Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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Re-Submission

co-careldopa (levodopa 20mg/mL and carbidopa monohydrate 5mg/mL) intestinal gel (Duodopa®) SMC No. (316/06)

Abbvie Ltd.

06 May 2016

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a 2nd resubmission assessed under the orphan process

co-careldopa (Duodopa®) intestinal gel is accepted for restricted use within NHS Scotland.

Indication under review: treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyper-/dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results.

SMC restriction: for use in patients not eligible for deep brain stimulation.

In a phase III, 12-week study, co-careldopa intestinal gel significantly reduced 'off' time compared with oral levodopa plus a dopa decarboxylase inhibitor.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of co-careldopa intestinal gel. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

For the treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyper-/dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results.

Dosing Information

By continuous intestinal administration directly into the duodenum or upper jejunum by a permanent tube via percutaneous endoscopic gastrostomy. Establishment of the transabdominal port and dose adjustments should be carried out in association with a neurological clinic.

The total daily dose is delivered through a portable CADD-legacy 1400 pump and comprises three individually adjusted doses: the morning bolus dose, the continuous maintenance dose and extra bolus doses administered over approximately 16 hours. The total morning dose is usually equivalent to 100mg to 200mg levodopa, and should not exceed 300mg levodopa. The continuous maintenance dose should be kept within a range of 20mg to 200mg levodopa per hour and is usually 40mg to 120mg levodopa per hour. The maximum recommended daily dose is 4000mg levodopa. In exceptional cases a higher dose may be needed. Extra bolus doses, usually of 10mg to 40mg levodopa can be given as required and adjusted individually. In rare cases a higher dose may be needed. If the need for extra bolus doses exceeds five per day then the maintenance dose should be increased.

Co-careldopa intestinal gel should be given initially as monotherapy. If required, other medicinal products for Parkinson's disease can be taken concurrently.

Product availability date

21 January 2004. Co-careldopa intestinal gel meets SMC criteria for orphan status in this treatment setting.

Summary of evidence on comparative efficacy

Parkinson's disease is a chronic, progressive, neurodegenerative condition which arises due to the death of dopamine-containing cells in the substantia nigra.[1,2] Co-careldopa intestinal gel is a combination of levodopa and carbidopa in a 4:1 ratio. Levodopa exerts its effect by undergoing decarboxylation to dopamine in the brain, and is administered in combination with carbidopa which inhibits extracerebral levodopa decarboxylation. Continuous infusion of the intestinal gel aims to reduce motor fluctuations and 'off' time for patients with advanced Parkinson's disease as a result of less variable plasma concentrations.[3]

The submitting company has requested that SMC considers co-careldopa intestinal gel when positioned for use in patients that are not eligible for deep brain stimulation (DBS).

Study S187.3.001/002 was a phase III, randomised, placebo-controlled, double-blind, 12-week study to assess the efficacy and safety of co-careldopa intestinal gel for the control of advanced Parkinson's disease with motor complications.[4,5] Long-term safety and efficacy was assessed in a 52-week, open-label extension study (S187.3.003).[6,7] The studies recruited adults aged at least 30 years old with advanced Parkinson's disease complicated by 'off' periods which could not be satisfactorily controlled by an adequate trial of oral co-careldopa, a dopamine agonist, and either a catechol-O-methyl

transferase (COMT) inhibitor or monoamine-oxidase-B (MAO-B) inhibitor. Eligible patients were required to be on a stable dose of oral immediate-release co-careldopa capsules for at least four weeks prior to study enrolment, have recognisable 'on' and 'off' time, and experience a minimum of three hours 'off' time each day. Concurrent anti-parkinsonian medicines (excluding apomorphine) were permitted if patients were stabilised on treatment for at least four weeks prior to randomisation and the dose did not change during the studies. The baseline mean (standard deviation) 'off' time per day in the co-careldopa intestinal gel and oral immediate-release capsule groups, respectively, was 6.3 (1.7) hours and 7.0 (2.1) hours, and the baseline mean (standard deviation) 'on' time without troublesome dyskinesia per day was 8.7 (2.0) hours and 7.8 (2.5) hours.

Patients were admitted to hospital for jejunal placement of a percutaneous gastrojejunostomy tube and then randomised equally to treatment with oral immediate-release co-careldopa capsules (levodopa 100mg, carbidopa 25mg) and placebo intestinal gel infusion (n=34), or to co-careldopa intestinal gel infusion (levodopa 20mg/mL , carbidopa 5mg/mL) and oral placebo (n=37). The treatments were initially administered at the patient's usual daily levodopa dose, and then adjusted accordingly during a four-week titration phase. During the eight-week maintenance phase, the oral capsules were administered in divided doses and the intestinal gel was administered as a morning bolus dose followed by a continuous infusion over the course of each patient's waking day for approximately 16 hours. Rescue therapy with open-label oral immediate-release co-careldopa for persistent 'off' episodes was permitted for use by patients in both groups.

A 24-hour home-diary assessment of motor status was completed by patients at 30-minute intervals, for three consecutive days immediately prior to each visit. Patients recorded if they were in an 'off' state, 'on' state without dyskinesia, 'on' state with non-troublesome dyskinesia, 'on' state with troublesome dyskinesia, or asleep. The primary outcome was the change from baseline to final visit (week 12) in the mean number of 'off' hours recorded in the home diary during the three days before each visit, normalised to a 16-hour waking day. Treatment with co-careldopa intestinal gel achieved a significantly greater reduction (improvement) in 'off' time compared with oral immediate-release co-careldopa capsules. Least squares mean change (standard error) from baseline to week 12 in 'off' time was -4.04 (0.65) hours per day for the intestinal gel and -2.14 (0.66) hours per day for the oral immediate-release capsules; treatment difference -1.91 (95% confidence interval [CI]: -3.05 to -0.76), p=0.0015.

The key secondary outcome assessed change from baseline to week 12 in 'on' time without troublesome dyskinesia, in which co-careldopa intestinal gel demonstrated a significantly greater improvement compared with oral immediate-release co-careldopa capsules. Least squares mean change (standard error) from baseline to week 12 was 4.11 (0.75) hours per day for the intestinal gel and 2.24 (0.76) hours per day for the oral immediate-release capsules; treatment difference 1.86 (95% CI: 0.56 to 3.17), p=0.0059. Other secondary outcome measures included the change from baseline in 'on' time without dyskinesia, 'on' time with non-troublesome dyskinesia, 'on' time with troublesome dyskinesia, Parkinson's Disease Questionnaire (PDQ-39) summary index, Clinical Global Impression–Improvement (CGI-I) score, Unified Parkinson's Disease Rating Scale (UPDRS), Zarit caregiver Burden Interview (ZBI) score, and EuroQual quality of life-5 Dimensions (EQ-5D) summary index. Compared with oral immediate-release co-careldopa capsules, the intestinal gel was found to provide a significantly greater improvement (from baseline to week 12) in 'on' time without dyskinesia, PDQ-39 summary index score, mean CGI-I score at final assessment, and UPDRS part II score. There were no significant improvements in the other secondary outcomes.

A total of 62 patients entered the extension study (S187.3.003) and received treatment with co-careldopa intestinal gel. Patients were designated based on their allocation in the previous 12-week study as 'continuing' the gel (n=33) or 'naive' to the gel (n=29). The primary outcome evaluated long-term safety; efficacy and quality of life measures were secondary outcomes. A significant reduction (improvement) in 'off' time from baseline of the extension study to week 52 was demonstrated in the

intestinal gel 'naive' group only; mean change (standard deviation) from baseline to week 52 in 'off' time was -2.34 (2.78) hours per day (95% CI: -3.44 to -1.24), p<0.001. Patients in the 'continuing' group maintained their improved 'off' time achieved during the 12-week study although further improvement from baseline of extension phase was not statistically significant. A significant improvement in 'on' time without troublesome dyskinesia was demonstrated from baseline to final visit (week 52) in both the intestinal gel 'naive' and 'continuation' groups. A significant improvement was found in the mean CGI-I score at final assessment in both groups (p<0.001), however there were no significant improvements in either group for the UPDRS total score, PDQ-39 summary index, EQ-5D summary index or ZBI score.

A further phase III, open-label, single-arm, 54-week study (S187.3.004) of monotherapy with co-careldopa intestinal gel (n=354) assessed efficacy and quality of life measures as secondary outcomes (safety was assessed as the primary outcome). A significant reduction in 'off' time was demonstrated from baseline to week 54 with a mean change (standard deviation) of -4.4 (2.9) hours per day, p<0.001. There was also a significant improvement in 'on' time without troublesome dyskinesia of 4.8 (3.4) hours per day (p<0.001), and a reduction in 'on' time with troublesome dyskinesia of -0.4 (2.8) hours per day (p=0.023). Significant improvements were also demonstrated for UPDRS, PDQ-39, EQ-5D Summary Index and the EuroQoL visual analogue scale (EQ-VAS), p<0.001.[8] The results of this study have been used to support the economic case.

Data from a number of case-control and observational studies were also presented in the submission. A UK-based, case-control study involving 26 patients compared co-careldopa intestinal gel (n=17) with conventional treatments for Parkinson's disease (n=9) in patients responsive to levodopa with dyskinesias and considered unsuitable for/intolerant of apomorphine/DBS. Statistically significant improvements in the UPDRS scales III and IV, PDQ-8 and Non-Motor Symptoms Scale (NMSS) total score were observed from baseline to six months in the intestinal gel group compared with the conventional treatment group (all p<0.027).[9] Interim data were also presented for an ongoing, 24-month, multinational, observational study which recruited 375 patients with advanced Parkinson's disease and motor complications treated with co-careldopa intestinal gel. Twelve-month interim results demonstrated a statistically significant reduction in mean (standard deviation) daily 'off' time of -4.7 (3.4) hours (p<0.0001) and in 'on' time with dyskinesias of -1.7 (5.0) hours (p= 0.0228) from baseline to month 12. Statistically significant improvements were also observed between baseline and month 12 for UPDRS II and III 'on' scores, NMSS, and PDQ-8 score.[10]

Summary of evidence on comparative safety

In study S187.3.001/002, adverse events were reported by 95% (35/37) and 100% (34/34) of patients in the co-careldopa intestinal gel and oral immediate-release capsule groups, respectively, with serious adverse events occurring in 14% (5/37) and 21% (7/34) of patients. Treatment discontinuation as a result of adverse events occurred in 2.3% (1/37) of patients in the intestinal gel group, and in 5.9% (2/34) in the oral immediate-release capsule group. Overall, two patients discontinued the study as a result of complications from surgery.[4]

The majority of adverse events were related to device complications (92% [34/37] in the intestinal gel group and 85% [29/34] in the oral immediate-release capsule group) including pump malfunctions, intestinal tube dislocation, and the insertion of the percutaneous gastrojejunostomy and stoma. Other reported adverse events that were likely to be due to the device included procedural pain (30% [11/37] and 35% [12/34] in the intestinal gel and oral immediate-release capsule groups, respectively), and wound infection (11% [4/37] and 24% [8/34]). Abdominal pain (51% [19/37] and 32% [11/34]), nausea (30% [11/37] and 21% [7/34]), constipation (22% [8/37] and 21% [7/34]), and orthostatic hypotension (14% [5/37] and 24% [8/34]) were also reported.[4]

Similar results were observed in the extension study, with adverse events reported in 95% (59/62) of patients, and serious adverse events in 23% (14/62). Treatment discontinuation as a result of adverse events occurred in 4.8% (3/62) of patients. Frequently reported adverse events included injection site erythema (29% [18/62]), falls (21% [13/62]), decreased vitamin B6 (21% [13/62]), and postoperative wound infection (18% [11/62]). Serious adverse events included complication of device insertion (4.8% [3/62]), abdominal pain (3.2% [2/62]), asthenia (3.2% [2/62]) and pneumonia (3.2% [2/62]).[6]

Summary of clinical effectiveness issues

Parkinson's disease is characterised by the core features of bradykinesia, rigidity, tremor and postural instability ('motor symptoms'). The pharmacological agents currently used in Parkinson's disease only provide symptomatic relief.[11] The mainstay of treatment is levodopa in combination with a dopa decarboxylase inhibitor; however, fluctuating response to treatment can occur with continued use of levodopa, referred to as 'on' states (control of motor symptoms) and 'off' states (less control of motor symptoms). For the management of motor complications in advanced Parkinson's disease, Scottish guidelines recommend treatment with dopamine agonists, MAO-B inhibitors and COMT inhibitors taken as adjuvants with levodopa. Strategies used in the management of motor complications include the manipulation of oral/topical treatments, the use of more invasive treatments (e.g. apomorphine infusion or intraduodenal levodopa), and neurosurgery (e.g. DBS).[1] Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area in patients who are not suitable for, or intolerant of, apomorphine/DBS and consider co-careldopa intestinal gel to be a therapeutic advancement in the management of motor fluctuations in those patients who have failed treatment with apomorphine.

Co-careldopa intestinal gel has been designated an orphan medicine by the European Medicines Agency (EMA). The submitting company has requested that SMC considers co-careldopa intestinal gel when positioned for use in patients that are not eligible for DBS. In the studies presented, previous surgery for Parkinson's disease was not permitted. The submitting company has advised that since patients who were eligible for DBS would have already received it, the studies reflect the proposed positioning.

In the phase III, 12-week S187.3.001/002 study, co-careldopa intestinal gel significantly improved 'off' time (a reduction of approximately two hours per day) and 'on' time without troublesome dyskinesia (an increase of approximately two hours per day) compared with co-careldopa oral immediate-release capsules. The magnitude of effect of these results in clinical practice is unclear; however they may significantly impact on the daily lives of patients with the disease. It was noted by the authors that as a result of recruiting patients with at least three hours of 'off' time per day and very low baseline levels of dyskinesia, the study could not provide evidence of the effect of the intestinal gel on patients with established dyskinesia. Further evidence was provided by the 52-week extension study, demonstrating a continued safety profile and significant improvement in 'on' time without troublesome dyskinesia. A significant reduction in 'off' time was only demonstrated in the 'naive' treatment group; the authors note this may be due to patients in the 'continued' treatment group having potentially reached maximal improvement in the previous study, or as a result of disease progression. The extension study was limited by the use of open-label treatments, the absence of a control group and a small sample size. No significant improvements over the long term were observed for the quality of life measures PDQ-39, ZBI, or EQ-5D. In the 54-week S187.004 study, significant improvements from baseline were demonstrated for 'off' time and in the quality of life measures PDQ-39, EQ-5D and EQ-VAS, although the study was limited by its open-label design and the absence of a control group. Concomitant use of other anti-parkinsonian medicines was permitted in these phase III studies, with

the exception of apomorphine; data on the comparative and combined use of the intestinal gel with apomorphine are therefore lacking.

Patients must undergo surgical placement of a permanent percutaneous endoscopic gastrostomy with jejunal tube (PEG-J), via which the intestinal gel is administered. This is an intervention that is associated with potentially serious complications.[3,4] Small patient numbers are anticipated to be eligible for this treatment in Scotland; however, the training of clinicians, nurses and patients on administration of the intestinal gel and the associated stoma maintenance is likely to have service implications.

Summary of patient and clinician engagement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of co-careldopa intestinal gel, as an orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Advanced Parkinson's leads to a much reduced level of independence with little or no quality of life. In particular, fluctuations between the 'on' state (dyskinetic and mobile) and 'off' state (frozen and akinetic) can be unpredictable and have a significant impact on quality of life.

- Eventually oral and transdermal medication result in peaks and troughs of activity and is unable to control symptoms. Co-careldopa intestinal gel is the only advanced therapy option for patients who are not eligible for DBS and in whom subcutaneous apomorphine is unable to control unpredictable on/off symptoms.

- Continuous administration of levodopa (via co-careldopa intestinal gel) is able to provide a substantial reduction in the fluctuation between 'on' and 'off' states resulting in greater 'on' time, and may allow patients to regain independence, undertake normal activities and experience major improvements in quality of life. Clinicians also noted emerging evidence that co-careldopa intestinal gel may reduce distressing non-motor symptoms such as dysphoria, anxiety and aggression.

- The co-careldopa intestinal gel delivery system is burdensome and invasive, requiring inpatient stay for surgery to fit the duodenal tube. It requires careful selection of patients alongside ongoing monitoring to confirm maintenance of benefit.

- Clinicians noted that co-careldopa intestinal gel may be associated with substantial cost offsets due to reduced burden on health and social care services. Similarly, it may be able to reduce the burden on family members who have often given up work to become full-time carers.
- The PACE group felt strongly that this medicine should be made available in NHS Scotland in-line with the company positioning for the small number of suitable patients who have exhausted all other therapies.

Additional Patient and Carer Involvement

We received patient group submissions from Cure Parkinson's Trust and Parkinson's UK, which are both registered charities. The Cure Parkinson's Trust has received 0.6% pharmaceutical company

funding in the past two years, including from the submitting company. Parkinson's UK in Scotland has received <0.01%, but not from the submitting company. A representative from Parkinson's UK in Scotland also participated in the PACE meeting. Cure Parkinson's Trust did not participate in the PACE meeting, although highlighted many of the points captured through PACE.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing co-careldopa intestinal gel to standard care, which includes conventional oral/topical medication with or without subcutaneous apomorphine infusion for use in patients that are not eligible for DBS. The proportion of patients in the standard care group who received subcutaneous apomorphine infusion in addition to other treatments was 9%, with 91% assumed to receive oral/topical PD medication alone. The analysis focused on patients with advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyper-/dsykinesia when available combinations of Parkinson medicinal products have not given satisfactory results.

A Markov model consisting of 25 health states and one death state was submitted, whereby each health state was defined according to the combination of a patient's Hoehn and Yahr (H&Y) and 'off' scores, which assessed progression of patients motor symptoms and proportion of waking time spent in 'off' state respectively. Patients moved through the model based on transition probabilities. The time horizon used in the analysis was 20 years. Clinical experts have indicated that standard care is an appropriate comparator, and that apomorphine is used in a proportion of patients in Scotland.

The clinical data for the co-careldopa intestinal gel were taken from the S.187.3.004 single-arm study and several published literature sources. In the economic analysis, short term (1 year) efficacy associated with co-careldopa treatment was provided, based on patient distributions according to the H&Y and 'off' scores at various time points of the S.187.3.004 study i.e. baseline, 6 months and 1 year. It should be noted that data were not available for the advanced Parkinson's disease cohort (64 patients) at 12 months. Therefore, the company assumed that patient distribution for the advanced Parkinson's disease cohort at 12 months would match to the overall cohort at 12 months. Long term efficacy associated with co-careldopa intestinal gel was based on published literature. In the base case analysis, the economic model incorporates a relative risk reduction of 'off' time progression of 0.50 in the co-careldopa intestinal gel arm only. It should be noted that for the standard of care arm, no additional treatment benefit was assumed. Patients therefore progressed according to natural disease progression. In the standard of care arm, these transition probabilities were applied in cycle 1 onwards (i.e. throughout the whole model) and in the co-careldopa intestinal gel arm, these were applied in cycle 3 onwards (i.e. from year 1). These probabilities were derived from two recent published studies (2013/14) and one relatively dated study (2002). However, it should be noted that the probabilities from the 2002 study were updated using regression analysis.

Drug acquisition costs, administration costs and monitoring costs were included in the analysis. Co-careldopa intestinal gel was associated with a number of tests during the initial phase of treatment, including an X-ray to confirm nasgostric tube position, renal function, haematology and ECG tests. During the first year of treatment, 6 nurse/consultant follow up visits were assumed and 3 annual follow up visits in year 2 onwards were also assumed. The frequency of resource use was based on a single expert opinion. In the economic model, direct medical and professional carer costs were calculated for each health state based on data from the Adelphi Wave6 study, a retrospective UK dataset which captured resource use data on 703 Parkinson's disease patients. Professional care-giver costs constituted the highest proportion of overall health state costs. Adverse event costs associated with co careldopa intestinal gel (including repositioning the PEG tube with or without

surgery) were included in the analysis. Adverse event rates in cycles 1 to 3 were taken from published literature. Adverse events associated with standard of care were not included.

Utility values were derived for each health state via the pooling of EQ-5D data from the pivotal study and published literature. A regression analysis was then conducted in order to derive the utility weights for each health state. It should be noted that carer disutility was also captured and results have been presented in a scenario analysis.

A revised patient access scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered which reduced the list price of co-careldopa intestinal gel. Based on the without-PAS results, the company estimated co-careldopa intestinal gel resulted in an incremental cost effectiveness ratio (ICER) of £58,250 versus standard of care alone, based on an incremental cost of £73,291 and an incremental quality adjusted life year (QALY) gain of 1.26. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

Sensitivity analysis was provided and consisted of one-way, scenario and probabilistic sensitivity analysis. The variables most sensitive to change included health state costs and the percentage of patients using one co-careldopa intestinal gel cassette. It should be noted the base case analysis assumes that 90% of patients receive 1 cassette. As this proportion is based on data from a dated published study (1998), sensitivity analysis is useful. When health state costs were reduced by 30% and the percentage of patients assumed to use one co-careldopa intestinal gel cassette was reduced to 70% (from 90%), the ICER increased to £87,142 without PAS and £86,300 without PAS respectively. It should be noted that scenario analysis has also been provided which incorporates carer disutility which reduced the ICER to £52,835 without PAS.

In addition, the company provided some scenario analysis as part of the resubmission in response to issues and uncertainties raised by SMC. This included more conservative analysis on the long term treatment effect of the medicine and related to concerns that an initial treatment effect was still maintained in the model. As such, analysis was provided to give a treatment waning effect at year 5, and also to combine this with both a reduced time horizon of 10 years and removal of the 'off' time treatment benefit after the first 12 months. This resulted in ICERs of £61,436, £63,881 and £81,324 respectively without PAS.

In addition to the base case ICER being comparatively high, there were a number of uncertainties associated with the analysis:

- There is a lack of robust direct head-to-head studies or indirect comparisons comparing co careldopa to standard of care. As such, there are concerns surrounding the clinical data used in the economic analysis. Efficacy data for co-careldopa were derived from a single-arm open-label study. The use of these data in comparison with standard care therefore has limitations.
- In the base case analysis, standard of care is not assumed to provide additional treatment benefit i.e. patients progress according to natural disease progression. This assumption is somewhat uncertain, particularly as health state transition probabilities were derived using published literature sources, which contained some limitations i.e. 'off' state transition probabilities, were estimated using a dated study and updated via regression analysis. Therefore, the company was asked to provide additional analysis whereby standard of care is assumed to be associated with some treatment benefit; an ICER of £62,729 without PAS arose when it was assumed that the number of standard care patients reaching H&Y state 5 was reduced by 5%.
- In the economic analysis, the initial treatment benefit associated with co-careldopa appears to

be maintained over the duration of the model (20 years). As noted above, the company has provided some additional analysis assuming a 50% waning of treatment effect at year 5 (and also as part of combined analyses). This was helpful additional analysis to provide more conservative estimates of long term treatment benefit, and gave ICERs in the range £61k to £81k without PAS.

- The base case analysis included a 50% reduction in 'off' progression over the duration of the model time horizon in the co-careldopa arm, which may not be appropriate and is associated with some uncertainty. Additional sensitivity analysis was provided whereby the time horizon was reduced to 10 years and the relative risk associated with 'off' progression was increased to 1 i.e. no difference assumed between treatment arms. This resulted in a cost per QALY of £77,279 without PAS.
- SMC clinical experts indicated that there was use of apomorphine in this patient population, and this may be higher than assumed in the base case comparator. Increasing the proportion of apomorphine assumed within the weighted cost of the standard care comparator from the base line value of 9% to 20% or 30% lowered the ICERs to £54,705 and £51,611 without PAS.
- As noted above, the results were sensitive to changes in the health state costs used in the model. These costs were based on the Adelphi Wave6 study which contained a number of limitations including, importantly, a lack of data for the most of the severe health states and this may introduce some uncertainty into the analysis.
- Sensitivity analysis testing utility values was originally not provided and while the base case estimates were broadly reasonable the company was asked to provide additional sensitivity analysis using more conservative utility estimates i.e. 30% reduction in utility values. In this analysis, the ICER increased to £83,214 per QALY without PAS. However, it should be noted that a 30% reduction in utility values did result in particularly conservative levels of quality of life being assumed for patients in the better health states of the model.

The Committee also considered the benefits of co-careldopa intestinal gel in the context of the SMC decision modifiers and agreed that the criterion for the absence of other treatments of proven benefit was met. In addition, as co-careldopa intestinal gel is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee was able to accept co-careldopa intestinal gel for use in NHS Scotland.

*Other data were also assessed but remain commercially confidential.**

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published SIGN guideline 113 "Diagnosis and pharmacological management of Parkinson's disease" in January 2010. The mainstay of treatment is with levodopa in combination with a dopa decarboxylase inhibitor. Motor complications are managed by three main strategies: manipulation of oral/topical treatments, the use of more invasive treatments (e.g. apomorphine infusion or intraduodenal levodopa), or with neurosurgery (e.g. deep brain stimulation). For patients with advanced Parkinson's disease and motor complications, the guideline recommends treatment with dopamine agonists, MAO-B inhibitors and COMT inhibitors. Advice issued by SMC in September 2006 is included in the guideline: 'Co-careldopa intestinal gel (Duodopa®) is not recommended for use within NHSScotland for the treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyperkinesia/dyskinesia when available combinations of medicinal products for Parkinson's disease have not given satisfactory results (September 2006)'.[1]

The National Institute of Health and Care Excellence (NICE) published CG35 "Parkinson's disease: diagnosis and management in primary and secondary care", on 28 June 2006 (prior to licensing of co-careldopa intestinal gel in the UK). The guideline advises that in later Parkinson's disease most patients will develop, with time, motor complications that will eventually require treatment with levodopa therapy. Adjuvant treatments to take in combination with levodopa aim to reduce motor complications and improve quality of life, however there is no single drug of choice in the pharmacotherapy of later Parkinson's disease; treatment options include dopamine agonists, COMT inhibitors, MAO-B inhibitors, amantadine, and apomorphine. An update of this guideline is currently in development, with publication anticipated in 2017.[2]

The European Federation of Neurological Societies and Movement Disorder Society (EFNS/MDS-ES) published evidence based treatment recommendations for the management of Parkinson's disease in 2011.[12] Intrajejunal levodopa/carbidopa enteric gel is recommended as a treatment option for patients with severe motor fluctuations as significant motor improvement during 'on' phases and decreased 'off' time, dyskinesia and median total Unified Parkinson's Disease Rating Scale (UPDRS) score has been demonstrated. Therapy is administered through percutaneous gastrostomy and the publication notes that technical problems are frequently encountered. Other treatment options for severe motor fluctuations are subcutaneous apomorphine and DBS. Although DBS is effective against motor fluctuations and dyskinesia, the procedure is only recommended for patients <70 years old without major psychiatric or cognitive problems but because of the risk for adverse events.

Additional information: comparators

Co-careldopa intestinal gel is indicated for use when available combinations of Parkinson medicinal products have not given satisfactory results, therefore there are no relevant comparators.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Co-careldopa intestinal gel	**40mg to 120mg per hour for 16 hours by continuous intestinal infusion [A]**	**28,028**
Apomorphine	**0.015 to 0.06mg/kg/hour by continuous subcutaneous infusion over 12 hours [BC]**	**2,763 to 5,322**

Cost from eVADIS on 16 February 2016. The costs do not take any patient access schemes into consideration.
[A] Usual maintenance dose is presented, dose expressed in terms of levodopa and does not account for morning bolus dose.
[B] Dose based on suggested hourly infusion rate over 12 waking hours; does not account for initial dose or additional intermittent bolus doses.
[C] Dose based on 70kg body-weight.

Additional information: budget impact

The submitting company estimated there to be 84 patients eligible for treatment in each year, with an estimated uptake rate of 10% in all years.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Scottish Intercollegiate Guidelines Network (SIGN). Clinical guideline 113. Diagnosis and pharmacological management of Parkinson's disease. January 2010. http://www.sign.ac.uk/guidelines/fulltext/113/index.html

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This assessment is based on data submitted by the applicant company up to and including **15 April, 2016.**

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.