

HEALTH TECHNOLOGY BRIEFING SEPTEMBER 2020

Istradefylline for patients with Parkinson's disease experiencing end of dose fluctuations

NIHRIO ID	29100	NICE ID	10415
Developer/Company	Kyowa Kirin Ltd	UKPS ID	655521

Licensing and market availability plans	Completed phase III clinical trials
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SUMMARY

Istradefylline has been developed as an add-on treatment for adult patients receiving levodopa-based regimens for Parkinson's disease (PD), who are experiencing end of dose fluctuations. PD is neurodegenerative condition resulting from the loss of the dopamine-containing cells of the substantia nigra. There is no cure for PD and symptoms are usually seen in motor-development and include bradykinesia and tremor. OFF periods of treatment occur when the levodopa treatment provided starts to wear off, usually after long term use.

Istradefylline is a selective adenosine A_{2A} receptor inhibitor; these receptors are found in the region of the brain that suffers degeneration in PD. The treatment works by increasing the levels of dopamine in the substantia nigra. Current treatment for PD is associated with adverse events. Several phase III clinical trials have shown istradefylline, when taken orally, to be safe and effective in the treatment of PD during OFF periods. If licensed, istradefylline will provide a new therapeutic option to managing people with Parkinson's as the first non-dopaminergic add-on treatment.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

PROPOSED INDICATION

Istradefylline is indicated in adults as an add-on treatment to levodopa based regimens in patients with Parkinson's disease (PD) experiencing end of dose fluctuations.^a

TECHNOLOGY

DESCRIPTION

Istradefylline is a first-in-class selective adenosine A_{2A} receptor antagonist. These receptors are found in the basal ganglia, a region of the brain that suffers degeneration in PD and is also significantly involved in motor control. A_{2A} receptors are also expressed on GABAergic action of this pathway is thereby reduced.¹

In phase III trials (NCT01968031, NCT00199368, NCT00955045, NCT00199420, NCT00957203, NCT00199407, NCT00955526, NCT02610231, NCT00199394), participants received either 10mg, 20mg or 40mg istradefylline orally alongside a placebo.²⁻¹⁰

INNOVATION AND/OR ADVANTAGES

Current treatment approaches addressing motor fluctuations and the challenge of "off-time" management levodopa or the use of dopaminergic adjuncts such as dopamine agonists, monoamine oxidase-B inhibitors, or catechol-O-methyl transferase inhibitors.¹¹ Treatment with levodopa and dopaminergic adjuncts is associated with adverse events such as significant dyskinesia, hallucinations, and impulse control disorders.¹¹

A 2015 clinical trial showed that istradefylline treatment was well tolerated and produced a sustained reduction in off time in levodopa treated PD patients over a 52-week period.¹²

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

This product is not licensed for any other indications in the EU/UK.

This product is not currently in clinical trials for any other indication.

Common side effects of istradefylline include dyskinesia, dizziness, constipation, nausea, hallucinations and insomnia.¹³

PATIENT GROUP

DISEASE BACKGROUND

Parkinson's disease (PD) is a chronic, progressive neurodegenerative condition resulting from the loss of the dopamine-containing cells of the substantia nigra.¹⁴ The resulting dopamine deficiency within the basal ganglia leads to a movement disorder with classical Parkinsonian motor symptoms. PD is not clinically apparent until at least 50% of dopaminergic cell activity has been lost. Parkinsonism is an umbrella term for the clinical syndrome involving bradykinesia plus at least one of tremor, rigidity, and/or postural instability. Parkinson's disease is the most common form of parkinsonism. Other causes of parkinsonism include

^a Information provided by Kyowa Kirin

drug-induced parkinsonism, cerebrovascular disease, Lewy body dementia, multiple system atrophy, and progressive supranuclear palsy.¹⁴

Patients experience 'OFF' time where their medication is not as effective as when it is first administered; ideally levodopa is given in a way that prevents off-episodes occurring, but this isn't always possible without dyskinesia as levodopa levels peak. During 'OFF' periods, patients start to suffer with motor symptoms.¹¹

What initiates the loss of nerve cells in the substantia nigra is unclear. It is believed a combination of genetic changes and environmental factors are responsible. PD can be inherited but this is rare and is more associated with PD that is diagnosed in earlier life; this is associated with mutations in genes such as alpha synuclein, parkin, PINK1 and DJ-1.¹⁵ A change in the leucine-rich repeat kinase 2 (LRRK2) gene known as G2019S is probably the most common genetic variant linked to PD. In the UK, around one in 100 people with PD carry it. It's more common in North African and Jewish populations. People who carry this variant may develop the condition later in life and have around a 70% chance of being diagnosed by the age of 80.¹⁵ As well as single genetic changes that directly cause the condition, we now know that there are also changes that increase risk. The most common of these is having a variant in the glucocerebrosidase (GBA) gene. These changes are more common, but their effects are more subtle. Carrying one of them means you are more likely to develop PD but often only very slightly.¹⁵ The evidence linking environmental factors to PD suggests that pesticides and herbicides used in farming or traffic and pollution may contribute to its cause.¹⁶

Men are more likely to have PD with 2015 data showing that at all ages, the prevalence and incidence rates are higher for men. Similarly, older age is a risk factor with the incidence rates being highest in the 80-84 age category.¹⁷

The 3 main symptoms of PD affect physical movement; they are tremor, bradykinesia and rigidity. Other physical symptoms of PD include balance problems, anosmia, nerve pain, problems with urination, constipation, sexual dysfunction, dizziness, hyperhidrosis, drooling and insomnia. Similarly, cognitive and psychiatric symptoms can include depression, anxiety, mild cognitive impairment and dementia.¹⁸

CLINICAL NEED AND BURDEN OF DISEASE

The estimated number of people aged over 20 in England in 2018 with PD was 121,927; this results in a prevalence rate of around 218 per 100,000. The estimated number of new cases of PD per year in people aged over 45 in England is 15,465; this equates to an incidence rate of around 28 per 100,000. For the UK in 2015, the lifetime risk of being diagnosed with PD was 2.7% which is equivalent to 1 in 37 people being diagnosed with PD at some point in their life.¹⁷

Between 2012 and 2014, the death rate for Parkinsonism and other extrapyramidal disorders/tic disorder was 24.3 per 100,000 for those aged over 20. The mean age of death associated with these conditions was 82.¹⁹

According to hospital episode statistics for England in 2018-19 there were a total of 13,315 finished consultant episodes for PD (ICD-10 code G20) recorded as primary diagnosis of which 6,878 were recorded as admissions with a total of 1,624 day cases.²⁰

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Before starting adjuvant treatment for people with PD experiencing motor fluctuations, it is necessary to discuss the person's individual clinical circumstances, for example, their symptoms, comorbidities and risks from polypharmacy, the person's individual lifestyle circumstances, preferences, needs and goals and the potential benefits and harms of the different drug classes.¹¹ Antiparkinsonian medicines should not be withdrawn abruptly or allowed to fail suddenly due to poor absorption (for example, gastroenteritis, abdominal surgery) to avoid the potential for acute akinesia or neuroleptic malignant syndrome. As a first line treatment, levodopa is offered if the patient is in the early stages and their motor symptoms affect their quality of life.¹¹ A choice of dopamine agonists, levodopa or monoamine oxidase-B (MAO-B) inhibitors are recommended for patients in the early stages whose motor symptoms do not impact their quality of life. The above is also recommended when choosing an adjuvant for treatment during 'OFF' periods.¹¹

CURRENT TREATMENT OPTIONS

Current adjuvant treatments for PD when the patient is experiencing 'OFF' time:¹¹

- Dopamine agonists
- MAO-B inhibitors
- Catechol-O-methyl transferase (COMT) inhibitors
- Amantadine; this treatment has no evidence supporting an improvement in motor symptoms

Ergot-derived dopamine agonists must only be considered as an adjunct to levodopa for people with PD who have developed dyskinesia or motor fluctuations despite optimal levodopa therapy and whose symptoms are not adequately controlled with a non-ergot-derived dopamine agonist.

PLACE OF TECHNOLOGY

If licensed, istradefylline will provide a new therapeutic option to managing people with Parkinson's as the first available non-dopaminergic add-on treatment to levodopa-based regimens for adult patients.^b

CLINICAL TRIAL INFORMATION

Trial	NCT00199407 ; A 12-week, Double Blind, Placebo-controlled, Randomised, Parallel Group, Multicenter, Fixed Dose Study to Evaluate the Efficacy and Safety of a 20 mg/d Oral Dose of KW-6002 (Istradefylline) as Treatment for Parkinson's Disease in Patients With Motor Response Complications on Levodopa/Carbidopa Therapy Phase III - Completed Location(s): USA Study completion date: November 2005
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^b Information provided by Kyowa Kirin on UK PharmaScan

Trial design	Randomised, parallel assignment, double-blinded, placebo-controlled
Population	N = 230; 30 years and over; have PD in stage 2-4 in the OFF state; on at least 3 doses of levodopa/carbidopa per day for at least one year
Intervention(s)	Istradefylline 20mg/day orally
Comparator(s)	Matched placebo
Outcome(s)	To establish the efficacy of a 20 mg/d dose of istradefylline for reducing the percentage of OFF time in patients with advanced Parkinson's disease (PD) treated with levodopa/carbidopa. See trial record for full list of other outcomes
Results (efficacy)	<ul style="list-style-type: none"> Istradefylline-treated subjects had significant placebo-corrected reductions in daily OFF time from baseline to endpoint: 4.6% (P = 0.03) and 0.7 hours (P = 0.03)²¹
Results (safety)	<ul style="list-style-type: none"> Istradefylline was well tolerated, with 6 (5.2%) istradefylline-treated and 7 (6.1%) placebo-treated subjects withdrawing from the study because of adverse events. Dyskinesia, light headedness, tremor, constipation, and weight decrease were reported more often with istradefylline than placebo.²¹

Trial	6002-009, NCT00955526 ; Placebo-Controlled, Double-Blind, Parallel Group, Fixed Dose Study of KW-6002 (Istradefylline) in the Treatment of Parkinson's Disease (Phase 3) Phase III – Completed Location(s): Japan Study completion date: February 2011	6002-010, NCT00957203 ; Long-Term Safety Study of KW-6002 (Istradefylline) in the Treatment of Parkinson's Disease (Phase 3) Phase III – Completed Location(s): Japan Study completion date: September 2011
Trial design	Randomised, parallel assignment, double-blinded, placebo-controlled	Single group assignment, open-label
Population	N = 373; 20 years and older; PD stage 2-4 in the OFF state; have an average of 2 hours OFF time on 24-hour diaries; on at least 3 doses levodopa/dopa-decarboxylase inhibitor for at least one year)	N = 308; 20 years and older; Completion of the study 6002-009
Intervention(s)	<ul style="list-style-type: none"> Istradefylline 20mg orally (two 10mg tablets once daily for 12 weeks) Istradefylline 40mg orally (two 20mg tablets orally once daily for 12 weeks) 	<ul style="list-style-type: none"> Istradefylline 20mg orally Istradefylline 40mg orally
Comparator(s)	Two placebo tablets once daily for 12 weeks	No comparator
Outcome(s)	Reducing the mean total hours of awake time per day spent in the OFF state See trial record for full list of other outcomes	Adverse events See trial record for full list of other outcomes

Results (efficacy)	<ul style="list-style-type: none"> The change in daily OFF time was significantly reduced in the istradefylline 20 mg/day (-0.99 hours, P=.003) and istradefylline 40 mg/day (-0.96 hours, P=.003) groups compared with the placebo group (-0.23 hours).²² 	<ul style="list-style-type: none"> The mean change in the daily off time from day 1 was -0.65 hour in week 2, fluctuating between -0.71 and -0.04 hour until week 52 in patients who had previously taken placebo in the preceding double-blind study. The OFF time reduction from baseline of the double-blind study remained at similar levels between weeks 2 and 52 in patients who had previously taken istradefylline 20 and 40 mg/d in the preceding double-blind study.¹²
Results (safety)	The most common adverse event was dyskinesia (placebo, 4.0%; istradefylline 20 mg/day, 13.0%; istradefylline 40 mg/day, 12.1%). ²²	The most frequently reported treatment-emergent adverse events were nasopharyngitis (24.4%) and dyskinesia (21.4%). ¹²

Trial	<p>NCT00199420; A 12-week, Double Blind, Placebo-controlled, Randomized, Parallel Group, Multicenter, Fixed Dose Study to Evaluate the Efficacy and Safety of 10, 20 and 40 mg/d Oral Dose of KW-6002 (Istradefylline) as Treatment for Parkinson's Disease in Patients With Motor Response Complications on Levodopa/Carbidopa Therapy. Phase III - Completed Location(s): USA Study completion date: November 2005</p>
Trial design	Randomised, parallel assignment, double-blinded, placebo-controlled
Population	N = 610 ^c ; 30 years and older; on levodopa/carbidopa for at least one year; have an average of 180 minutes of OFF time on two 24-hour diaries
Intervention(s)	<ul style="list-style-type: none"> 10mg/day istradefylline orally for 12 weeks 20mg/day istradefylline orally for 12 weeks 40mg/day istradefylline orally for 12 weeks
Comparator(s)	Matched placebo
Outcome(s)	<p>To establish the efficacy of 10, 20 and 40 mg/day istradefylline for reducing the percentage of OFF time in patients with advanced Parkinson's disease (PD) treated with levodopa/carbidopa</p> <p>See trial record for full list of other outcomes</p>
Results (efficacy)	At endpoint, the amount and percentage of OFF time did not differ between Istradefylline and placebo, however a dose-ordering response was observed. Changes from baseline in the UPDRS motor score in the on state for the 40 mg were

^c Information provided by Kyowa Kirin

	modest but significant compared to placebo (2.9 vs. 0.8; p < 0.05). ²³
Results (safety)	<ul style="list-style-type: none"> ▪ Number (%) of subjects with any TEAE: placebo 115 (76.2); 10mg istradefylline 126 (82.4); 20mg istradefylline 125 (83.9); 40mg istradefylline 128 (84.2) ▪ Number (%) subjects with dyskinesia: placebo 29 (19.2); 10mg istradefylline 33 (21.6); 20mg istradefylline 25 (16.8); 40mg istradefylline 40 (26.3).^d

Trial	<p>NCT00199394; A 16-week, Double-Blind, Placebo-Controlled, Randomised, Parallel-Group, Multicentre, International Study to Evaluate the Efficacy and Safety of 40 mg/Day KW-6002 (Istradefylline) and That of Entacapone Versus Placebo as Treatment for Parkinson's Disease in Patients With Motor Response Complications on Levodopa Therapy. Phase III - Completed Location(s): EU (incl. UK), US, Canada plus more than 4 other countries.^d Study completion date: October 2005</p>	
Trial design	Randomised, parallel assignment, double-blinded, placebo-controlled	
Population	N = 464 ^d ; 30 years and older; received levodopa treatment for at least one year; have an average of at least three hours OFF time as recorded in two 24-hour ON/OFF diaries	
Intervention(s)	40mg/day istradefylline orally for 16 weeks	
Comparator(s)	Matched placebo	
Outcome(s)	Change in percentage OFF time between baseline and endpoint assessed by patient diaries at endpoint. See trial record for full list of other outcomes	
Results (efficacy)	<ul style="list-style-type: none"> ▪ The LS mean changes from baseline to endpoint in the percentage of awake time per day spent in the OFF state were -5.14% (istradefylline 40 mg/day, -7.82% (entacapone), and -4.53%, (placebo).^d 	
Results (safety)	<ul style="list-style-type: none"> ▪ The incidence of TEAEs regardless of relationship to study drug were similar across all treatment groups: 64.8% (istradefylline 40mg/day), 66.0% (entacapone), and 63.8% (placebo) ▪ The most frequent TEAEs for the Safety population were dyskinesia, worsening of Parkinson's disease, weight decreased, constipation, and nausea ▪ TEAEs leading to study discontinuation were experienced by 7 (4.4%) subjects in the istradefylline 40 mg/day group, 10 (6.5%) subjects in the entacapone group, and 10 (6.6%) subjects in the placebo group.^d 	

Trial	NCT01968031 ; A Phase 3, 12-week, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study to	NCT02610231 ; A Phase 3, Long-term, Open-label Study of Istradefylline in Subjects With
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^d Information provided by Kyowa Kirin

	<p>Evaluate the Efficacy of Oral Istradefylline 20 and 40 mg/Day as Treatment for Subjects With Moderate to Severe Parkinson's Disease</p> <p>Phase III - Completed</p> <p>Location(s): EU (not incl. UK), US, Canada and Israel</p> <p>Study completion date: October 2016</p>	<p>Moderate to Severe Parkinson's Disease</p> <p>Phase III - Completed</p> <p>Location(s): EU (not incl. UK), US, Canada and Israel</p> <p>Study completion date: December 2017</p>
Trial design	Randomised, parallel assignment, quadruple-blinded, placebo-controlled	Single group assignment, open-label
Population	N = 613; 30 years and older; PD stage 2- 4 in the ON state; On levodopa therapy for at least 1 year with beneficial clinical response at the baseline visit; Have an average of two hours of OFF time per day	N = 239; subjects who completed Study No. 6002-014 inclusive of the 30-day follow-up period; currently taking levodopa combination (carbidopa/levodopa or benserazide/levodopa) therapy plus at least one adjunctive PD medication
Intervention(s)	<ul style="list-style-type: none"> ▪ Istradefylline 20mg/day orally for 12 weeks ▪ Istradefylline 40mg/day orally for 12 weeks 	<ul style="list-style-type: none"> ▪ Istradefylline 20mg/day orally for 52 weeks ▪ Istradefylline 40mg/day orally for 52 weeks ▪ Subjects will start on 20mg/day with an option for dose adjustment to 40mg at week 12. Subjects who had a dose adjustment to 40 mg/d can have their dose decreased to 20 mg/d by the Investigator at a second unscheduled dose adjustment visit if there are tolerability issues. The istradefylline dose should remain fixed between Week 26 to Week 52
Comparator(s)	Matched placebo	No comparator
Outcome(s)	<p>The primary efficacy variable is change from Baseline in the total hours of awake time per day spent in the OFF state. [Time Frame: Baseline, Week 2, Week 6, Week 10 and Week 12.]</p> <p>See trial record for full list of other outcomes</p>	<p>Evaluation of the Long-term Safety and Tolerability of Oral Istradefylline (20mg or 40mg/Day [mg/d]) [Time Frame: From screening through to study completion, an average of 52 weeks]</p> <p>See trial record for full list of other outcomes</p>
Results (efficacy)	<ul style="list-style-type: none"> ▪ The LS mean changes from baseline were -1.20 hours (istradefylline 20 mg/day), -1.15 hours (istradefylline 40 mg/day), and -0.88 hours (placebo) 	<ul style="list-style-type: none"> ▪ A total of 243 subjects were enrolled in this study ▪ Of those who participated, 239 subjects (98.4%) received at least 1 dose of study drug

	<ul style="list-style-type: none"> For istradefylline 20 and 40 mg/day, the change from baseline in the reduction in OFF time was seen as early as Week 2 and was maintained through Week 12.^e 	<p>and 179 subjects (73.7%) completed the 52-week treatment period. Overall, 64 (26.3%) subjects prematurely discontinued from the study. The most common reasons for premature discontinuation were withdrawal of consent 27 (11.1%) subjects and AEs 25 (10.3%) subjects^e</p>
Results (safety)	<ul style="list-style-type: none"> The incidence TEAEs regardless of relationship to study drug were similar across all treatment groups: placebo (55.9%), istradefylline 20 mg/day (58.7%), and 40 mg/day (64.7%) The most frequently reported TEAE was dyskinesia reported in 14 (6.9%) istradefylline 20mg/day, 23 (11.4%) istradefylline 40mg/day, and 34 (16.4%) placebo A total of 44 subjects were discontinued because of TEAEs, 13 (6.4%) placebo, 10 (5.0%) istradefylline 20mg/day, and 21 (10.1%) istradefylline 40mg/day.^e 	<ul style="list-style-type: none"> Of the 239 subjects who received study drug, 59% of subjects experienced at least one treatment-emergent adverse event (TEAE), regardless of relationship to study drug, and 12.6% of subjects experienced treatment emergent SAEs during the study. The most frequently reported TEAE was dyskinesia reported by 18% of subjects. Other TEAEs reported by at least 5% of subjects included fall (12.1%), and Parkinson's disease [worsening] (7.9%).^e

Trial	<p>NCT00955045; A Long-Term, Multicenter, Open-Label, Safety Study With a Flexible Dose Range of KW-6002 as Treatment for Parkinson's Disease in Patients With Motor Response Complications on Levodopa/Carbidopa Therapy Phase II/III - Completed Location(s): US Study completion date: October 2003</p>
Trial design	Open-label, long-term
Population	30 years and older; had completed participation in a prior double-blind istradefylline trial; had predictable end-of-dose wearing-off; had been treated with levodopa for at least 1 year
Intervention(s)	<ul style="list-style-type: none"> The starting dose of istradefylline was 40 mg/day. The dose was to remain constant for the first 2 weeks of treatment <p>After 2 weeks, the Investigator could adjust the dose of istradefylline up to 60 mg/day to achieve the desired therapeutic response or down to 20 mg/day in order to reduce adverse events.^e</p>
Comparator(s)	No comparator
Outcome(s)	Establish the long-term tolerability and safety of istradefylline treatment in subjects with Parkinson's disease treated with levodopa/carbidopa

^e Information provided by Kyowa Kirin

	The prespecified primary efficacy endpoints included the change from baseline in OFF time as hours per day and as percentage of awake time. ^f
Results (efficacy)	Results from these open-label study demonstrated that istradefylline 20 and 40 mg/day maintained the reduction in OFF time and the increase in ON time without troublesome dyskinesia for 52 weeks
Results (safety)	<ul style="list-style-type: none"> The most frequently reported TEAEs for subjects in the Prior Istradefylline group were dyskinesia/aggravated dyskinesia (24.1%), dizziness (13.7%), worsening Parkinson's disease (13.3%), nausea (12.4%), insomnia (11.4%), and accident (10.8%). The most frequently reported TEAEs for subjects in the Prior Placebo/Group B group were dyskinesia/aggravated dyskinesia (32.6%), dizziness (23.8%), nausea (17.1%), accident (13.8%), and insomnia (12.2%).^f

Trial	<p>NCT00199368; A Long-Term, Multicenter, Open-Label Safety Study With Oral 20 or 40 mg/d Doses of KW-6002 (Istradefylline) as Treatment for Parkinson's Disease in Patients With Motor Response Complications on Levodopa Therapy.</p> <p>Phase III - Completed</p> <p>Location(s): EU (incl. UK), US, Canada plus more than 4 other countries.^f</p> <p>Study completion date: March 2007</p>
Trial design	Non-randomised, single group assignments, open-label
Population	N = 1100; 30 years and older; completion of study 6002-EU-007, 6002-US-013 or 6002-US-018
Intervention(s)	<ul style="list-style-type: none"> Istradefylline 20mg/day orally Istradefylline 40mg/day orally
Comparator(s)	No comparator
Outcome(s)	To confirm the long-term tolerability and safety of oral 20 or 40 mg/day doses of istradefylline.
Results (efficacy)	-
Results (safety)	<ul style="list-style-type: none"> For 68.3% of subjects, TEAEs were assessed by Investigators as related to study drug. The most common drug-related TEAEs were dyskinesia (29.9%), worsening of Parkinson's disease (12.1%), constipation (7.0%), hallucination (6.9%), and insomnia (6.7%) TEAEs that led to study discontinuation were reported for 11.5% of subjects (143 subjects) and were assessed as drug-related for 8.4% of subjects (104 subjects).^f

ESTIMATED COST

The estimated cost of istradefylline is not yet known.

^f Information provided by Kyowa Kirin

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Parkinson's disease in adults (NG71). July 2017.
- NICE quality standard. Parkinson's disease (QS164). February 2018.
- NICE interventional procedure guidance. Subthalamotomy for Parkinson's disease (IPG65). June 2004.
- NICE interventional procedure guidance. Deep brain stimulation for Parkinson's disease (IPG19). November 2003.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/S/a.

OTHER GUIDANCE

- NICE Clinical Knowledge Summary. Parkinson's Disease. February 2018.¹⁴

ADDITIONAL INFORMATION

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 7. Clinicaltrials.gov. A Study of Istradefylline (KW-6002) for the Treatment of Parkinson's Disease in Patients Taking Levodopa. Trial ID: NCT00199407. Status: Completed. Available from: <https://clinicaltrials.gov/ct2/show/study/NCT00199407> [Accessed 12 August 2020]
 8. Clinicaltrials.gov. Study of KW-6002 (Istradefylline) for the Treatment of Parkinson's Disease in Patients Taking Levodopa (6002-009). Trial ID: NCT00955526. Status: Completed. Available from: <https://clinicaltrials.gov/ct2/show/NCT00955526> [Accessed 12 August 2020]
 9. Clinicaltrials.gov. Long Term Study of Istradefylline in Subjects With Moderate to Severe Parkinson's Disease. Trial ID: NCT02610231. Status: Completed. Available from: <https://clinicaltrials.gov/ct2/show/NCT02610231> [Accessed 12 August 2020]
 10. Clinicaltrials.gov. A Study of Istradefylline (KW-6002) for the Treatment of Parkinson's Disease. Trial ID: NCT00199394. Status: Completed. Available from: <https://clinicaltrials.gov/ct2/show/study/NCT00199394> [Accessed 12 August 2020]
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