidence of multiple system atrophy, 3 patients terminated treatment due to problems with handling the system due to dementia and 1 patient stopped due to lack of improvement. Twelve patients required additional anti-parkinsonian medications. Further follow up data supplied by Solvay involves 66 patients treated with Duodopa™ from 1991 to 2002.¹⁰ Fifty two of these patients were treated for at least 12 months with a mean duration of treatment of 4.1 years (range 1-10.7 years). The mean Duodopa™ dose at discharge from hospital was 1417±583mg levodopa/day (range 66-2998mg). The dose at the last follow up visit or at discontinuation was 1333±558mg levodopa/day (range 412-3158mg). The average difference in dose between initiation of Duodopa™ and the last dose was -77±553mg levodopa/day. Twenty-one patients discontinued Duodopa™. Of these 7 patients died (cause unrelated to Duodopa™), 6 were due to worsening Parkinson's disease or concurrent illness such as confusion, 4 were caused by adverse events relating to the infusion system (e.g. tube dislocation or leaking or stomach pain) and 4 patients withdrew consent.¹⁰ A series of case studies published recently to demonstrate that 24 hour infusion of Duodopa™ could further improve motor performance in deteriorating patients acknowledges that Duodopa™ requirements do increase with time and even necessitate 24 hour infusion in some patients.¹⁵ In the five patients described

24 hour infusions, improved disease control. It does not provide adequate follow up data to fully assess long term safety and effectiveness.

- **Are there any complications specific to PEG tubes which have not been highlighted?** The main clinical trial used naso-duodenal tubes for administration, however a PEG tube is recommended for permanent administration. A number of complications are associated with PEG tube post insertion including infection at insertion site, peristomal leaks, accidental tube removal, tube fracture, gastro-colic fistula, peritonitis, septicaemia and necrotising fasciitis.¹⁶ Mortality rates of 20% within one month of insertion have occurred, although many of these patients had significant co-morbid factors such as terminal illness and severe dysphagia.¹⁶ The correct selection of suitable patients is essential.¹⁶ Patients and their carers must be taught how to look after the tube correctly to prevent infection and also to prevent blockage or dislodgement of the tube. The procedure can be traumatic.

No deaths due to the insertion of a PEG tube have occurred with Duodopa™.¹⁷ In a small follow up study, 6 cases of post op infection were reported.¹⁴ Minor discharge from the PEG site was common but deemed to be acceptable by the study co-ordinators. Problems relating to the infusion which led to a change or adjustment of the catheter by gastroscopy occurred on 35 occasions.¹⁴

- **Is the administration of Duodopa™ affected by diet and or enteral feeding via the PEG tube. Enteral feeding may be possible at night when the Duodopa™ infusion is switched off, does this have any affect on Duodopa™ administration during the day?** The efficacy of Duodopa™ is not affected any differently by food than conventional levodopa therapy.¹⁷ Enteral feeds can be given at night using the PEG tube system. However, the system is designed so that the enteral feed is administered in the gap between the outer PEG tube and the inner tube. Duodopa™ when it is given passes through the inner tube directly into the jejunum; the enteral feed passes directly through the PEG tube into the stomach. Although Duodopa™ and enteral feeding can be administered concurrently; Solvay recommends that feeding is done at night.¹⁷

- **What will be the practical arrangements regarding supply and monitoring of patients? Will shared care guidance need to be produced? Is home delivery required?**

During the initial titration phase Solvay Healthcare will provide a specialist nurse to the hospital to ensure that the patient receives the optimum dose and that all relevant staff and the patient are trained in the use of the Duodopa™ pump and its various attachments (tubes, connector etc). In addition training is provided on the insertion of the PEG tube. The Duodopa™ used by the patient whilst in hospital during the initiation period is also provided free of charge. A charge is only initiated for future supplies once patients who are known to respond to treatment are discharged.¹⁷

Supply of Duodopa™ to patients at home will be through the use of Healthcare@Home who will deliver direct to their door. Healthcare@Home will also organise replacement tubes, connectors and maintain the pump as necessary.¹⁷

A shared-care protocol will not be needed as the GP will not be prescribing. However, a guideline for treatment is available from Solvay Healthcare.¹⁷

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