Meeting number: SM1783NEU
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Date of prep: September 2019

Update in APD – 3rd October 2019
Exeter

Advanced Treatments in PD

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with interest in Movement Disorders
Southmead Hospital
With support from Abbvie

5-2-1

Consider referral for advanced therapies if any of the 5-2-1 present

- 5 doses of l-dopa a day
- 2 hours of OFF a day
- 1 hour of disabling dyskinesia a day

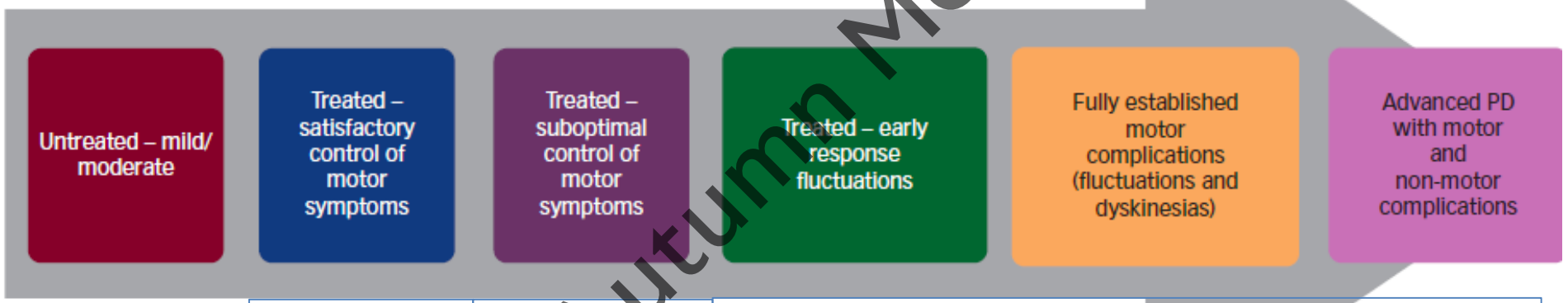
Antonini et al., Curr Med Res Opin, 2018 Dec

Outline

- **Stages of PD**
- Advanced therapies – introduction
- Apomorphine
- DBS
- Duodopa
- Advanced therapies - comparison
- Lesion therapies

Please refer to the relevant SmPCs

Stages of PD



1x oral med | 2x oral meds

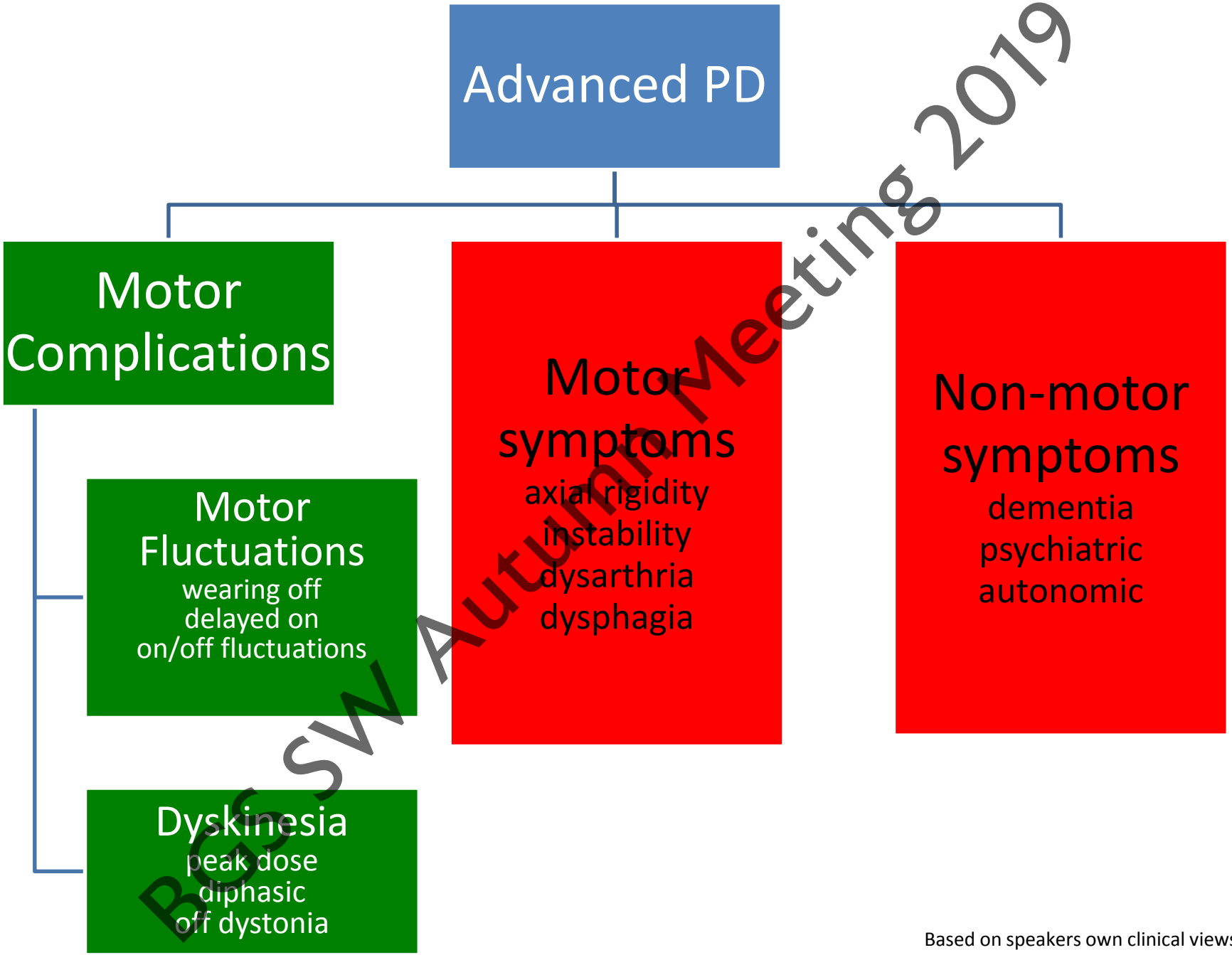
3x oral meds
incl. COMT, Amantadine, MAO-I
Dose fractionation
Discussion re advanced treatments

Advanced treatments

National Parkinson Foundation, http://www.parkinson.org/understanding-parkinsons/what-is-parkinsons/The-Stages-of-Parkinsons-Disease [accessed August 2017]

Treatment guidance is based on speakers own clinical views

Please refer to the relevant SmPCs



Based on speakers own clinical views

Wearing OFF

- Increase administration frequency
- Complemented by MAOB/COMT inhibitors, long-acting Dopamine agonists (nocturnal symptoms, wearing off)
- Rescue treatment (e.g. dispersible L-dopa)

Treatment guidance is based on speakers own clinical views
Please refer to individual drugs SPCs on the electronic medicines compendium

Dyskinesia

- Reduce total L-dopa dose – significant risk > 400mg L-dopa per day (STRIDE-PD, MovDis 2013)
- Fractionation of L-dopa – small frequent doses
- Dopamine sparing - Dopamine agonists/amantadine/MAOB inhibitors
- Reduce/stop COMT inhibitors

Treatment guidance is based on speakers own clinical views

STRIDE-PD study, Factors predictive of the development of Levodopa-induced dyskinesia and wearing-off in Parkinson's disease, Warren Olanow C *et al*., Movement Disorders 2013;25(8) 1064-71.

Outline

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Rationale for Advanced Treatments

- Pulsatile dopaminergic stimulation leads to motor complications
  - Pharmacokinetic causes
  - Pharmacodynamic causes
- Continuous dopaminergic stimulation will improve complications
  - Pharmacologic
  - Electrical

Treatment guidance is based on speakers own clinical views

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Antonini et al., Curr Med Res Opin, 2018 Dec

Indications for Advanced Therapies

Indications (Any)

***L-dopa responsive, Idiopathic PD, on optimal Rx

- Disabling fluctuations
- Disabling dyskinesia
- Disabling tremor (DBS)
- Intolerance to levodopa (DBS)

Contraindications (Any)

- Dementia
- Uncontrolled psychiatric conditions
- Severe disability from comorbidities

Treatment guidance is based on speakers own clinical views

Caveats

- Advanced therapies are not a cure
- Do not prevent dementia
- Patients only as good as their best ON
- Axial symptoms may not improve, incl. dysarthria and ON freezing
- Unclear effect on NMS

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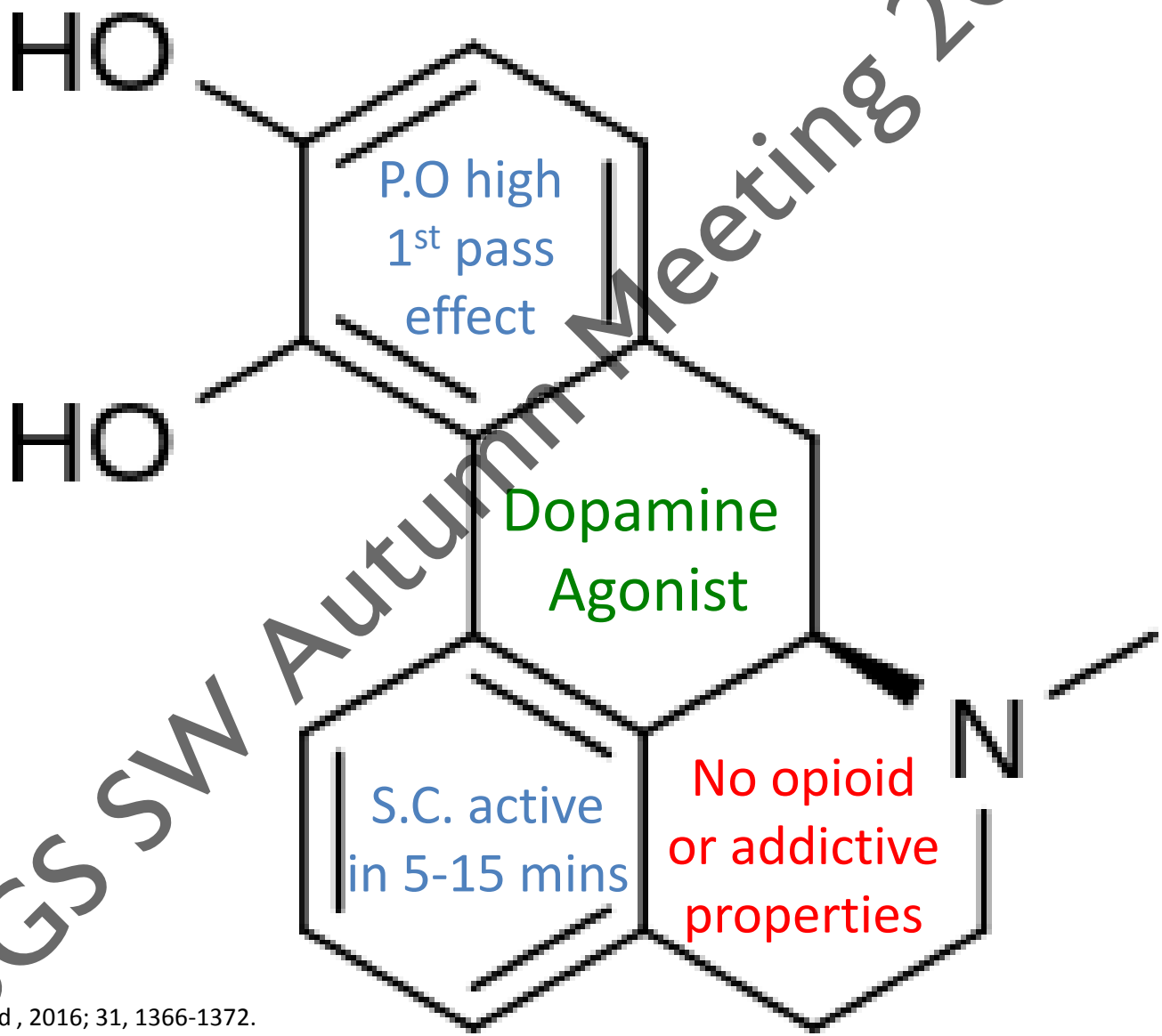
Apomorphine

How it works



1. Hauser RA et al., Mov Disord , 2016; 31, 1366-1372.
2. Apomorphine SPC, https://www.medicines.org.uk/emc/medicine/12941#PHARMACOLOGICAL_PROPS

Apomorphine

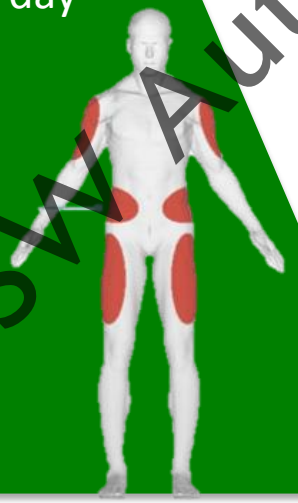
TOLEDO study, Lancet Neurology, Sep 2018

- First double-blind, placebo-controlled RCT on 106 patients
- OFF time -2.47h
- ON time w/o dyskinesia +2.77h
- LEDD -33%

Apomorphine
Administration

Apo-Pen

- For delayed ON
- Unpredictable OFFS
- Up to 6/day

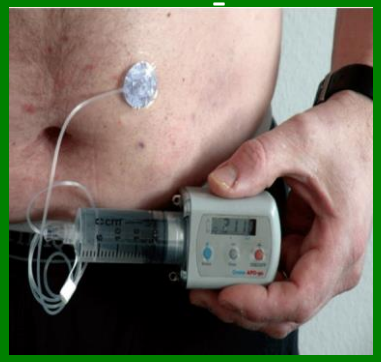


Apomorphine Challenge

- by Apo-nurse
- to set dose
- to identify SE's

Infusion

- For severe fluctuations
- If Apo-pen > 6x/day



Please refer to individual drugs SPCs on the electronic medicines compendium

Selection criteria

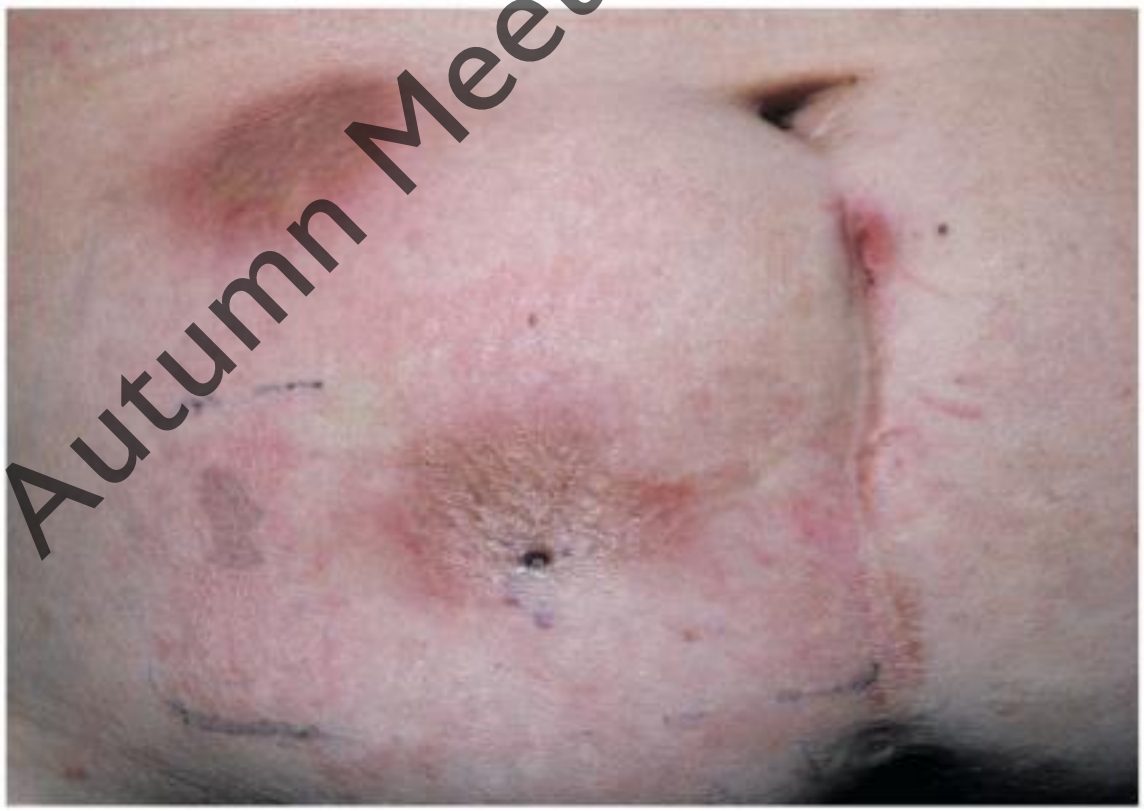
	DBS	Duodopa	Apomorphine
Dementia			
MCI			
Severe Depression			
Axial Symptoms			
Psychiatric OFFs			
PPM, ICD			
Malnutrition			
Neuropathy			
GI problems			
Severe Tremor or Dystonia			
No social support			
Agonist SE: somnolence, hypotension			
Mild Hallucinations			
Anticoagulation			
ICD			

Please note, this information reflects the speakers own clinical view

Please refer to individual drugs SPCs on the electronic medicines compendium

Apomorphine
Complications

Cutaneous reactions 87%
- Nodules
- Panniculitis



Psychiatric 43%
- Confusion
- Hallucinations
- ICDs

Systemic 41%
- Nauseas
- Somnolence
- Orthostatic hypo
- Dizziness
- Coomb's and aneamia

Please refer to individual drugs SPCs on the electronic medicines compendium

Apomorphine practical points

- Early add on
- Available locally – through Apo-nurse
- Fast set-up
- Least invasive set-up
- Care-intensive
- Continuous need for oral medication

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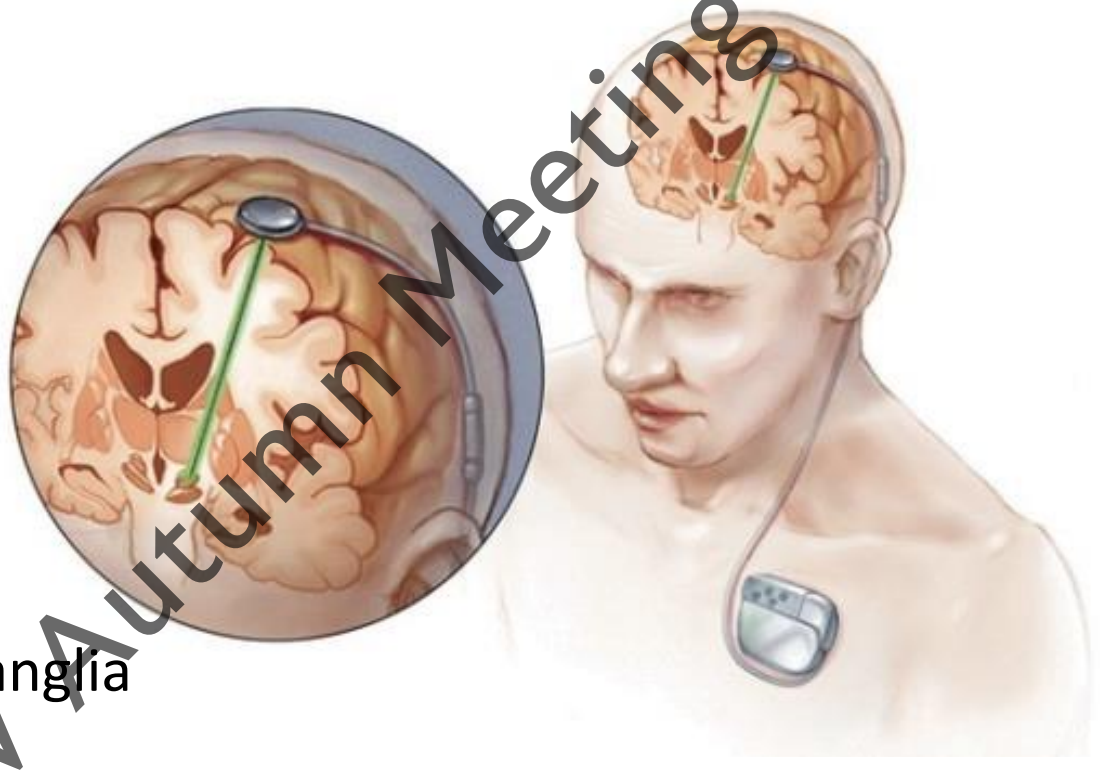
DBS
Device

- Bilateral electrical stimulation of:
  - STN
  - Zona incerta
  - VIM, Gpi
- Disrupting abnormal discharges in basal ganglia



DBS in Advanced PD

- Several RCTs showed superiority of DBS over best medical therapy (improved ON time by ~ 4 hours) and improved QoL (Giugni & Okun, Curr Opin Neurol 2014)
- Good long-term data (Krack et al, NEJM 2003)
- Open label: Improved non-motor symptoms esp pain (Cury et al, Neurology 2014)

1. Giugni & Okun, Curr Opin Neurol 2014
2. Krack et al, NEJM 2003
3. Cury et al, Neurology 2014

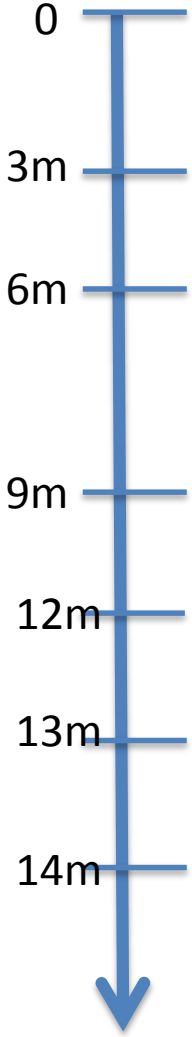
DBS in patients with early motor complications

- EARLYSTIM study (NEJM, 2013) – STN DBS superior to best medical therapy in primary (QoL) and secondary outcomes at 2 years
- Selective patient group: Mean age 52 yrs, UPDRS motor scores 33, disease duration 7 yrs, mean LED ~ 900 mg/day
- Early DBS in patients with no motor complications – not better than best medical treatment (Charles et al, Parkinsonism Relat Disord 2016)

1. Schuepbach et al., 2013, N Engl J Med;368:610-22.
2. Charles et al, Parkinsonism Relat Disord 2016.

DBS

Process



- Referral
- Selection – DBS clinic
- Assessment – overnight, levodopa challenge, UPDRS, NMS, cognition, mood
- Planning scan – GA
- Surgery – GA (5hr)
- Activation – day case
- Follow-up: 3m, 6m, 1y

Treatment guidance is based on speakers own clinical views

Selection criteria

	DBS	Duodopa	Apomorphine
Dementia			
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Severe Depression			
Axial Symptoms			
Psychiatric OFFs			
PPM, ICD			
Malnutrition			
Neuropathy			
GI problems			
Severe Tremor or Dystonia			
No social support			
Agonist SE: somnolence, hypotension			
Mild Hallucinations			
Anticoagulation			
ICD			

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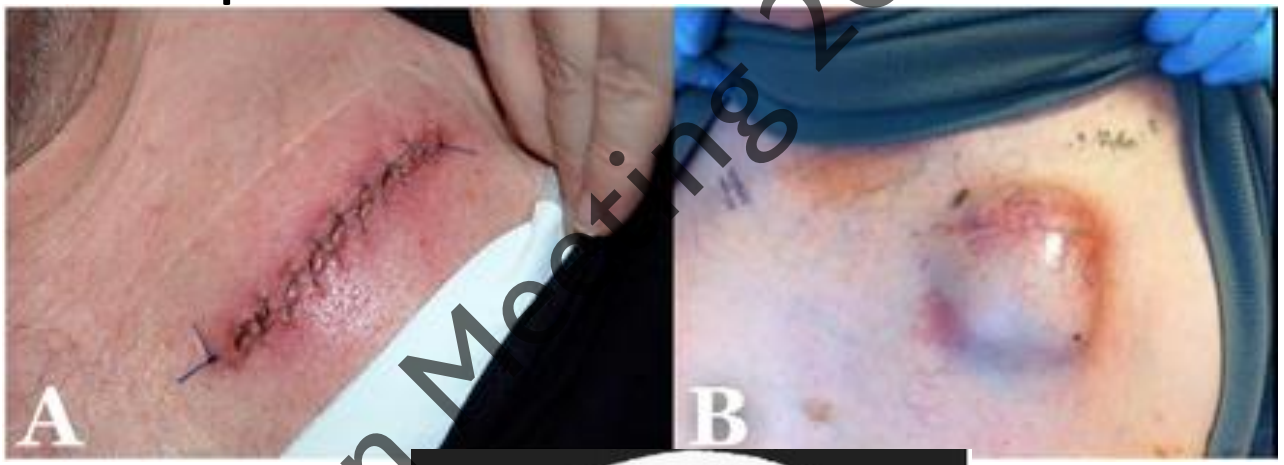
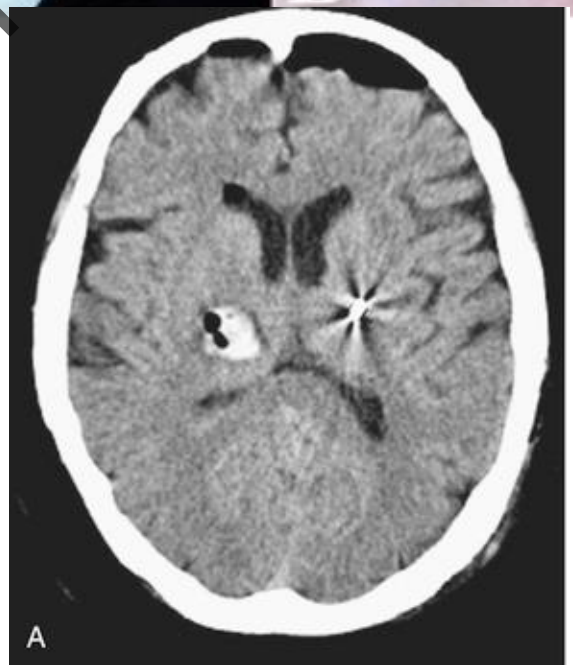
DBS

Complications



Device related

- ICH <1%
- Infection 2-4%
- Electrode migration



Stimulation related

- Confusion
- Postural sx
- Dysarthria, dysphagia
- Verbal fluency decline
- Mania, depression
- Weight gain

Based on speakers own clinical views

DBS
practical points

- Most invasive
- Little care from patient
- Continuous need for oral medication

Outline

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Duodopa
How it works

- Levodopa + carbidopa as intrajejunal gel
- Continuous infusion
- Bypassing stomach

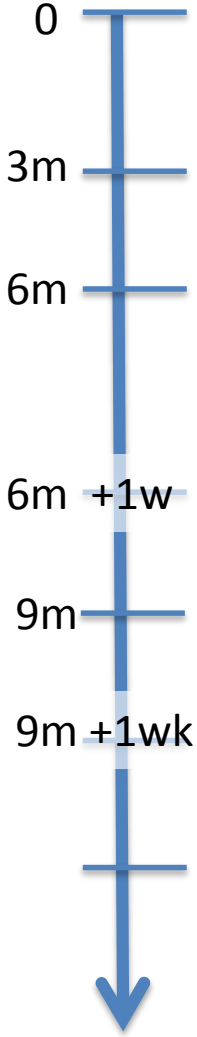
Duodopa SPC: https://www.medicines.org.uk/emc/product/6231/smpc

Duodopa

- RCT in advanced PD: reduction in OFF time by ~ 2 hrs/day compared to oral L-dopa (in total ~4h) (Olanow et al, Lancet Neurol 2014)
- improvement in ON time without troublesome dyskinesias (Olanow et al, Lancet Neurol 2014)
- improved QoL (Olanow et al, Lancet Neurol 2014)
- Improved non-motor symptoms, especially: sleep/fatigue, GI sx, mood/cognition (GLORIA Registry, Antonini et al, Park & Rel Disord 2017)

Duodopa

Process



- Referral
- Selection – Adv. Therapy Clinic
- Assessment – overnight, levodopa challenge, UPDRS, NMS, cognition, mood
- HAH Nurse home visit
- Duodopa admission 1 wk: NJ/PEG-J, titration
- HAH Nurse home visit 1wk
- Southmead Follow-up: 3m, 6m, 1y

Treatment guidance is based on speakers own clinical views

Selection criteria

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Dementia			
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Severe Tremor or Dystonia			
No social support			
Agonist SE: somnolence, hypotension			
Mild Hallucinations			
Anticoagulation			
ICD			

Please note, this information reflects the speakers own clinical view

Please refer to individual drugs SPCs on the electronic medicines compendium

Duodopa

Complications

Device related 96%

- Tube dysfunction
- Pump failure

PEG related 65%

- Stoma infection
- Pressure sore
- Granulation
- Abdo pain
- peritonitis

Treatment related 35%

- Confusion, hallucinations
- Weight loss
- B12 peripheral neuropathy

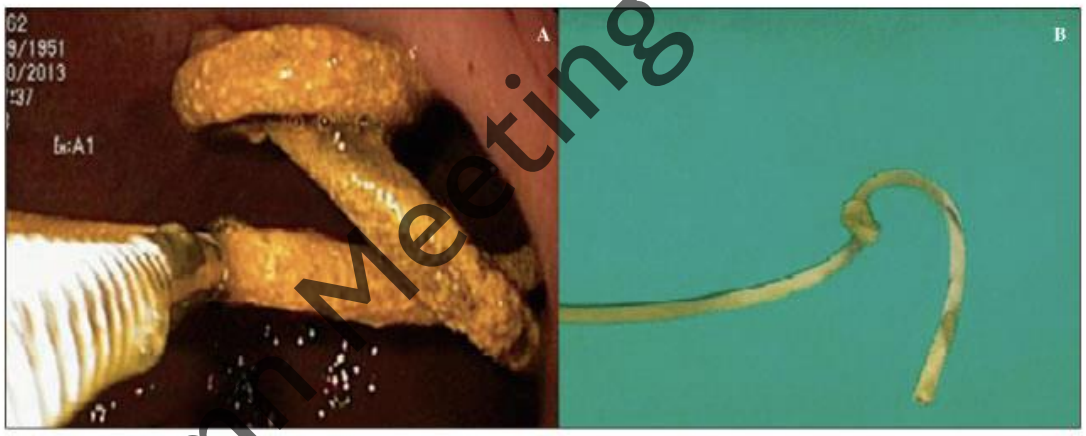
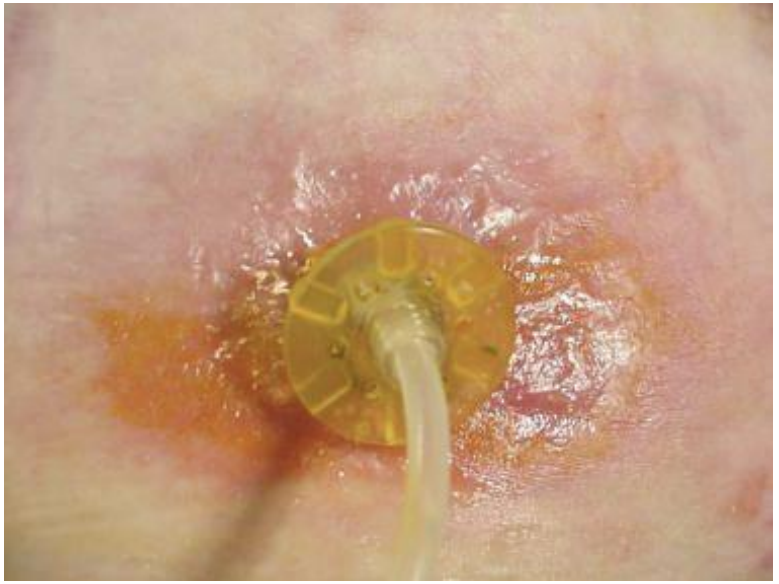


Fig. 1. Endoscopic view (A) and after endoscopic extraction (B) of the knotted duodenal tube of the Duodopa® infusion system.



Duodopa SPC: https://www.medicines.org.uk/emc/product/6231/smpc

Duodopa
practical points

- Moderately invasive set-up
- Care-intensive
- No need for oral medication

Outline

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Advanced Therapies

Comparison

	STN-DBS	Duodopa	Apomorphine
OFF time	-4.2h [2]	-4h [1]	-2.47h[4]
ON time w/o dysk.	+4.4h [2]	+4h [1]	+2.77h[4]
Dyskinesia	-50%[2]	-24%[3]	?
Medication	-50%[2]	+9% (control +22%)[1]	-33%[3]
PDQ-39	-23%[2]	-31%[1]	?

1 Lancet Neurol. 2014 Feb;13(2):141-9
2 N Engl J Med. 2006 Aug 31;355(9):896-908
3 Neurology. 2005 Jan 25;64(2):216-23
4 Lancet Neurology. 2018 Sep; 749-759

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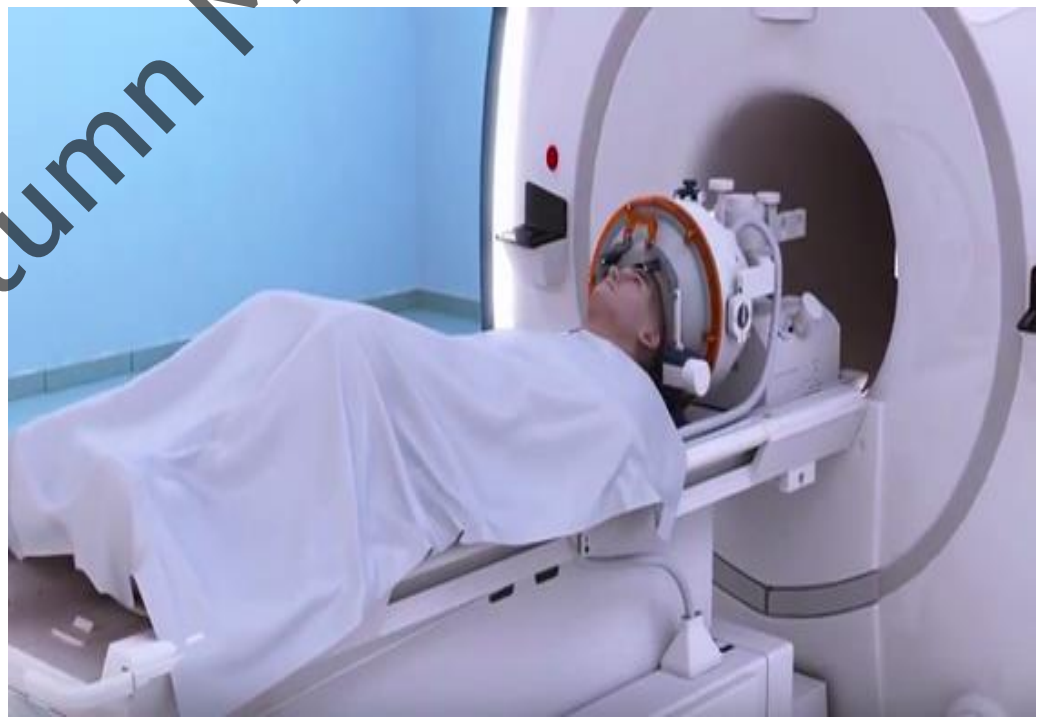
- **Lesion therapies**

Please refer to individual drugs SPCs on the electronic medicines compendium

Lesion therapy

- Pallidotomy or subthalamotomy for PD
- MRI-guided focussed ultrasound thalamotomy for Essential Tremor
- Role in PD



Insightec.com

Image provided by speaker

5-2-1

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- 1 hour of disabling dyskinesia a day

Antonini et al., Curr Med Res Opin, 2018 Dec

Questions

Thank You

PRESCRIBING INFORMATION DUODOPA 20mg/ml + 5mg/ml intestinal gel:

The Summary of Product Characteristics (SPC) should be read thoroughly for full prescribing information.

PRESENTATION: Intestinal gel containing 20mg/ml levodopa and 5mg/ml carbidopa monohydrate

INDICATION: Advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyperkinesia or dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results.

DOSAGE AND ADMINISTRATION: *Adults/Elderly:* Administration by portable pump directly into the duodenum or upper jejeunum via a percutaneous endoscopic gastrostomy (PEG) or radiological gastrojejunostomy tube. Duodopa is given initially as monotherapy and dose adjusted to optimal response for the individual patient. Total dose/day is composed of three individually adjusted doses: morning bolus, continuous maintenance and extra bolus doses. Total morning dose is usually 5-10ml (100-200mg levodopa) but not exceeding 15ml (300mg levodopa). Continuous maintenance dose should be between 1-10ml/hour (20-200mg levodopa) but usually 2-6ml/hour (40-120mg levodopa/hour). Extra bolus doses (if patient becomes hypokinetic during the day) are normally 0.5-2.0ml. The maximum recommended daily dose is 200 ml. Fine adjustments to the morning bolus, maintenance and extra bolus doses should be made over a few weeks after the initial dose setting. Sudden deterioration in response with recurring motor fluctuations indicates the tube may have moved from the duodenum into the stomach and needs repositioning. The medicine cassettes are for single use only and should not be used for longer than one day (up to 16 hours). In addition to daytime, if medically justified Duodopa may be administered during the night. Opened cassettes should not be reused. *Children:* There is no relevant indication for use in children and adolescents.

CONTRAINDICATIONS, WARNINGS, PRECAUTIONS: *Contraindications:* Hypersensitivity to ingredients, narrow-angle glaucoma, severe heart failure or cardiac arrhythmia, acute stroke. Conditions where adrenergics are contraindicated. Non-selective MAO-inhibitors and selective MAO type A inhibitors are contraindicated and should be withdrawn at least two weeks before starting Duodopa. Duodopa should not be used in patients with suspicious undiagnosed skin lesions or a history of melanoma

Warnings/Precautions: Not recommended for drug-induced extrapyramidal reactions. Caution in severe pulmonary or cardiovascular disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease or of convulsions, past or current psychosis, chronic wide-angle glaucoma, co-administration with antipsychotics with dopamine receptor blocking properties or with medicines which may cause orthostatic hypotension. In patients with a history of myocardial infarction who have residual nodal or ventricular arrhythmias, cardiac function should be monitored with care during initial dose adjustments. Monitor all patients for mental changes, depression with suicidal tendencies and other serious mental changes. Neuroleptic malignant like syndrome with secondary rhabdomyolysis has not been reported with Duodopa but may occur on abrupt dose reduction/withdrawal. Periodically evaluate hepatic, haematopoietic, cardiovascular and renal function during extended therapy. Increases in impulse control disorders have been reported and patients should be monitored and reviewed. Patients and providers are advised to monitor for melanomas on a regular basis when using Duodopa. Dose may need to be adjusted downwards to avoid levodopa induced dyskinesia. Sudden or gradual worsening of bradykinesia may indicate an obstruction in the device and should be investigated. Duodopa contains hydrazine, a degradation product of carbidopa that can be genotoxic and possibly carcinogenic. Reported complications in the clinical studies include bezoar, ileus, implant site erosion/ulcer, intestinal haemorrhage, intestinal ischaemia, intestinal obstruction, intestinal perforation, intussusception, pancreatitis, peritonitis, pneumoperitoneum and post-operative wound infection.

Drug Interactions: Antihypertensives, tricyclic antidepressants, anticholinergics, dopamine receptor antagonists, benzodiazepines, isoniazide, phenytoin, papaverine, sympathicomimetics, iron, protein-rich diet, COMT inhibitors (e.g. tolcapone, entacapone) and amantadine may increase levodopa related adverse events. Duodopa dose adjustment may be needed when used with these medicines. Duodopa can be taken with MAO type B inhibitors (e.g. selegiline) although serious orthostatic hypotension may occur and the dose of levodopa may need to be reduced.

PREGNANCY AND LACTATION: Potential risk in pregnancy is not known. Women should not breast feed.

ABILITY TO DRIVE AND OPERATE MACHINERY: Caution; Duodopa has a major influence on the ability to drive and use machines. Refrain if somnolence or sudden sleep onset occur.

SIDE EFFECTS: *Very Common & Common:* Anaemia, weight change (increase or decrease), amino acid level increased, decreased appetite, Vitamin B6 & B12 deficiency, anxiety, depression, insomnia, abnormal dreams, agitation, confusional state, hallucination, impulsive behaviour, psychotic disorder, sleep attacks, sleep disorder, dyskinesia, Parkinson's disease, dizziness, dystonia, headache, hypoaesthesia, on and off phenomenon, paraesthesia, polyneuropathy, somnolence, syncope, tremor, irregular heartbeat, orthostatic hypotension, hypertension, hypotension, dyspnoea, oropharyngeal pain, pneumonia, aspiration, nausea, constipation, abdominal distension, diarrhoea, dry mouth, dysgeusia, dyspepsia, dysphagia, flatulence, vomiting, contact dermatitis, hyperhidrosis, peripheral oedema, pruritus, rash, muscle spasms, neck pain, urinary incontinence or retention, fatigue, pain, asthenia and fall.

Serious side effects include: Anaphylactic reaction, leucopenia, thrombocytopenia, agranulocytosis, neuroleptic malignant syndrome, eye disorders, gastrointestinal bleeding and duodenal ulceration, malignant melanoma. *Laboratory values*: May change. **Other less common and rarely reported side effects are listed in the SPC.**

Complications of the device & surgery: *Very common & common:* postoperative wound infection, incision site cellulitis, post-procedural infection, abdominal pain, abdominal discomfort, upper abdominal pain, peritonitis, pneumo-peritoneum, excessive granulation tissue, complications of device insertion, device dislocation, device occlusion, incision site erythema, post procedural discharge, procedural pain, procedural site reaction, gastrointestinal stoma complication, incision site pain, postoperative ileus, post-procedural complication, discomfort or haemorrhage. Occlusions, kinks or knots in tube occur. **See SPC for complete listing of side effects.**

MARKETING AUTHORISATION NUMBER: PL 41042/0001

BASIC NHS PRICE: 7 x 100ml cassettes: £539 **LEGAL CATEGORY:** POM

FURTHER INFORMATION AVAILABLE FROM MARKETING AUTHORISATION HOLDER: AbbVie Ltd, Maidenhead, SL6 4UB

DATE OF REVISION OF PI: September 2017 PI/Duodopa/04

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk

Adverse events should also be reported to AbbVie at UK_PVVendor@abbvie.com