OPINION ON MEDICINAL PRODUCTS

levodopa/carbidopa/entacapone

LECIGIMON 20 mg/5 mg/20 mg per ml,

intestinal gel

Reassessment

Adopted by the Transparency Committee on 14 December 2022

SUMMARY

The legally binding text is the original French opinion version

Key points

Approval of reimbursement for the treatment of advanced-stage Parkinson's disease with motor fluctuations and hyperkinesia or severe dyskinesia, where oral antiparkinsonism drug associations available have not given satisfactory results.

Therapeutic improvement?

No therapeutic improvement for the treatment of patients with advanced-stage Parkinson's disease with motor fluctuations and hyperkinesia or severe dyskinesia, where oral antiparkinsonism drug associations available have not given satisfactory results.

Role in therapeutic strategy?

The initial disease treatment strategy depends on the presence or not of parkinsonian symptoms with functional impairment, with treatment initiation only in the presence of impairment. In cases of minimal impairment, treatments will be considered according to the predominant symptom and age among monoamine oxidase type b (MAO-B) inhibitors, dopaminergic agonists by the oral or transdermal route and anticholinergic drugs.

In cases of functional impact, dopaminergic agonists will be preferred for patients under 65 years, whereas L-Dopa will be preferred for older subjects.

After a stabilisation period of varying duration, clinical status deteriorates due to the onset of dopaminergic treatment-related motor complications (motor fluctuations, on/off effects, dyskinesia) and

the onset or worsening of non-dopa-dependent disease-specific signs. The medical prescription and associated medicinal products likely to worsen motor and non-motor complications must be reviewed, with, if needed, subsequent dopa therapy optimisation to promote continuous dopaminergic stimulation (daily dose fractionation, administration time adaptation, change of dosage form, dietary modifications).

As such, addition to L-Dopa treatment may subsequently be envisaged with:

As a first-line approach:

- dopaminergic agonists administered orally or transdermally:
  - non-ergot derivatives as a first-line approach: ropinirole, piribedil, pramipexole, rotigotine (transdermal device).
  - ergot derivative agonists which require annual echocardiographic heart monitoring (risk of onset of valve disease): bromocriptine, lisuride;
- Catechol-O-Methyl-Transferase (COMT) inhibitors with:
  - entacapone, which offers the benefit of significantly increasing ON episode duration and can often make it possible to lower L-dopa doses;
  - tolcapone, if entacapone lacks efficacy or is poorly tolerated (tolcapone treatment must not exceed 3 weeks in cases of inefficacy, on account of its toxicity, particularly in the liver and ASAT-ALAT levels must be measured regularly)
- MAO-B inhibitors.

An association of these different drugs can also be envisaged.

As a second-line approach:

- antitremor anticholinergic drugs only, for patients with no cognitive impairment only
- amantadine remains a useful therapeutic option for the management of dyskinesia or fluctuations induced by levodopa. In other clinical scenarios in respect of Parkinson's disease, in particular at disease onset, immediate-release amantadine has no role in the therapeutic strategy in view of the alternative medications.
- apomorphine in discontinuous subcutaneous injections, indicated for adjuvant therapy of severe dopa therapy activity fluctuations during Parkinson's disease (on-off phenomenon).

In last-resort scenarios and according to national, European (EFNS/MDSES) and international guidelines, invasive treatments such as deep brain stimulation, apomorphine in continuous subcutaneous infusions or enteral administration of levodopa/carbidopa may be envisaged for some patients.

Role of the medicinal product

The Committee deems that LECIGIMON (levodopa/carbidopa/entacapone) is an alternative for the treatment strategy of adult patients with advanced-stage Parkinson's disease with motor fluctuations and hyperkinesia or severe dyskinesia, when the oral antiparkinsonism drug associations available have not given satisfactory results.

As for the proprietary medicinal product DUODOPA (levodopa / carbidopa), treatment with LECIGIMON (levodopa/carbidopa/entacapone) may be envisaged:

- **for patients ineligible for deep brain stimulation,**
- **in the event of contraindication, intolerance, failure to respond to apomorphine in continuous subcutaneous infusion, or as an alternative.**

Treatment is initiated in a hospital setting with determination of the tailored individual dosage. Patient education on pump use is required.

Committee's conclusions

Actual Clinical Benefit

- Parkinson's disease is a neurodegenerative disease with multi-systemic involvement characterised by symptoms of insidious onset and intermittent progression. It progresses towards disability and major impairment of quality of life.
- The proprietary medicinal product LECIGIMON (levodopa/carbidopa/entacapone) is a symptomatic medicinal product.
- Considering the low level of evidence of the data, the efficacy/adverse effect ratio of LECIGIMON (levodopa/carbidopa/entacapone) is moderate.
- Medicinal and non-medicinal alternatives are available.
- LECIGIMON (levodopa/carbidopa/entacapone) is an alternative for the treatment strategy of adult patients with advanced-stage Parkinson's disease with motor fluctuations and hyperkinesia or severe dyskinesia, when the oral antiparkinsonism drug associations available have not given satisfactory results.

Public health benefit

Considering:

- the severity of the disease in patients at an advanced stage and its prevalence,
- the partially met medical need,
- the lack of evidence of an impact on morbidity-mortality in view of the low level of evidence of the data
- the lack of evidence of an impact on quality of life,
- the lack of evidence of an additional impact of the delivery of care or on the patient's care and life pathway,

LECIGIMON (levodopa/carbidopa/entacapone) is not likely to have an additional impact on public health.

Considering all of these elements, the Committee deems that the actual clinical benefit of LECIGIMON (levodopa/carbidopa/entacapone) is significant in the marketing authorisation indication.

The Committee approves inclusion in the list of proprietary medicinal products approved for community use for the marketing authorisation indication and dosages.

Clinical Added Value

Considering:

- the data assessed for the first inclusion from a pharmacokinetic study versus DUODOPA (levodopa/carbidopa) conducted in the short term (two days) on a small sample size (n=11), failing to demonstrate the clinical benefit of adding entacapone to levodopa/carbidopa bitherapy administered by an implantable pump,
- the new efficacy data with a low level of evidence from the literature,
- the lack of robust data on patient quality life,

and also considering:

- the known safety profile of the three drugs (levodopa/carbidopa/entacapone)
- the modes of administration allowing enteral administration of entacapone where oral administration is only available,
- the partially met medical need with only one proprietary medicinal product available for continuous intestinal administration (DUODOPA (levodopa/carbidopa)),

the Committee deems that LECIGIMON (levodopa/carbidopa/entacapone) provides no clinical added value (CAV V) for the treatment strategy of adult patients with advanced-stage Parkinson's disease with motor fluctuations and hyperkinesia or severe dyskinesia, where oral antiparkinsonism drug associations available have not given satisfactory results.