24 September 2015
EMA/CHMP/672104/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Numient

International non-proprietary name: levodopa / carbidopa

Procedure No. EMEA/H/C/002611/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

γ	Hill coefficient
AC	Active-controlled
ADL	Activities of daily living
AE	Adverse event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of variance
ASPD	Advanced stage Parkinson's disease
AUC	Area under the curve
BBB	Blood brain barrier
BDI-II	Beck Depression Inventory II
BID	Twice a Day
BMI	Body mass index
BOCF	Baseline observation carried forward
CD	Carbidopa
CEP	Certificate of Suitability of the EP
CGI	Clinician Global Impression
CI	Confidence Interval
CLE	Carbidopa/Levodopa + Entacapone
Cmax	Maximum concentration
CMH	Cochran-Mantel-Haenszel
CHMP	Committee for Human Medicinal Products
CO	Cross-over
COMT	Catechol-O-methyl transferase
CQA	Critical Quality Attribute
CPP	Critical process parameter
CR	Controlled release
CRC	Child resistant closure

CSR	Clinical study reports
C-SSR	Columbia Suicide Severity Rating Scale
DA	Dopamine agonist
DB	Double-blind
DD	Double-dummy
DDC	Dopa-decarboxylase
DDCI	Dopa decarboxylase inhibitor
DSC	Differential Scanning Calorimetry
E_0	Baseline pharmacodynamic effect
EC_{50}	Effect compartment concentration at which 50% of the maximum effect occurs
ECG	Electrocardiogram
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicines Agency
E_{max}	Maximum pharmacodynamic effect
EOS	End of Study
ESPD	Early stage Parkinson's disease
EQ-5D	Measure of Health Status from EuroQoL Group
ER	Extended-Release
ESPD	Early stage Parkinson's disease
EU	European Union
g	Gram
GC	Gas Chromatography
GCP	Good Clinical Practice
h	Hour
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography

ICH	International Conference on Harmonisation
IGA	Investigator's Global Assessment
IR	Immediate release
ISE	Integrated Summary of Efficacy
ITT	Intention-to-treat
IVIVC	*in-vivo in-vitro* correlation
keo	First-order rate constant
kg	Kilogram
LD	Levodopa
LD-CD	Levodopa-Carbidopa
LC-MS	Liquid chromatography mass spectrometry
L-dopa+	Levodopa plus a dopa-decarboxylase inhibitor/ COMT inhibitor
LOCF	Last Observation Carried Forward
LSD	Least Significant Difference
m	Meter
MAA	Marketing Authorisation Application
MAO-B	Monoamine oxidase-B
MDS	Movement Disorders Society
mg	Milligram
MMRM	Mixed Model Repeated Measure
MMSE	Mini Mental State Examination
MR	Modified-release
mRS	Modified Rankin Scale
N	Number of Patients
NA	North America
NOR	Normal Operating Range

ns	Not specified
OL	Open label
OPDM	Objective Parkinson's Disease Measurement
PA	Parallel group study
PAR	Proven Acceptable Range
PC	Placebo-controlled
PD	Parkinson's disease
PDQ	Parkinson's Disease Questionnaire
PDSS	Parkinson's Disease Sleep Scale
PGI	Patient Global Impression
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
POC	Proof of concept
PP	Polypropylene
QOL	Quality of Life
QTPP	Quality target product profile
Rd	Randomized
RH	Relative Humidity
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCOPA-S	Scales for Outcomes in Parkinson's Disease Sleep Scale
SD	Standard deviation
SF-36	Short form 36, Health Survey Questionnaire
SmPC	Summary of Product Characteristics
SN	Substantia nigra

TID	Three times a day
TDD	Total daily dose
TSE	Transmissible Spongiform Encephalopathy
UK	United Kingdom
ULN	Upper Limit of Normal
UPDRS	Unified Parkinson's Disease Rating Scale
U.S. FDA	United States Food and Drug Administration
USP	United States Pharmacopoeia
UV	Ultraviolet
VAS	Visual Analogue Scale
XR(P)D	X-Ray (Powder) Diffraction
yrs	Years

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Impax Laboratories Netherlands BV submitted on 5 November 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Numient through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 May 2014. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of therapeutic innovation

The applicant applied for the following indication: symptomatic treatment of idiopathic Parkinson's disease in adults.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that levodopa/carbidopa was considered to be a known active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMA/626402/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's request for consideration

Scientific Advice

The applicant received Scientific Advice from the CHMP on 29 May 2009, 21 January 2010 and 21 June 2012. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Agnes Gyurasics

- The application was received by the EMA on 5 November 2014.
- The procedure started on 26 November 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 February 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 1 March 2015.
- The PRAC RMP Advice and assessment overview was adopted by PRAC on 12 March 2015.
- During the meeting on 26 March 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 27 March 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 May 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 June 2015.
- The PRAC Rapporteur Risk management Plan (RMP) assessment report was adopted by PRAC on 9 July 2015.
- During the CHMP meeting on 23 July 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 24 August 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 3 September 2015.
- The PRAC Rapporteur Risk management Plan (RMP) assessment report was adopted by PRAC on 10 September 2015.
- The CHMP adopted a report on similarity of Numient with Duodopa on 24 September 2015.
- During the meeting on 24 September 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Numient.

2. Scientific discussion

2.1. Introduction

Numient contains Levodopa and Carbidopa as active substances. After gastrointestinal absorption and uptake in the blood, Levodopa is able to cross the blood-brain barrier. In the brain Levodopa is converted into dopamine. This way the lack of dopamine in case of Parkinson's disease is supplemented. Only a small fraction of administered Levodopa crosses the blood-brain barrier, since a lot of Levodopa is metabolized to dopamine in the periphery by the enzyme dopa-decarboxylase. Carbidopa, an aromatic amino acid decarboxylase, is added

to Levodopa in order to reduce this peripheral metabolism. Levodopa-Carbidopa products have been registered for decades for symptomatic treatment of Parkinson's disease.

The objective of the Numient development program was to develop a modified-release Levodopa-Carbidopa capsule formulation:

1. which provides rapid absorption of levodopa (similar to immediate release (IR) L-dopa+ and faster than controlled release (CR) L-dopa+) to allow fast onset of effects.
2. which provides prolonged stable therapeutic levodopa concentrations, which allows dosing approximately every 6 hours: 3 times daily during waking hours or 4 times daily if bedtime dosing is needed for patients with early and advanced stage Parkinson's disease.
3. for which, in early stage Parkinson's disease (ESPD) three-times-daily dosing mimics continuous dopaminergic stimulation and reduces the risk of motor complications with long-term therapy.
4. which, in advanced stage Parkinson's disease, decreases 'OFF' time and increases good 'ON' time ('ON' time without troublesome dyskinesia), with consequent reduction in motor fluctuations.

Numient contains Levodopa-Carbidopa which are to be released in a modified release fashion during passage through the gastrointestinal tract.

Numient has been developed in four different strengths of Levodopa-Carbidopa (ratio 4:1): 95 mg/ 23.75 mg, 145 mg/ 36.25 mg, 195 mg/ 48.75 mg, 245 mg/ 61.25 mg. The indication applied for was:

Numient is indicated in adults for the symptomatic treatment of idiopathic Parkinson's disease.

The proposed posology for levodopa-naïve patients was:

The starting dose is one modified-release hard capsule containing 95 mg of Levodopa and 23.75 mg Carbidopa three times daily for the first three days; this may be increased to a dose of one modified-release hard capsule containing 145 mg of Levodopa and 36.25 mg Carbidopa three times daily from day 4 of treatment.

Further increases should be individualized based on clinical response. The daily dose must be determined by careful titration. Maintain patients on the lowest dose required to achieve symptomatic control and to minimize adverse reactions such as dyskinesia and nausea.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as modified release hard capsules containing levodopa and carbidopa as active substances in a fixed dose combination. Numient is presented in four different strengths: containing 95 mg/23.75 mg, 145 mg/36.25 mg, 195 mg/48.75 mg and 245 mg/61.25 mg of levodopa/carbidopa respectively.

Other ingredients of the capsule content are: microcrystalline cellulose, mannitol, tartaric acid, ethylcellulose, hypromellose, sodium starch glycollate, sodium laurilsulfate, povidone, talc, methacrylic acid – methyl methacrylate copolymers (1:1), methacrylic acid – methyl methacrylate copolymers (1:2), triethyl citrate, croscarmellose sodium and magnesium stearate;

the capsule shell contains: indigo carmine (E132) lake, yellow iron oxide (E172), titanium dioxide (E171) and gelatine;

the ink contains: SB-6018 blue ink, shellac (E904), propylene glycol and indigo carmine (E132) lake, as described in section 6.1 of the SmPC.

The product is available in opaque, white, high-density polyethylene (HDPE) bottle with polypropylene screw closure. Desiccant is included in the bottle, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

Levodopa

General information

The chemical name of levodopa is (2S)-2-amino-3-(3,4-dihydroxyphenyl)propanoic acid, corresponding to the molecular formula $C_9H_{11}NO_4$ and it has a relative molecular mass 197.2 g/mol and the following structure:

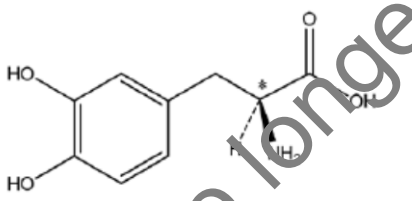


Figure 1: Levodopa molecular structure.

Levodopa is a white or almost white, non-hygroscopic crystalline powder. It is slightly soluble in water, practically insoluble in ethanol (96 percent). It is freely soluble in 1M hydrochloric acid and sparingly soluble in 0.1M hydrochloric acid.

Levodopa has an enantiomer referred as impurity D in Ph. Eur. No polymorphic forms are reported in literature. DSC and XRD analysis is consistent with a single crystalline form.

As there is a monograph of levodopa in the European Pharmacopoeia, the manufacturers of the active substance have been granted Certificates of Suitability of the European Pharmacopoeia (CEP) which have been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

Levodopa is supplied by two different suppliers. Valid Ph. Eur. certificates of suitability (CEP) were provided for both suppliers. The description of manufacturing process steps and in-process controls, characterisation, control of materials and of critical steps and intermediates, process validation and manufacturing process development are all covered by the CEPs. The holders of the certificate have declared the absence of use of material of human or animal origin in the manufacturing of the substance. The relevant information on the manufacture was assessed by the EDQM before issuing each CEP.

Specification

The control tests comply with the specifications and test methods of the Ph. Eur. monograph, as confirmed by the CEPs. The CEP from the first supplier includes additional control for a residual solvent. The CEP from the

second supplier does not include any additional test. The finished product manufacturer has presented a consolidated specification for Levodopa which complies with the Ph. Eur. requirements and includes in addition a test for appearance, three impurities, residual solvents and particle size.

The analytical methods used are those in the Ph. Eur. and where in house methods are used they have been validated and also cross-validated against Ph.Eur. methods where appropriate.

Results of batch analysis have been provided of six recent production scale batches of material from each manufacturer tested according the proposed specifications and with the proposed methods. The results are consistent from batch to batch and comply with the specification.

Stability

The proposed re-test period and packaging material for levodopa from the first supplier are covered by the respective CEP.

For the second supplier three commercial scale batches have been stored in the commercial packaging under long term (25 °C / 60% RH) for 48 months and under accelerated condition (40 °C / 75% RH) for 6 months. The following tests have been performed: appearance, specific rotation, state of solution, related substances, enantiometric purity, loss on drying, assay, pH. The methods used on stability are the test methods described in the CEP. The presented results comply with the specification.

The proposed retest period of and storage conditions are accepted.

Both suppliers have committed to place one batch of levodopa on long term stability per year, unless none is produced that year; this is acceptable.

Carbidopa

General information

The chemical name of carbidopa is (2S)-3-(3,4-dihydroxyphenyl)-2-hydrazino-2-methylpropanoic acid monohydrate, corresponding to the molecular formula $C_{10}H_{14}N_2O_4.H_2O$ and it has a relative molecular mass 244.2 g/mol (monohydrate) and the following structure:

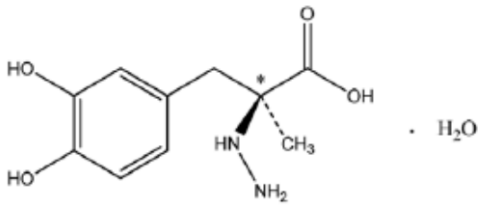


Figure 2: Carbidopa molecular structure.

Carbidopa is a white or yellowish white powder, non-hygroscopic crystalline powder. It is slightly soluble in water, very slightly soluble in ethanol (96 percent). Carbidopa dissolves in dilute solutions of mineral acids.

Carbidopa has a single chiral centre and is the L-enantiomer with an S-configurational assignment. No polymorphic forms are reported in literature. DSC and XRD analysis is consistent with a single crystalline form.

As there is a monograph of carbidopa in the European Pharmacopoeia, the manufacturers of the active substance have been granted Certificates of Suitability of the European Pharmacopoeia (CEP) which have been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

Carbidopa is supplied by two different suppliers. Valid Ph. Eur. certificates of suitability (CEP) were provided for both suppliers. The description of manufacturing process steps and in-process controls, characterisation, control of materials and of critical steps and intermediates, process validation and manufacturing process development are all covered by the CEPs. The holders of the certificate have declared the absence of use of material of human or animal origin in the manufacturing of the substance. The relevant information on the manufacture was assessed by the EDQM before issuing each CEP.

Specification

The control tests comply with the specifications and test methods of the Ph. Eur. monograph, as confirmed by the CEPs.

The CEP from the first supplier includes additional control for related substances by HPLC. The CEP from the second supplier includes an additional test for a residual solvent by GC. A non-compendial specified impurity is observed as both a process impurity and a possible degradant of the active substance. The analytical methods used are those in the Ph. Eur. and where in house methods are used they have been validated and also cross-validated against Ph.Eur. methods where appropriate.

Batch analyses data for three commercial scale batches of material from each manufacturer tested according the proposed specifications and with the proposed methods were provided. The results are consistent from batch to batch and comply with the specification.

Stability

The proposed re-test period and packaging material are covered by the CEP.

Both suppliers have committed to place at least one batch of carbidopa on long-term stability per year, unless none is produced that year; this is acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The aim of the pharmaceutical development was to develop a modified release levodopa-carbidopa (LD-CD) formulation which attains therapeutic LD plasma concentrations rapidly and maintains a sustained therapeutic LD concentration for duration longer than the currently approved LD-CD products and reaches a better patient compliance via less frequent dosing.

The Quality Target Product Profile (QTTP) was defined as providing a flat and sustained LD plasma profile with low fluctuation when dosed approximately every 6 hours as well as being safe (with regard to impurities) and easy to identify the different strengths. The Critical Quality Attributes (CQA) of the developed product were identified as its appearance and identity, LD, CD and tartaric acid assay, content uniformity, dissolution and residual solvents and related substances levels. During the pharmaceutical development elements and terminology of Quality by Design, such as: risk assessment, QTPP, CQAs and Critical Process Parameters (CPPs)

Proven Acceptable Ranges (PARs) and Normal Operating Range (NOR) have been used but no design space or regulatory freedom is claimed and no Continuous Process Verification is applied.

The active substances are not hygroscopic and do not exhibit polymorphism. In line with ICH Q6A Decision Tree #3, the particle size of LD and CD are not considered to have an impact on the performance (or manufacturability of the finished product or individual components.

The excipients used in the product are conventional and comply with the requirements of the current Ph. Eur., with the exception of the capsule shells. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The selection of the excipients was based on the requirements of the QTPP, and the amounts are within standard quantities of usage in pharmaceutical products. Compatibility of the active substances with the excipients was evaluated in an excipient compatibility study using ternary mixtures of levodopa, carbidopa and excipient. The use of these excipients in the formulation is considered critical and was further justified. No compatibility issues were identified between LD and CD. The combination of these drug substances has been used in currently approved drug products to treat Parkinson's disease.
To achieve a sustained LD plasma profile with low plasma concentration fluctuation and desirable LD plasma concentration profile, a multi-particulate formulation strategy was designed. The levels and choice of excipients have been justified on the basis of ensuring robust process and physicochemical stability of the active substances. Analyses were performed to evaluate the impact of the particle size within the supplied range for both active substances. The impact of particle size on core bead attributes was also evaluated. The function of each excipient has been studied and the amounts of excipients were optimised. The desired plasma profile was determined by bioavailability studies and simulations. The final composition was selected and the PK performance of the final composition was assessed in BA study IPX066-B08-10 and in an additional Phase II study. The batches used in the clinical phase III studies had the same composition and have been manufactured according the same process as proposed. The only difference was the amount of colorants and the site of manufacture. The bioequivalence of batches manufactured between the site used during development and the proposed commercial site was shown by study IPX066-B10-01. Dissolution profiles of the batches used in the five quoted studies have also been provided for all strengths. The different strengths of the final formulation are dose proportional and vary only in fill weight, size and colour of capsule shells.

Hydrazine is a known genotoxic agent and is listed as a potential impurity (degradant) of CD in the current Ph. Eur. monograph with a limit of 20 ppm. A discussion of the possibility that this impurity may form during routine manufacture and subsequent storage of the finished product has been provided and a test for hydrazine has been included in the finished product specification (see below in Product specification). The test for hydrazine has also been included in the stability protocols prospectively.

The proposed dissolution method for quality control is acceptable. In the absence of a Level A IVIVC the dissolution test can be used only as a quality control method and not to waive the requirements for in vivo demonstration of bioequivalence in case of a future variation applications. The proposed dissolution specification limits are acceptable without an established IVIVC. The discriminative properties of the proposed dissolution method have been confirmed. Specific dissolution studies have demonstrated that a risk for unexpected release caused by alcohol ingestion is not expected.

The product primary packaging is opaque white high-density polyethylene (HDPE) bottles with white polypropylene (PP) child resistant closures (CRC) sealed with an induction inner-seal. Silica gel in high-density polyethylene fibre packs are included as desiccant in the bottles. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of the following main steps: wet granulation, drying, milling, blending and packaging. Intermediate products have been defined and holding times have established. The process is considered to be a non standard manufacturing process. The potential Critical Process Parameters (CPPs), Proven Acceptable Ranges (PARs) and Set Points of process parameters for the commercial scale manufacture were provided. Following the final risk assessment no CPPs were identified in the manufacture. Acceptable control strategies including IPCs have been presented. The encapsulation process is considered to be a critical process step for the manufacture of the final capsules. Based on the process characterisation study results, it was concluded that the proposed encapsulator machine is capable of encapsulating capsules of all four strengths.

The batch size has been defined. However the approved batch sizes for each strength are considered to be the ones which have been validated (see process validation below).

The finished product manufacture is considered to be a non-standard process. Process validation results of three consecutive commercial scale batches manufactured at the proposed manufacturer have been provided. It has been demonstrated that the manufacturing process is capable of producing the finished product of the intended quality in a reproducible manner.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for this kind of dosage form including appearance (visual), identification of LD and CD (UV, HPLC), assay of LD, CD and TA (HPLC), degradation products (HPLC), uniformity of dosage units for LD and CD (Ph. Eur.), dissolution of LD, CD, TA (Ph. Eur. - HPLC), hydrazine (LC-MS) and microbial limits and (Ph. Eur.).

Loss on drying in not included in the finished product specification because it is tested as an IPC. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Microbiological testing will be performed as skip testing and also as part of the annual stability program as described in Section 3.2.P.8.2 (post-approval stability commitment). Skip testing has been justified. Finally the omission of testing for residual solvents in the finished product is considered also justified because they are controlled as part of the intermediate specifications and during encapsulation as IPC by a validated GC method.

With regards to hydrazine the release specification was based on the current data analysis and on the hydrazine toxicity assessment. According to Table 4 in Note 7 of ICH M7 (step 4), the usual TTC of 1.5 µg/day should be applied for chronic use indications with high likelihood for lifetime use across broader age range. Examples given include Alzheimer's disease and COPD. Compared to these diseases Parkinson's Disease should be considered to fall in the same category. Consequently, the justification for the proposed end of shelf life limit for hydrazine can be accepted. However, as more stability data become available (including hydrazine levels), additional analysis and refinement of the release and shelf life specifications will be performed (see 2.2.6 Recommendations). The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards of active substance and impurities has been presented.

Batch analysis results are provided for three production scale batches of each strength from the proposed production site and for 34 batches for the development site. All batches demonstrated compliance with the release specification in place at the time. The presented results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on the product have been provided for 20 primary stability pilot scale batches manufactured at the development site and stored for up to 36 months under long term conditions (25º C / 60% RH), for up to 12 months under intermediate conditions (30º C / 75% RH), all packed in the proposed packaging, were provided. The following tests have been performed on these batches: appearance, carbidopa and levodopa assay, drug-related impurities (degradation products), dissolution of carbidopa, levodopa and tartaric acid, loss on drying. The results showed no significant change in appearance, assay, carbidopa, levodopa and tartaric acid dissolution for the long-term or intermediate storage conditions. There was no obvious stability data trend and LD and CD results met the specification in place at the time. The only noticeable change was an increase in a carbidopa degradation product, which remained within the proposed specification limit for all batches on stability.

The 20 primary stability batches were also tested under accelerated conditions (40° C/75% RH) for up to 6 months. A significant change was observed in some batches at 6 months, where the Total Impurities were above the specification limit. The primary cause was an increase in the carbidopa degradation product. At the same time, intermediate storage condition (30° C/65% RH) testing was initiated, and the accelerated storage condition was removed from the study protocol per ICH guidelines for the stability study of commercial scale batches (see below).

Data were also provided for six commercial scale batches manufactured at the proposed site and stored in the proposed packaging for up to 36 months under long term conditions (25º C / 60% RH), for up to 24 months under intermediate conditions (30º C / 75% RH). An acceptable bracketing approach with regard to the proposed pack sizes put in stability has been applied.

The following tests have been performed: appearance, carbidopa and levodopa assay, degradation products, dissolution of carbidopa, levodopa and tartaric acid, and loss on drying. The analytical procedures used are stability indicating. The results at long-term and intermediate stability study conditions are consistent with the results of the primary stability batches. No significant changes have been observed in any of the tested parameters and all results comply with specification limits in place at the time of testing. As expected, the only noticeable change has been an increase in the carbidopa degradation product. There is an increase in hydrazine levels in the drug product over time. This effect was more profound when stored at 30°C/65%RH compared to 25°C/60%RH. In addition as more stability data become available (including hydrazine levels), additional analysis and refinement of the release and shelf life specifications should be performed (see 2.2.6 Recommendation(s) for future quality development.

Additionally photostability studies per ICH Q1B, and forced degradation studies as part of the analytical method validations have been performed. The data show that the container closure system adequately protects the drug product. No significant changes were observed in Appearance, Assay (LD or CD), Dissolution (LD or CD), or LOD, and all results comply with specification limits. The only noticeable change was an increase in the CD degradation product. The conclusion of the study was that the product is slightly light sensitive, and the container closure system provides adequate light protection. Therefore the following instruction has been included in the section 6.4 of the SmPC *"Store in the original package in order to protect from light and moisture"*.

In-use stability study has been performed on two batches on the highest strength according to the Note for Guidance (NfG) on in-use stability testing of human medicinal products. The results of this study support the proposed in-use storage period of 60 days (section 6.3 of the SmPC). In this regard the post-approval Commercial Stability Commitment provided is also acceptable.

The overall stability results support a shelf-life of 18 months when stored below 30°C in the original packaging to protect from light and moisture (as stated in section 6.4 of the SmPC).

Adventitious agents

Except for the gelatin used in the hard capsule shells no materials of human or animal origin are used in either the synthesis of the active substances, carbidopa and levodopa, or the manufacture of the finished product. Gelatine obtained from bovine sources is used in the finished product. Valid TSE Certificates of Suitability issued by the EDQM were provided by the supplier of the gelatine used in the manufacture.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substances has been presented in a satisfactory manner. The development of the finished product has been well performed and described, in line with the Guideline on quality of oral modified release products. During the pharmaceutical development elements and terminology of Quality by Design have been used but no design space or regulatory freedom is claimed and no Continuous Process Verification is applied. Proven Acceptable Ranges (PARs) and Normal Operating Range (NOR) have been defined. The formulation development has been considered satisfactory. Several supportive bioavailability studies have been performed to support the choices made during the development. The dissolution profile has been examined at many conditions and suitable controls are put in place. The proposed specification is acceptable and the limits put in place are considered justified, however as more stability data become available (including hydrazine levels), additional analysis and refinement of the release and shelf life specifications will be performed.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Sufficient information has been presented to give reassurance on TSE safety.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- as more stability data become available (including hydrazine levels), additional analysis and refinement of the release and shelf life specifications should be performed.

2.3. Non-clinical aspects

2.3.1. Introduction

The marketing authorisation application for this product (Numient LD-CD modified release capsules, hard) is submitted as a full mixed application and consists of both novel data and summaries of bibliographic references prepared according to EMA guidelines.

No original non-clinical pharmacology studies were conducted by the Applicant for the product.

2.3.2. Pharmacology

Principal findings from representative published studies on the primary and secondary pharmacodynamics of LD, CD, and LD-CD are summarized below:

- LD, a dopamine precursor, is converted to dopamine by endogenous L-aromatic amino acid decarboxylation.
- Dopamine concentrations in the brain increase after peripheral administration of LD.
- CD inhibits peripheral decarboxylation of LD by inhibiting L-aromatic amino acid decarboxylase (AAD).
- CD at therapeutic doses does not penetrate the blood-brain barrier (BBB), has low intrinsic pharmacological activity, and has no notable effects on cardiovascular, gastrointestinal, renal, or central nervous systems.
- At very high doses, LD increases motor activity in laboratory animals. CD pre-treatment markedly enhances the ability of LD to increase motor activity, suggesting that enhanced brain dopamine levels are responsible for this behaviour.
- LD and LD-CD reverse motor deficits, reduce rigidity, and decrease tremors in animal models of PD.
- Pulsatile fluctuations in LD plasma concentrations after administration of LD or LD-CD induce motor complications, including dyskinesia and motor fluctuation in healthy animals and animal models of Parkinson's Disease. Sustained, stable LD plasma concentrations reduce the expression of dyskinesia in animal models of Parkinson's Disease.
- Although the mechanism of action of LD is considered to be mainly through LD conversion to dopamine in the brain, LD itself may also serve as a neurotransmitter in the brain to activate receptors and facilitate the release of other neurotransmitters.

Principal safety pharmacology findings from representative references on LD, CD, and LD-CD are listed below:

- Administration of CD with LD to rodent and non-rodent species increases levels of brain LD and consequently dopamine, thereby potentiating the central nervous system (CNS) activity of LD; i.e., increases motor activity, irritability, and locomotion.
- LD and LD-CD decrease hypoxic ventilation in mice, consistent with dopaminergic stimulation of central nervous pathways regulating breathing.
- LD exerts dose- and species-dependent hemodynamic effects largely as a result of the peripheral effects of dopamine. In most species studied, LD causes tachycardia, arrhythmias, and hypertension followed by hypotension. Increase in blood pressure (BP) after LD administration is prevented by prior administration of an aromatic amino acid decarboxylase inhibitor (AADI).

- Peripheral conversion of LD to dopamine may cause emesis and transient gastric stasis.
- Peripheral actions of LD related to dopamine formation within the gastrointestinal system are inhibited by CD because the formation of extracerebral dopamine is prevented. Undesirable peripheral systemic effects of LD, such as emesis and pressor cardiovascular effects, are attenuated when LD is co-administered with CD.
- CD administered orally (PO) reduced the mean volumes of gastric secretion in rats by around 25% and produced marked reductions of histidine decarboxylase activity in the antral and fundal regions of the stomach.
- Intrarenal infusion of LD resulted in reversible phosphaturia and sodium excretion accompanied by increased renal blood flow in dogs; intrarenal infusion of LD following CD intravenously administered (IV) did not alter renal blood flow or glomerular filtration rate. CD alone had no effect on renal blood flow, renal excretion of phosphate and sodium, or glomerular filtration rate in dogs.

Although most of the safety pharmacology data predate the adoption of ICH guidelines and do not fully meet current ICH technical standards, taken together, the nonclinical data and the clinical safety and exposure data from the extensive clinical use of LD-CD and from the Numient clinical development program adequately address the safety pharmacology of Numient.

The principal pharmacodynamic drug interaction findings from representative references on LD, CD, and LD-CD in combination are listed below:

- A selective serotonin reuptake inhibitor, fluoxetine, reduced LD-derived extracellular dopamine levels in the 6-hydroxydopamine (6-OHDA) lesion rat model of PD.
- The catechol-O-methyltransferase (COMT) inhibitor U-0521, the monoamine oxidase-B inhibitor Ro 19-6327, and the M1 muscarinic acetylcholine receptor (mAChR) antagonist trihexyphenidyl potentiated the effect of LD on motor behaviour in animal models of PD.
- The NMDA (glutamate) receptor antagonist amantadine potentiated the effect of LD on motor behaviour in rodents.
- A 5-HT1A receptor agonist, sarizotan or 8-OH-DPAT, and an NMDA (glutamate) receptor antagonist, MK-801, reduced LD-induced dyskinesia in animal models of PD.

Agents such as yohimbine, methysergide, p-chlorophenylalanine, and reserpine prevented the hypotensive and bradycardic effects of LD in MAO-inhibited dogs.

2.3.3. Pharmacokinetics

The PK characteristics of LD, CD and their combinations have been investigated and extensively reported in the literature. Absorption, tissue distribution, metabolism, and excretion following both PO and parenteral administration in both radiolabelled and unlabelled forms have been reported. Species assessed include, but are not limited to rats, dogs and primates, and are consistent with the species used in published toxicological studies.

In addition to summarizing the salient nonclinical PK attributes of LD and CD from the literature, the toxicokinetics of LD and CD in combination (4:1 ratio in solution) were evaluated in two GLP studies sponsored by the Applicant in the rat and monkey (species used in the toxicological evaluations of LD-CD in the literature).

These two GLP studies were conducted to establish and confirm that systemic exposures of LD and CD following PO administration when characterized by state-of-the-art analytical methodologies are consistent with those reported by studies in the literature.

PK of L-DOPA

LD is a naturally occurring precursor to the catecholamine neurotransmitters dopamine, epinephrine, and norepinephrine, present in most mammals, and is synthesized directly from tyrosine via tyrosine hydroxylase. The metabolic fate of exogenous LD therefore follows the path of endogenous LD, with almost complete metabolic clearance driven by LD catabolism, involving mammalian intermediary metabolic routes and enzymes. Exogenous LD is rapidly and completely absorbed in all mammalian species studied, with peak plasma concentrations typically noted within 1 h of a PO dose. Studies in rats, dogs and monkeys indicated that elimination from the plasma compartment occurs in a bi-exponential manner and is characterised by a relatively short elimination half-life in the range of 0.5 to 1.5 h. Pharmacokinetic comparisons following single and chronic administration of LD have demonstrated no significant change (defined as > 2-fold) in LD systemic exposure in rats upon repeat dosing. The generally low plasma concentration of LD after PO administration is due to high presystemic metabolism in the GI tract, such that the oral bioavailability is approximately 35% and 36% in the rat and dog respectively.

In nonclinical species, significant first-pass metabolism of LD is the key determinant in limiting its oral bioavailability, particularly by decarboxylation to form dopamine in the gastrointestinal tract. This enzymatic pathway is saturable as evidenced by the dose-dependent bioavailability data in dogs (Sasahara, Nitanai et al. 1980b). Dopamine formed from the action of AADC can in turn be further metabolized to DOPAC and HVA, while 3-OMD is the major product of LD O-methylation catalysed by COMT. LD is predominantly O-methylated to 3-OMD when the peripheral decarboxylation of LD is maximally inhibited by CD. These intermediary metabolic routes are consistent across mammalian species, and do not involve the CYP450 superfamily of enzymes. As such CYP450-derived drug-drug interactions are unlikely to manifest, and therefore interactions with common CYP450 inhibitors or substrates have not been investigated.

The excretion of LD and metabolites occurs predominantly via the urine with between 60-90% of the administered dose recovered in urine in nonclinical species. Excretion was rapid in all nonclinical species, particularly rat and monkey with approximately 90% of a PO dose recovered in 0-24 h post PO and IV administration in these species, respectively. By comparison, one third of a PO dose to fasted patients was recovered in 2 h and approximately 85% of the total administered dose excreted in 24 h. Of this excreted dose, intact LD generally accounts for only a minor proportion of the administered dose, again highlighting the near complete metabolic clearance of LD through the action of AADC and COMT.

LD is not appreciably bound to human plasma proteins (<30% at therapeutic concentrations) (Rizzo, Memmi et al. 1996). The partition ratio of LD between rat erythrocytes and plasma was approximately 1.0, confirming equal distribution between the cellular and aqueous compartments. The initial tissue distribution of (14C)-LD was similar to other protein forming amino acids in rats and mice, with radioactivity rapidly taken up from blood by the pancreas and other glands involved in rapid protein synthesis. High initial concentrations of DRM were also observed in other tissues of both species including kidney, liver, and small intestine. Radioactivity was also shown to penetrate freely into the brain.

The tissue distribution of LD, including to the CNS and intestinal absorption, is subject to transport mechanisms comprising the L-type amino acid transporters LAT1, LAT2, TAT1, and the efflux transporter P-gp. The absorptive transporters are responsible for the active uptake of endogenous and exogenous neutral amino acids, such as L-leucine. As a consequence, certain amino acids can compete with LD for transport across the

gastrointestinal mucosa, renal epithelium, and BBB. LD is also subject to efflux by P-gp, which is expressed on the luminal side of intestine epithelial cells and brain capillary endothelial cells. However, in light of the prominent role played by amino acid transporters in LD absorption and disposition, the clinical relevance of P-gp in affecting LD absorption is likely to be minimal. Active transporters for LD uptake and efflux are probably present in humans, based on findings from in situ regional intestine perfusion studies and *in vitro* assessments using cell lines of human epithelial and endothelial origin.

PK of carbidopa

CD is a close structural analogue of LD. The PK of CD after PO and parenteral administration have been studied in rats, dogs and monkeys, and humans. Time to peak plasma concentrations after PO administration is 1 to 2 h in animals and 3 to 5 h in humans. Approximately 40% to 70% of CD PO is absorbed in the monkey and dog; absorption is less in the rat, with a PO BA based on plasma radioactivity similar in the rat and monkey, approximately 40%, but higher in the dog. After CD IV to the rat, highest concentration of DRM was present in kidneys, lungs, small intestine, and liver with no discernible distribution across the BBB at the dose studied. DRM has been confirmed in fetal tissue following IV administration to pregnant rats on gestation day 19, confirming that CD crosses the placental barrier in rats, with highest levels observed in the placenta. Like LD, CD does not bind substantially to human plasma proteins with a free unbound fraction of approximately 64% (Vickers, Stuart et al. 1974).

The metabolism of CD has been extensively characterized in rats, dogs, monkeys and humans, following PO administration, with the principal route of metabolism involving initial loss of the hydrazine moiety. In humans, unchanged CD and four metabolites were all positively identified in urine: 2-methyl-3'-methoxy-4'-hydroxyphenylpropionic acid (II), 2-methyl-3,4-dihydroxyphenylpropionic acid (III), 2-methyl-3'-hydroxyphenylpropionic acid (VII) and 3,4-dihydroxyphenylacetone (IV). Metabolites II, III and VII each represented approximately 10% of total drug-related material excreted in urine over 24 h, while VII accounted for less than 5%. All metabolites detected in humans were confirmed in at least one or more of the nonclinical species investigated. Although loss of the hydrazine functional group is the first and common metabolic event in all species, hydrazine itself was not detected in either monkey plasma or urine. N-deamination of the hydrazine moiety to form α-methyldopa (AMD) has also been suggested, based on detection of α-methyldopamine in rat brain following repeated PO administration of CD.

The enzymology of CD metabolism is less well characterized than that of LD. The common loss of hydrazine has been shown to be catalysed by a ubiquitous tyrosinase (monophenol monooxygenase); the involvement of other enzymes, such as peroxidases, cannot be ruled out. Therefore, as with LD, CD is not expected to participate in any PK drug interactions and hence interactions with common CYP450 inhibitors or substrates have not been investigated.

CD is excreted almost entirely in urine in all species investigated. Following PO administration at 20 mg/kg, urinary excretion accounted for 16%, 66%, and 40% of the radioactive dose in rats, dogs, and monkeys, respectively, with unchanged drug comprising approximately 38%, 65%, and 20% of this recovered dose over 24 h. In contrast, 52%, 11%, and 33% of the PO dose was excreted in the feces of rat, dog, and monkey, respectively. Where investigated, elimination in bile was minor following both PO and IV administration. For comparison, an average of 50% of a CD PO dose of is recovered in urine following administration to healthy human volunteers with 29% of this urine radioactivity present as intact CD. Human fecal excretion accounts for approximately 47% of the PO dose over a 3-day period. Similar levels of excretion have been observed in parkinsonian patients, with intact CD representing 32% of the 24 h urinary label, from which it is inferred that patients with Parkinson's disease metabolize CD to the same degree as healthy subjects. These urinary

excretion profiles are consistent with moderate/high absorption in monkey, dog, and human; however, they are not consistent with the low absorption observed in the rat.

PK of LD-CD

Administration of LD concomitant with decarboxylase inhibition by CD has a profound effect on LD pharmacokinetics in nonclinical species. Parenteral administration of CD to rats, prior to oral administration of LD, increased the elimination half-life and decreased the plasma clearance of LD in a dose-related manner. Pre-treatment with CD increased the exposure to LD, as measured by plasma AUC, by as much as 5-fold, and also increased exposure to the LD metabolite 3-OMD, formed by COMT. Systemic exposure to the downstream metabolites of LD decarboxylation, DOPAC and HVA were decreased in rats in a dose related manner. Increases in blood plasma exposure and the elimination half-life of LD were also potentiated in dogs following oral administration of CD prior to IV LD, compared to LD administered alone, with almost a 2-fold increase in measured plasma AUC observed in the presence of CD. In rats and monkeys, CD has also been shown to reduce excretion of urinary LD DRM, largely attributed to a decrease in the levels of dopamine excreted. The improvement in oral bioavailability of LD by CD is attributed mostly to inhibition of intestinal decarboxylation.

Pharmacokinetic studies conducted in animals and humans with LD-CD combination indicate that CD is a peripheral decarboxylase inhibitor and is effective in increasing the amount of LD that enters the brain where it is subsequently converted to dopamine. The combination treatment enables at least an 80% reduction in the amount of LD necessary to achieve the same therapeutic effect as when LD is taken alone in Parkinson's Disease patients. In addition, CD also decreases peripheral dose-related side effects of LD and dopamine, such as nausea, vomiting, and hypotension. The tissue distribution of injected tracer levels of LD were not appreciably altered by pre-treatment with CD, compared to LD alone, with the highest relative organ uptake observed in the kidney, followed by the pancreas and the liver in all species examined. Uptake of LD into skeletal muscle has been demonstrated in both rats and dogs, and is enhanced by CD pre-treatment, which presumably reflects the proportional increase in plasma LD concentration.

In the GLP conforming PK studies in rats and monkeys sponsored by the Applicant, maximum plasma concentrations of CD were detected between 0.5 and 2 h post-dose; maximum plasma concentrations of LD were detected between 0.25 and 1 h post-dose, with concentrations quantifiable up to at least 6 h post-dose. There were no marked differences (defined as >2-fold) in systemic exposure between the sexes in either species for either CD or LD. After single dose oral administration of 60/15 mg/kg LD/CD in rats or 40/10 mg/kg LD/CD in monkeys, the LD-CD exposures determined in these animal studies are consistent with those reported in the literature and comparable to those observed in humans following single Numient LD-CD dose of 4 × 245-61.25 mg in Parkinson's patients.

2.3.4. Toxicology

This application relies on the established safety and efficacy of LD, CD, and LD-CD products in laboratory animals and in humans over a period of more than 35 years. A large body of knowledge exists in the form of peer-reviewed scientific publications.

In light of the available data, no de-novo nonclinical toxicology studies were conducted by the Applicant to support the development of the product, with the exception extrapolation of data from two pharmacokinetics studies in rats and monkeys which were deemed necessary to validate the toxicity data. The value of these two small pharmacokinetic studies is very limited, as only a single dose and a single dose level were applied, assuming a lack of accumulation and dose-linearity.

Nonclinical evaluations of LD and CD published in the scientific literature generally used rodents (mouse and rat) and non-rodent species (dog and primate). The rat was the primary rodent species; the monkey was the primary non-rodent species. CD is poorly tolerated by dogs due to its induction of treatment-related, species-specific pyridoxine (vitamin B6) deficiency. Reproductive toxicology studies were conducted in rats and rabbits.

In rats, at lower dose levels no organ-specific toxicity was seen, but only clinical signs, including hyperactivity, weakness, irregular respiration and ptyalism. At these dose levels, the C_{max} in rats were estimated to be similar or in excess of the C_{max} observed in PD patients treated with high or regular doses of LD-CD, respectively. At higher dose levels, organ-specific effects were observed, including increased kidney and liver weight, increased leucocyte count, salivary gland hypertrophy and squamous ductal metaplasia, superficial necrosis of the gastric mucosa and rarefaction of the adrenal glomerulosa. At these dose levels, the AUCs in rats were estimated to be similar or slightly above those anticipated in PD patients treated with regular doses.

The neuropathological and gastrointestinal tract findings (e.g., mucoid gastritis and focal necrosis) in dogs treated with daily oral doses of CD were considered to be due to CD-induced pyridoxine (vitamin B6) deficiency, as they were associated with low plasma concentrations of pyridoxine and co-administration of CD/pyridoxine markedly attenuated the development of the lesions.

In monkeys, reported adverse effects of LD-CD were fewer in number than those reported in rats, with hyperactivity, incoordination, and weakness being the primary dose-limiting clinical signs. At dose levels were signs were so severe that the animals were euthanized, the estimated C_{max} levels in the monkeys were clearly in excess of expected C_{max} levels in patients treated with LD-CD.

Despite uncertainties on the systemic exposure levels in the literature studies that reduce the value of the toxicokinetic comparison provided by the Applicant, there is no need to provide additional data or make alternative calculations. New calculations would inevitably suffer from the same limitations. Moreover, the safety profile of levodopa and carbidopa is well-known, and exposure in patients will always be monitored clinically and adjusted on the basis of clinical signs. The Applicant reviewed the available literature on the genotoxic potential of L-DOPA and carbidopa. It appears that L-DOPA has weak mutagenic potential in both mammalian and non-mammalian *in vitro* systems, possibly by the formation of oxidative intermediates. The presence of a metabolic system generally reduced the mutagenic potential. Carbidopa also showed weak mutagenic potential in non-mammalian *in vitro* systems, however a unscheduled DNA repair assay in primary rat hepatocytes was negative up to 50 µM.

No formal carcinogenicity studies were performed for LD-CD, however it was reported that a fixed dose of CD combined with increasing doses of LD at ratios up to 1:10 was not carcinogenic in rats following PO administration for up to 106 weeks. The estimated systemic exposure (AUC) to LD and CD in these studies is lower than exposure in PD patients. Therefore the absence of any effect in the rat study provides only very limited reassurance. As indicated by the Applicant, apparently thus far there is no evidence that LD-CD would increase the risk of tumours, except for melanoma, a tumour type that has been shown most consistently to occur with an increased incidence amongst PD patients in several epidemiological surveys. Yet, whether this association can be attributed to the exposure to LD-CD is not known. Taken together the data suggest there is no concrete evidence that LD – CD is carcinogenic, but the non-clinical data set is rather limited. The causality of melanomas in Parkinson's Disease patients is unknown and a potential relationship with exposure to LD-CD is uncertain.

There are no detailed publications of nonclinical female reproduction studies with LD and/or CD, although it should be noted that no effects on the gonads of either sex were reported in chronic toxicology studies in rats or monkeys. The copulatory behaviour of male rats was evaluated following treatment with LD. The findings in rats

on sexual activity could be relevant for humans. Amongst other compulsive behaviours, increased libido and hypersexuality can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa and this has been included in the SmPC. In mice, mating performance and fertility were unaffected in animals when LD concentrations in the diet were 10 or 20 g/g diet, but the number of pregnancies and offspring born to females given a dietary concentration of 40 mg LD/g diet were reduced.

Effects on fetal development in utero were determined for LD in mice and rabbits. Apparently L-DOPA causes, at least in one species, the rabbit, embryofetal developmental effects, notably of the circulatory system, but also evident as decreased litter weight and by an increased incidence of stunted and resorbed fetuses. No toxicokinetic data are available. Therefore a comparison on the basis of systemic exposure is not possible. In rats, one study focussed on one specific effect during various phases of development: hemorrhages in brown fat tissue pats. The strongest effect occurred when dams were exposed during the first week of pregnancy. The relevance of this effect for humans is unknown.

No data on CD or the LD/CD combination were submitted, except for the limited data on the hemorrhagic effects in brown fat tissue, and that CD is excreted in milk. In light of the effects of LD in developing rodents and rabbits, the Applicant proposes to recommend that Numient should not be used in pregnancy unless the benefits for the mother outweigh the possible risks to the fetus. It can be anticipated that further data on CD will not affect the risk assessment and the advice given to pregnant women will not change. Also it is noted that the age of PD patients will make it less likely that pregnancy will occur. Based on these considerations, there is no merit to be gained in asking for additional data on CD or the combination of LD-CD.

LD treatment significantly decreased anti-SRBC hemagglutinating antibody levels and markedly reduced the formation of splenic plaque-forming cells when given to BALB/c mice daily for 5 consecutive days before or after immunization with sheep red blood cells (SRBC). In another experiment, mitogen-induced proliferative responses of spleen lymphocytes cultured ex vivo were inconsistently increased, but reduced the capacity of these spleen cells to respond to an allogeneic stimulus. These latter suppressive effects were correlated with a decrease in spleen T-cell numbers, suggesting that subsets of T lymphocytes may be under the control of endogenous dopamine. LD or LD-CD also suppressed immuno-inflammatory skin reactions in mice and rats. From the data presented it appears that L-DOPA has immunosuppressive potential.

LD crosses the BBB and is metabolised by AAD to dopamine. The increase in brain dopamine levels overcomes the dopaminergic deficit present in PD subjects, resulting in a therapeutic effect. According to the Applicant, the need for chronic administration of LD to be effective and the severe side effects associated with high doses would preclude any potential for abuse. However, there is experimental evidence in an α-synuclein rat model of PD supporting the hypothesis that dopamine replacement therapy can acquire psychostimulant-like properties in some patients with Parkinson disease (Engeln et al., 2013). This study and related information was not discussed by the Applicant. Inappropriate (excessive) use of levodopa has been mentioned as part of the broader term impulse control disorder, which has been included in the SmPC, although abnormal (excessive) use of levodopa is not included in the list of symptoms in the SmPC

Nevertheless, despite the omission of a thorough discussion on dependence potential/substance use disorder as part of impulse control disorder, we raise no concern, since the risk is not considered to be different from other levodopa products.

Since LD impurities in Numient are compendial impurities and are controlled in the drug substance, no further discussion of these impurities is required. With respect to carbidopa, the impurities were sufficiently discussed from a toxicological point of view. However, hydrazine is considered a genotoxic carcinogen and should be controlled at low levels in accordance with the Ph. Eur. Monograph (20 ppm). The Applicant states that it can

form during Numient manufacture and in storage to reach levels in excess of 20 ppm in the drug product. The Applicant has provided an adequate justification that these higher levels do not lead to a relevant increase in carcinogenic risk. It is not expected that the excipients present in the current formulation will pose a significant risk for Parkinson's disease patients.

2.3.5. Ecotoxicity / environmental risk assessment

Levodopa is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, levodopa is not expected to pose a risk to the environment.

The predicted environmental concentration in surfacewater (PECsw) value of carbidopa was determined using a refined Fpen based on the prevalence of Parkinsons' disease in the EU. The value obtained of 80 µg/L, exceeds the action limit of 0.01 µg/L for a phase II environmental risk assessment according to the Guideline on "Environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00 Corr 2[1]*).

The n-octanol:water partition coefficient (LogKow) was determined using a shake-flask method (non-OECD) showing a log Pow of -1.92. In agreement with the guideline, the CHMP concluded that carbidopa is not a PBT or vPvB substance as the LogKow does not exceed 4.5. The CHMP discussion took into account that for known active substances (e.g. Art. 10 applications) according to the guideline and the Q&A document on environmental risk assessment (EMA/CHMP/SWP/44609/2010) questions 1 and 2, a complete ERA is not always required, provided that the introduction on the market of a new medicinal product would not result in a significant increase in environmental exposure compared to the current use of the same substance in other products marketed in EU.

Considering the clinical practice for treating Parkinson Disease patients, the CHMP agreed that the introduction of Numient would not lead to a significant increase in the levels of carbidopa currently prescribed in the EU. Therefore, the absence of a phase II environmental risk assessment for carbidopa was considered to be acceptable.

Table 1 Summary of main study results

Substance (INN / Invented Name): carbidopa			
CAS-number (if available): 18821-49-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential - log K_{ow}	OECD 107	log P_{ow} of -1.92 ± 0.02	Not B
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	log P_{ow} of -1.92 ± 0.02	Not B
Persistence	ready biodegradability	-	potentially P
	DegT50	-	potentially P
Toxicity	NOEC algae NOEC crustacea NOEC fish	-	potentially T
	CMR	-	potentially T
PBT-statement :	carbidopa is not PBT nor vPvB		
Phase I			

Calculation	Value	Unit	Conclusion
$PEC_{surfacewater}$, refined	0.80	µg/L	> 0.01 threshold
Other concerns (e.g. chemical class)			(N)

2.3.6. Discussion on non-clinical aspects

The marketing authorisation application for Numient (LD-CD modified release capsules, hard) is submitted as a full mixed application and consists of both novel data on Numient and summaries of bibliographic references prepared according to EMA guidelines. No original nonclinical pharmacology studies were conducted with Numient by the Applicant. The pharmacology of LD-CD is adequately summarised by the Applicant.

The PK characteristics of LD, CD and their combinations have been investigated and extensively reported in the literature. In addition to summarizing the salient nonclinical PK attributes of LD and CD from the literature, the toxicokinetics of LD and CD in combination (4:1 ratio in solution) were evaluated in two GLP studies sponsored by the Applicant in the rat and monkey (species used in the toxicological evaluation of LD-CD in the literature). Nevertheless, to extrapolate these data to estimate the exposure in toxicity studies reported in the literature would inevitably be biased by several uncertainties, such as the design of the studies, the strains of animals used, the formulation and assumptions on lack of accumulation after repeated dosing and dose-linearity.

At exposures comparable to those expected at relatively high therapeutic doses, non-organ specific adverse effects occurred in animals. However, the clinical safety profile of levodopa and carbidopa is well-known, and exposure in patients will always be monitored clinically and adjusted on the basis of clinical signs.

Both L-dopa and carbidopa showed weak mutagenic potential in non-mammalian *in vitro* systems, however a unscheduled DNA repair assay with carbidopa in primary rat hepatocytes was negative up to 50 µM. No formal carcinogenicity studies were performed for LD-CD, however it was reported that a fixed dose of CD combined with increasing doses of LD at ratios up to 1:10 was not carcinogenic in rats following PO administration for up to 106 weeks. The estimated systemic exposure (AUC) to LD and CD in these studies is lower than exposure in Parkinson's Disease patients. Therefore the absence of any effect in the rat study provides only very limited reassurance. As indicated by the Applicant apparently thus far there is no evidence that LD-CD would increase the risk of tumours, except for melanoma, a tumour type that has been shown most consistently to occur with an increased incidence amongst PD patients in several epidemiological surveys. Yet, whether this association can be attributed to the exposure to LD-CD is not known. Taken together the data suggest there is no concrete evidence that LD – CD is carcinogenic, but the non-clinical data set is rather limited. The causality of melanomas in PD patients is unknown and a potential relationship with exposure to LD-CD is uncertain.

No data on embryofetal or pre/postnatal developmental toxicity of CD or the LD/CD combination were submitted, except for the limited data on the hemorrhagic effects in brown fat tissue, and that CD is excreted in milk. However, it can be anticipated that further data on CD will not affect the risk assessment and the advice given to pregnant women will not change. Also it is noted that the age of PD patients will make it less likely that pregnancy will occur. Based on these considerations, it was concluded that no additional data on CD or the combination of LD-CD are needed.

2.3.7. Conclusion on the non-clinical aspects

The CHMP considers that the LD-CD combination is a well-established treatment for Parkinson's Disease patients, for which considerable knowledge on the pharmacology, pharmacokinetics and safety profile is available.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

- Tabular overview of clinical studies

Clinical pharmacology and clinical efficacy/safety have been investigated in the Numient development program.

The clinical pharmacology program consisted mainly of biopharmaceutical studies evaluating relative bioavailability against currently registered levodopa-carbidopa products, food-effect, dose-proportionality, in vivo interaction with alcohol and bioequivalence between the Numient manufactured at two different manufacturing sites (Table 4). In addition, a study evaluating pharmacokinetics of Numient formulations with different in vitro release profiles, the results of which were included in the development of the IVIVC model. A single and multiple dose pharmacokinetics were assessed in patients with Parkinson's disease.

Pharmacodynamic studies have been integrated within the clinical efficacy and safety studies (see below). Main pharmacodynamic investigations have been conducted within study IPX066-B08-11.

Table 2 The overview of the pharmacokinetic studies

Category	Study number	Objective
Healthy Subject PK and Initial Tolerability	IPX066-B08-10	Bioavailability of levodopa from Numient relative to levodopa from Sinemet, Sinemet CR, and Stalevo in healthy subjects
	IPX066-B10-01	Bioequivalence study comparing two manufacturing sites
	IPX066-B08-09	Dose proportionality of levodopa over Numient capsule strength range
	IPX066-B12-01	PK of Numient formulations with different in-vitro release profiles
Patient PK and Initial Tolerability	IPX066-B08-11	PK of levodopa from Numient relative to IR levodopa-carbidopa (Sinemet IR) following single- and multiple dosing in PD patients
	IPX066-B09-06	PK of levodopa from Numient relative to levodopa-carbidopa-entacapone (Stalevo) following single dosing in PD patients
	IPX066-B11-01	PK of levodopa from Numient relative to levodopa-carbidopa Controlled-Release (Sinemet CR) in PD patients
Extrinsic Factors	IPX066-B09-01	Impact of co-administration of food with Numient on PK of levodopa

	IPX066-B09-04	Effect of alcohol on PK of levodopa from Numient

The clinical efficacy of Numient in patients with Parkinson's disease has been investigated in three, double-blind, randomized controlled Phase 3 studies.

In addition, the efficacy of Numient has been investigated in four open-label studies. The main features of the clinical studies are presented in Table 5

Table 3 Summary of main features of pivotal studies

Study	Design	Study-arms (n_{RD} / $n_{Completed}$)	Main endpoints / assessments
Controlled trials			
Early stage Parkinson's disease (ESPD)			
IPX066-B08-05 2009-2010 POC Fixeddose NA/EU	Rd DB PC PA 30 week ESPD patients* Average agerange across treatment groups: 64 – 65	145 mg Numient TID n=87/72 245 mg Numient TID n=104/83 390 mg Numient TID n=98/74 Placebo Numient TID n=92/71	***Primary*** Change from baseline in UPDRS ADL and motor scores at end of study ***Other*** Other UPDRS based outcomes, PGI, CGI, PDQ-39
Advanced Parkinson's disease (ASPD)			
IPX066-B09-02 2009-2011 Flexible dose Superiority NA/EU	Rd DB DD AC PA 22 week ASPDpatients with insufficient control of motor symptoms or motor fluctuations** Age: mean 63 (SD 9)	Numient mean daily dose 1622 mg n=201/186 IR L-Dopa+ mean daily dose 825 mg n=192/182	***Primary*** Percent 'OFF'-time during waking hours ***Other*** Total 'OFF'-time, 'ON'-timewithout troublesome dyskinesia, UPDRS, PGI, CGI, PDQ-39, EQ-5D
IPX066-B09-06 2010-2011 PK/PD/Efficacy NA/EU	Rd DB DD AC CO 2 treatment periods of 2 weeks with 1 week of Numient treatment in between/period. Total study duration: 11 week ASPD Patients with with motor fluctuations on a Levodopa/Carbidopa/Entacapone regimen** Age: 64 (SD 9)	Numient followed by Carbidopa/Levodopa/Entacapone: n=48/45 Carbidopa/Levodopa/Entacapone followed by Numient: n=43/39	***Primary*** Percent 'OFF'-timeduring waking hours ***Other*** Total 'OFF'-time, 'ON'-timewith and without troublesome dyskinesia, UPDRS scores, Subject preference of treatment, EQ-5D, SF-36, PDSS
Open-label studies			
IPX066-B08-11 (Phase 2 trial) 2008-2009 PK/PD	Rd OL CO 2 weeks/period ASPD Patients on a stable drug regimen for Parkinson's disease for at least one month with at	Numient followed by IR L-Dopa+ n=14/14 IR L-Dopa+followed by Numient n=13/13	***Primary*** Not specified ***Other*** Tapping, walk time,

NA	least 3 hours of predictable 'OFF'-time per day, a total daily dose of 500-1,600 mg IR L-Dopa+, and a dosing frequency of ≥4 times daily Age: mean 63 (SD 9)		'ON/OFF'-time with and without dyskinesias assessed by patient and investigator, UPDRS motor score, pharmacokinetic parameters
IPX066-B09-03 2010-2011 Open label extension NA/EU	OL 9 months Patients with Parkinson's disease from studies IPX066-B08-05 (ESPD),IPX066-B08-11 and IPX066-B09-02 (ASPD)	Participants from study: -IPX066-B08-05 n= 268/254 -IPX066-B08-11 n=13/9 -IPX066-B09-02 n=336/304 All patients: n=617/567	***Primary*** Safety outcomes **Other** UPDRS scores, PGI, PDQ-39, EQ-5D, SF-36
IPX066-B09-06 2011-2012 Open label extension NA/EU	OL 6 months ASPD Patients from study IPX066-B09-06 Part 1	Numient daily dosage 1696 mg n=74/66	***Primary*** UPDRS **Other** UPDRS scores during 'ON'-time, UPDRS ADL score in the 'OFF' state
IPX066-B11-01 2011-2013 Switching study/open label extension NA	OL 3 parts: 1.Dose conversion: 6weeks 2.Open label extension: 6 months 3.Second open label extension: 6 months ASPD patients using L-Dopa+ CR with or without L-Dopa+ IR Age: mean 66 (SD 11)	Part 1: n=43/33 Part 2: n= 32/25 Part 3: n= 12/12	***Primary*** N/A ***Other*** PGI, CGI, PDQ-8, subject preference of treatment, time to stable Numient regimen, OPDM

Legend: *AC: active-controlled, CGI: Clinical global impression,CO: Cross-over, DB: Double blind, DD: double-dummy, EU: Europe, EQ-5D: Measure of health status from the European Quality of Life group, mRS: modified Rankin Scale, NA: North America, OL: Open-label, OPDM: Objective Parkinson's Disease Measurement, PA: Parallel group study, PC: Placebo-controlled, PD: Pharmacodynamics, PDQ: Parkinson's disease questionnaire, PDSS: Parkinson's Disease Sleep Scale,PGI: Patient Global Impression, PK: Pharmacokinetics, POC: Proof of concept, Rd: Randomised, SCOPA-S: Scales for Outcomes in Parkinson's Disease Sleep Scale, SF-36: Health survey questionnaire, UPDRS: Unified Parkinson's Disease Rating score.*

*Patients were not previously treated with Levodopa and/or dopamine agonist for more than 30 days and not within 4 weeks of study start

**Patients must have been on a stable anti-Parkinson's disease regimen for at least 1 month with at least 2.5 hours of predictable 'OFF' time per day, total daily Levodopa dose of ≥400 mg and Levodopa dosing frequency ≥4 times daily (excluding night time dosing)

2.4.2. Pharmacokinetics

After single-dose, the initial rate of levodopa absorption following administration of Numient was similar to that observed for Sinemet IR and faster than that observed for Sinemet CR and Stalevo (see Figure 4 Mean levodopa Plasma Concentration-Time Profiles for Numient and Marketed levodopa Products, Study IPX066-B08-10). The maximum plasma concentration of levodopa from Numient were however reached 3-3.5 hr later (median: 4.5 hrs, range: 0.5-8 hrs) as compared to Sinemet IR (median: 1 hrs), Sinemet CR (median: 1.5 hrs) and Stalevo (median 1.5 hrs). On a dose-normalized basis, levodopa Cmax following Numient was approximately 32%, 41%, and 34% of that following Sinemet IR, Sinemet CR, and Stalevo, respectively. The bioavailability of

levodopa from Numient was 80% as compared to Sinemet IR and Sinemet CR, and 60 % as compared to Stalevo.

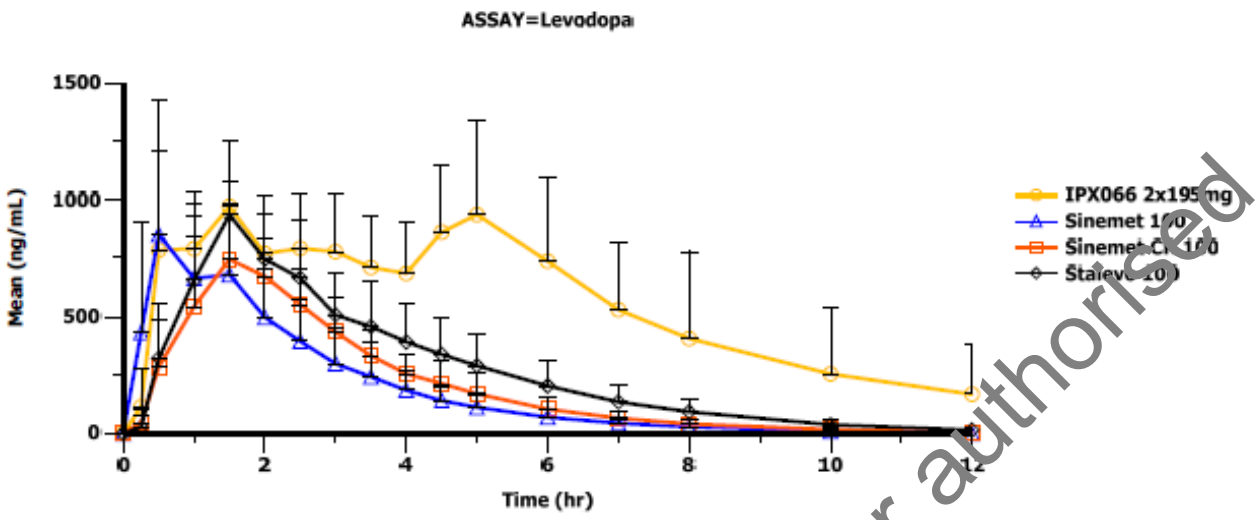


Figure 3 Mean levodopa Plasma Concentration-Time Profiles for Numient and Marketed levodopa Products, Study IPX066-B08-10

Levodopa concentrations above 50% of Cmax were maintained longer with Numient as compared to the other levodopa-carbidopa products, i.e. 4.9 hrs for Numient as compared to 1.5, 2.1, and 2.1 hrs for Sinemet IR, Sinemet CR, and Stalevo, respectively. The terminal elimination half-life of levodopa was comparable between Numient (1.9 hrs) and other marketed formulations levodopa-carbidopa formulations (1.6 hrs). Therefore, the fact that concentrations above 50% of the Cmax were maintained longer for Numient is attributed due to the modified released characteristics but also due to higher dose of levodopa in this new formulation. This observation would also explain thrice daily dosing for this new Numient formulation, which is comparable to Sinemet CR (every 4 to 12 hrs during the waking day), might be lower as compared to Stalevo (up to 8 times a day) and is lower than for IR Sinemet (even every 2 hrs).

The bioavailability of carbidopa from Numient was 50% relative to Sinemet IR and 60% relative to Sinemet CR and Stalevo.

Bioequivalence

Since Numient is a multiphasic formulation consisting from three components and it is characterized by the initial absorption followed by two additional absorption phases with their respective peak plasma concentrations, additional parameters were included in the evaluation of bioequivalencei.e. partial AUC between Numient formulations manufactured at two different sites has been sufficiently demonstrated using Cmax and partial AUC data.

Food effect

High-fat, high-calorie meal did not affect the overall extent of absorption of levodopa since the 90% confidence interval were within the 80-125% range. However, a high-fat meal significantly slowed the rate of absorption of levodopa, by delaying the T_{max} from 1.5 to 7 hrs and decreasing the C_{max} by 20%, as compared with the fasted state.

In the presence of high-fat meal, the maximum carbidopa concentrations and the total exposure were reduced by 60% and 50%.

Following administration of the capsule contents sprinkled on a small quantity of applesauce, the rate and extent of absorption of levodopa and carbidopa was similar to that observed when the Numient capsule was swallowed whole by subjects in the fasted state. It was clarified that the delayed release components exhibit significantly lower release below pH 7. Therefore, it is reasonable to assume the delayed release components keep their integrity when they are mixed with soft food like yoghurt and pudding, with a pH up to 6.

Numient is a multiphasic formulation consisting from three components and it is characterized by the initial absorption followed by twoadditional absorption phases with their respective peak plasma concentrations, under fasting conditions. Therefore, additional parameters were included in the evaluation of the food effect, i.e. partial AUC. This additional analysis further refines the conclusions regarding the food-effect of Numient. Concerning levodopa, the initial IR part of the formulation is most significantly reduced with a high feat meal, i.e., by more than 50%. In contrast, the AUC6-inf is increased more than two-fold. Overall, the extent of absorption of levodopa is changed only to a non-significant extent, and this is indicated in the SmPC.

The phase 2 and phase 3 studies were not standardized with regard to the concomitant food intake. Therefore, the intake of Numient with or without food, as indicated in the SmPC, is considered acceptable.

In vivo alcohol interaction study

Co-administration of Numient with up to 40% volume-to-volume (v/v) alcohol did not result in dose-dumping of levodopa or carbidopa as there was no rapid increase in initial absorption phase of levodopa or carbidopa. From the concentration-time profile it seems that alcohol caused more fluctuations in the concentration of levodopa as compared to the control group. However, the %CV was comparable between all four treatment arms and thus the concomitant intake of alcohol is not expected to affect the benefit/risk of Numient.

In-Vitro In-Vivo Correlation

The Numient formulations were sufficiently different from the to-be-marketed formulation to be suitable for an IVIVC study. Oral solution would be the most optimal as reference formulation for deconvolution considering limited permeability of carbidopa (BCS class III). However, considering the lack of registered oral solution of carbidopa-levodopa, the choice of immediate release Sinemet formulation as a reference formulation for deconvolution is understood.

The applicant claims that the established IVIVC model adequately described the levodopa and carbidopa concentration-time data and therefore can be considered as a Level A. Validation of the IVIVC was demonstrated based on internal and external validation with mean absolute prediction errors of less than 10% and individual absolute prediction errors of less than 15% for both C_{max} and AUC_{inf}. Based on this, it can be concluded that IVIVC model reasonably predicts C_{max} and AUC_{inf}. The Applicant therefore considers that a level A IVIVC has been obtained. Dose proportionality and time dependency

Dose proportionality of levodopa and carbidopa pharmacokinetics was demonstrated over the entire range of Numient dosage strengths as the 90% CI for the proportionality exponent estimate (β) were within the acceptance intervals (0.7645 to 1.2355) for Cmax, AUC0-t, and AUC0-∞. Two capsules of 245 mg Numient resulted in slightly more than dose-proportional manner regarding the AUC∞ for levodopa, according to the power model. However, since in the clinical studies dose of levodopa up to 5880 mg were included and Numient will be dosed to a clinical response, this is not considered an issue.

Multiple-dose pharmacokinetics was comparable to single-dose pharmacokinetics. Following multiple dosing, there was a minimal accumulation of levodopa from Numient when dosed Q6H and it was comparable to that after IR carbidopa-levodopa administration (1.4 and 1.1 for Numient and IR carbidopa-levodopa, respectively).

The mean accumulation of carbidopa from Numient was 1.6 and it was comparable to that from IR carbidopa-levodopa, which was 1.2.

Intra- and inter-subject variability

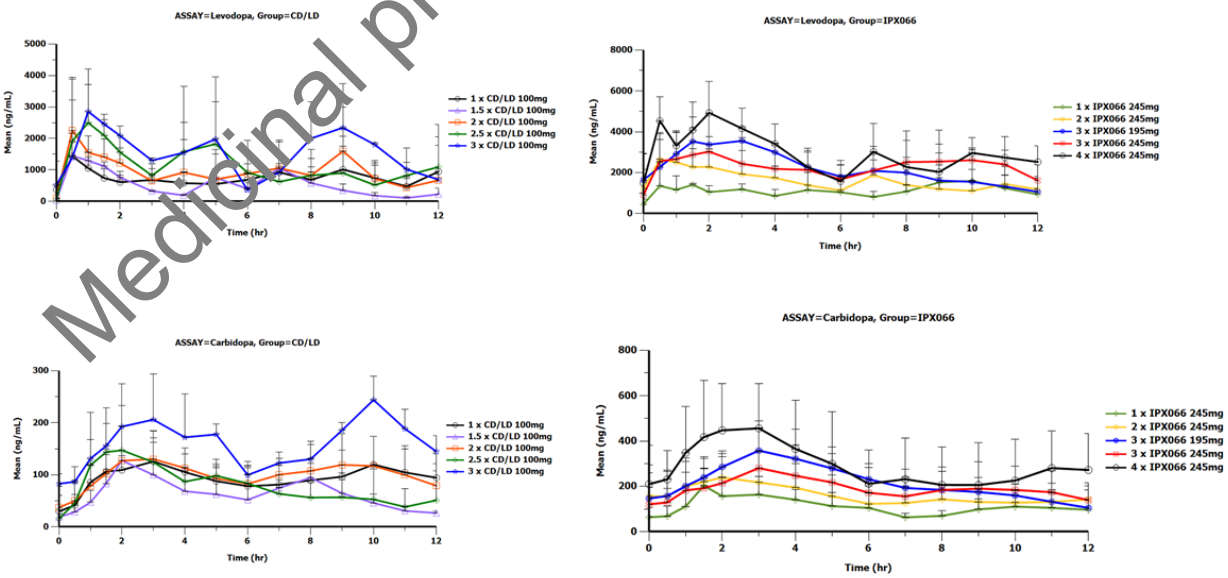
Based on the data from healthy volunteers, the intra-subject variability in levodopa C_{max} and AUC is considered to be moderately low, i.e. 19 and 17%, respectively. The intra-subject variability in carbidopa Cmax and AUC was slightly higher, i.e. 32 and 25%, respectively.

In subjects with PD, the intersubject variability of Cmax and AUC for levodopa was moderate, i.e. 40%. The intersubject variability of carbidopa Cmax and AUC in subjects with PD was high (54% and 53%, respectively).

Pharmacokinetic in target population

The BA (AUC) of levodopa from Numient relative to IR levodopa-carbidopa (Sinemet), CR levodopa-carbidopa (Sinemet CR), and levodopa-carbidopa-entacapone (Stalevo) in PD patients was 66%, 60%, and 44%, respectively. At comparable doses, Numient resulted in levodopa Cmax that was approximately 30% of those from IR levodopa-carbidopa and levodopa-carbidopa-entacapone and 50% of those from CR levodopa-carbidopa. These findings are approximately comparable to what was observed in healthy volunteers. Carbidopa exposure was comparable in subjects with PD and in healthy subjects.

In patients, following multiple dosing of Numient, levodopa had a lower peak-to-trough fluctuation than following IR Sinemet (approximately 1.5 versus 3.2). Carbidopa has longer half-life and probably this is the reason why there is no difference in fluctuations of carbidopa after Sinemet IR and Numient (1.5 vs. 1.2, respectively). The results substantiate the applicant claim that levodopa has more uniform plasma level after Numient compared to Sinemet IR (see Figure 5 Mean levodopa and carbidopa plasma concentrations after multiple doses of Sinemet IR (left panels) and Numient (right panels).).



Special populations

Impaired renal function

No studies in renally impaired subjects for the ***Numient*** formulation were performed. According to the SmPC, no dose adjustment in this special population is required based on the known elimination pathways of levodopa and carbidopa, i.e unchanged levodopa and carbidopa accounts for 10% and 30% of the total urinary excretion, respectively. This is agreed and in line with SmPC of other registered carbidopa-levodopa products.

Impaired hepatic function

Studies in patients with hepatic impairment were not performed. According to the SmPC, no dose adjustment in this special population is required based on the metabolism and known elimination pathways of levodopa and carbidopa. It is recommended to administer this medicine cautiously to patients with severe hepatic impairment.

Figure 4 Mean levodopa and carbidopa plasma concentrations after multiple doses of Sinemet IR (left panels) and Numient (right panels).

Since levodopa is predominantly cleared peripherally, hepatic impairment would not be expected to impact the PK of ***Numient***. This is agreed and consistent with SmPC of other registered carbidopa-levodopa products.

Gender

Dose-normalized levodopa Cmax and AUCinf following Numient administration were higher in females (25% to 35% for Cmax, 37 to 38% for AUCinf) than in males in healthy subjects and subjects with PD and consistent with the literature data. Since dosing for PD patients is individualized based on the clinical response, these differences are not considered as an issue.

Weight

In healthy volunteers and PD subjects, dose normalized AUCinf values was negatively correlated with body weight, which is consistent with the literature data.

Elderly

Dose-normalized levodopa AUCinf and Cmax was positively related to increasing age in subjects with PD. For carbidopa, only AUC was significantly correlated with age. These findings are consistent with the literature data. No dosage adjustment on the basis of age is recommended since Numient doses are individually titrated based on a efficacy and safety response. In addition, elderly were included in the safety and efficacy trials.

Drug-drug interactions

No drug-drug interactions have been performed by the applicant. A reference is made to the literature data. The information on the PK interactions with COMT Inhibitors, Ferrous Salts, Prokinetics (e.g. metoclopramide, domperidone, prucloprid) has been included in the SmPC. An interaction with the high-protein diet has been requested to be added into the section 4.5.

Exposure relevant for the safety

According to section 4.2 of the SmPC, the maximal daily dose of levodopa and carbidopa used in the clinical studies was 5880 mg and 1470 mg, respectively. Based on this, the maximal dose taken at one occasion can be 1960 mg and 490 mg of levodopa and carbidopa, when dosed tid. However, the maximal dose taken at one occasion for which pharmacokinetic data is available is 4 x 245mg-61.25 mg. Steady-state peak plasma concentrations following the 4 x 245 mg Numient treatment was 5423 and 498 ng/mL for levodopa and carbidopa, respectively.

2.4.3. Pharmacodynamics

Mechanism of action

Parkinson's disease is caused by degeneration of dopaminergic projections in the brain leading to dopamine depletion (Samii 2004). Supplementation with dopamine itself is not possible, since dopamine does not cross the blood-brain barrier.

Levodopa, a precursor of dopamine is able to cross the blood-brain barrier and is converted into dopamine in the brain. Upon oral administration, Levodopa is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. Carbidopa, a dopamine decarboxylase inhibitor, does not cross the blood-brain barrier and does not affect the metabolism of Levodopa within the central nervous system at therapeutic doses. Administration of Carbidopa with Levodopa enhances the amount of Levodopa available for transport to the brain. Levodopa-Carbidopa products have been registered for many years for the symptomatic treatment of Parkinson's disease.

There are currently two releasing modes of Levodopa-Carbidopa products: immediate release (IR) and modified release (often indicated as controlled release (CR)). Numient contains one IR Levodopa-Carbidopa component and two modified release Levodopa-Carbidopa components. Numient is therefore considered a modified release product.

Levodopa is actively transported across various cellular barriers by saturable amino acid transporters, which result in a relatively short Levodopa absorption window in the gastrointestinal tract (Gomes 1999; Gomes 2002; Quiñones 2004; Dave 2004). The activity of the LAT2 transporter appears to be pH-dependent and is optimal under non-alkaline conditions (Gomes 2002).

This is relevant with respect to Numient: apart from one IR Levodopa-Carbidopa component, the release of the other two Levodopa-Carbidopa components of Numient is dependent of different pH environments along the gastrointestinal tract. One of these Levodopa-Carbidopa components exhibits an insignificant drug release at acidic pH but a rapid drug release at neutral pH. The other Levodopa-Carbidopa component has similar properties but a modified drug release at neutral pH. Another component of Numient, tartaric acid, is hardly released at acidic pHs, but exhibits a controlled release at neutral pH. Tartaric acid is used to provide an optimum microenvironment in the alkaline region of the gastrointestinal tract for Levodopa absorption.

2.4.3.1. The subsequent release and absorption of the different Levodopa-Carbidopa components of Numient in different pH environments along the gastrointestinal tract are postulated to provide a rapid onset of action and prolonged therapeutic effects. Pharmacodynamic studies

No pharmacodynamic studies were conducted with Numient in healthy volunteers or in early stage Parkinson's Disease (ESPD) patients.

Pharmacodynamic investigations have been conducted in advanced stage Parkinson's Disease (ASPD) patients, as an integral part of studies IPX066-B08-11, IPX066-B09-06 Part 1, and IPX066-B11-01. These studies compared IPX066 to IR and CR Levodopa-Carbidopa, and to Carbidopa/Levodopa/Entacapone.

Study IPX066-B08-11

Study IPX066-B08-11 concerns a randomized, open-label, cross-over study to compare the pharmacokinetics and pharmacodynamics of Numient to IR L-dopa+ treatment in study patients with advanced Parkinson's

disease. There were 2 treatment periods of seven days with seven days of prestudy IR L-dopa+ treatment in between.

Methods

27 Patients were randomized to one of the two treatment sequences Numient (195 or 245 mg Levodopa) followed by IR L-dopa+ (100mg Levodopa) or vice versa. The suggested dose conversion schedule of IR L-dopa+ into Numient treatment is presented in Table 6.

Table 4 Suggested dose conversion schedule of IR L-dopa+ into Numient treatment

Prestudy Levodopa Dose (mg)	IPX066 (Levodopa Dose [mg])	
First AM IR CD-LD Dose (mg)	First AM IPX066 Dose (mg)	Suggested Subsequent IPX066 Dose(s) (mg)
100	2 x 245	1 x 245 to 2 x 245 Q6H
150	3 x 195	1 x 195 to 3 x 195 Q6H
200	3 x 245	1 x 245 to 3 x 245 Q6H
250	4 x 245	1 x 245 to 4 x 245 Q6H

Abbreviations: AM = morning, IR = immediate release, CD = carbidopa, LD = levodopa, Q6H = every 6 hours
Note: For doses not listed, LD doses were to be rounded up to the next higher dose.

The dosing schedule of Numient was allowed to be adjusted within the first three days of treatment if necessary. In between the 7-day treatment periods there was a period of approximately 7 days in which patients received prestudy IR L-dopa+ treatment.

On day 1 and 8 of each treatment period pharmacodynamic investigations have been conducted prior to and after administration of one dose of study treatment.

The following efficacy/pharmacodynamic variables were evaluated:

- Tapping: the number of times the study patient could tap two counter keys 20 cm apart alternately in 1 minute with the most affected arm, assessed every 30 minutes on day 1 and hourly on day 8 of each treatment period
- Walk Time: the time to rise from a chair, walk 6 meters, turn, return to the chair, and sit down, assessed every 30 minutes on Day 1 and hourly on day 8 of each treatment period. A ≥20% change from the average predose measurements was considered 'on' time.
- Parkinson's disease diary: recording 'ON', 'OFF', and state of dyskinesia, on 3 days immediately prior to the first treatment and immediately prior to the end of each treatment period.
- Assessment of 'ON', 'OFF', and state of dyskinesia by investigator or qualified site personnel on days 1 and 8 of each treatment period.
- UPDRS Part III score determined by qualified site personnel on days 1 and 8 of each treatment period.

Levodopa and Carbidopa plasma concentrations have been collected prior to and up to 12 hours after administration of one dose of study treatment on day 1 and 8 of each treatment period.

Results

The demographic data of the 27 included study patients at baseline are presented in Table 7

Table 5 Patient characteristics at study entry

	Included patients (n= 27)
Male	78%
Age (years), mean (SD)	62.7 (8.6)
Age at onset of Parkinson's disease, mean (SD)	52.3 (8.7)
Total number of taps in the 'ON' state, mean (SD)	170.4 (64.6)
Total number of taps in the 'OFF' state, mean (SD)	117.9 (44.1)
Pretreatment 'OFF' time (hours), mean (SD)	5.94 (2.21)

Functional test outcomes upon a single Numient and IR L-dopa+ dose on day 1

Numient turned study patients 'ON' at least as quickly as IR L-dopa+ treatment. Study patients showed significantly more hours 'ON' during Numient treatment than during the IR L-dopa+ treatment (mean 4.74 hours versus 2.98 hours, respectively, p = 0.01).

Study patients on Numient treatment also exhibited a significantly greater average number of taps over 8 hours compared to subjects on IR L-dopa+ treatment (mean 169.3 Taps versus 153.1 Taps, respectively, p = 0.0076). This analysis was repeated at each time point.

Study patients on Numient treatment had significantly more Taps at every time point from 3 hours through 7 hours (all p < 0.026), with the exception of the 4 hour (P = 0.06) and 6.5 hour time points (p = 0.07) (Figure 6).

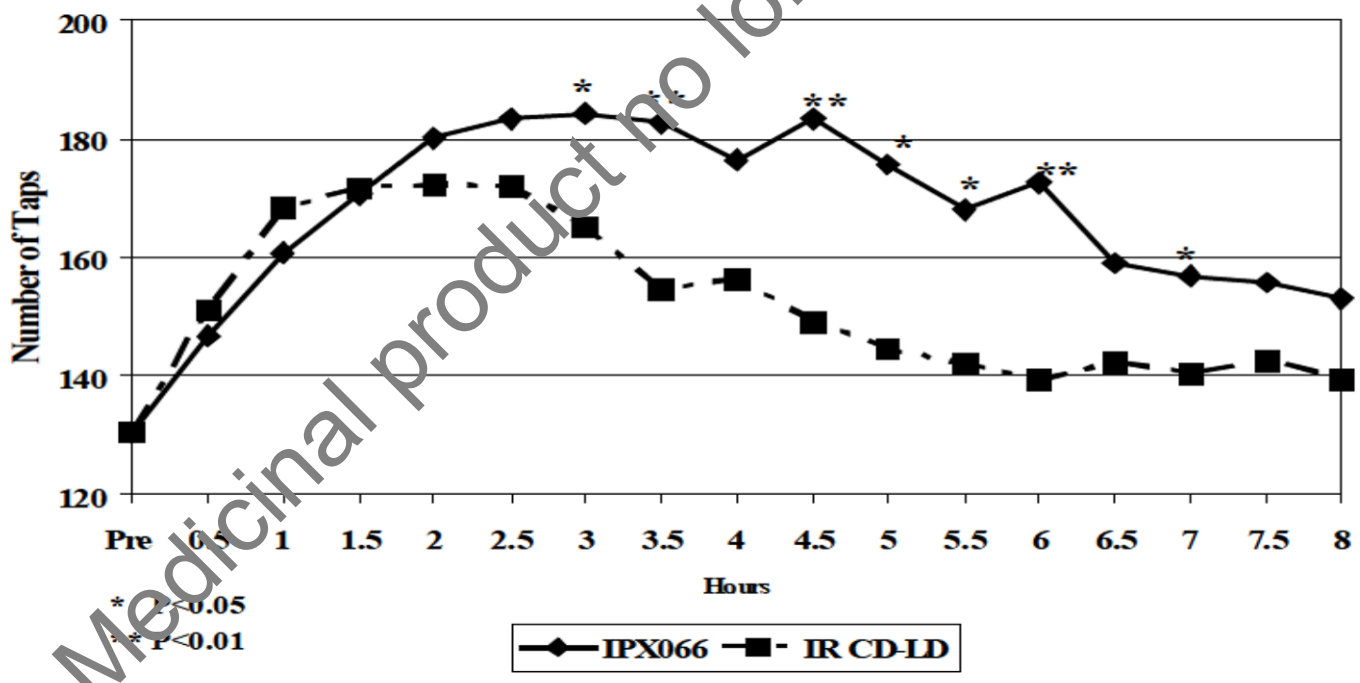


Figure 5 Mean total taps within one minute upon a single dose of study treatment

The results with respect to walk time, UPDRS III score, and investigator assessment of dyskinesia at day 1 were all similar to the observations with respect to tapping, all showing a larger statistically significant improvement upon Numient treatment compared to IR L-dopa+ treatment, 3 to 7 hours after dosing. Main results are presented in Table 8.

Table 6 Functional test outcomes expressed as mean (SD) upon a Numient and IR L-dopa+ dose on day 1

	Numient (n=27)	IR L-dopa+ (n=27)	p-value
Total number of finger taps	169.1	153.1	0.0076
Walk time (seconds)	17.1	19.3	0.0032
UPDRS III score	21.6	25.5	0.0389
'ON' time with no or non troublesome dyskinesia(hours)	5.56	3.26	<0.0001

Functional test outcomes upon a Numient and IR L-dopa+ dose on day 8

After completion of the 7-day treatment period, the functional tests of day1 were repeated on day 8 after administration of a single dose of Numient and IR L-dopa+ treatment (Table 8).

Compared to the observations at day 1, the number of taps within one minute tended to increase for both treatments, while the needed walking time and UPDRS III scores for these treatments tended to decrease with time (Table 8 vs. Table 8). Except for the number of finger tapping within one minute, differences in these outcome parameters remained statistically significant for a dose of Numient and IR L-dopa+ treatment.

Table 7 Functional test outcomes expressed as mean (SD) upon a Numient and IR L-dopa+ dose on day 8

	Numient (n=27)	IR L-dopa+ (n=27)	p-value
Total number of finger taps	180.7	169.8	0.12
Walk time (seconds)	15.9	17.1	0.02
UPDRS III score	18.9	21.5	0.03

The concentration-effect relationship for Numient seemed comparable to IR Levodopa-Carbidopa for tapping and UPDRS Part III in study IPX066-808-11.

2.4.4. Discussion on clinical pharmacology

The active substances of Numient are Levodopa and Carbidopa. Levodopa unlike Carbidopa is able to pass the blood brain barrier. In the brain Levodopa is converted into dopamine, which temporarily supplements the lack of dopamine in Parkinson's disease. Carbidopa, a dopamine decarboxylase inhibitor, inhibits peripheral conversion of Levodopa into dopamine. Numient contains one IR Levodopa-Carbidopa component and two modified release Levodopa-Carbidopa components. These components are released subsequently upon passage along the gastrointestinal tract, providing a modified release.

Pharmacokinetics

The initial rate of Levodopa absorption following administration of Numient was similar to that observed for Sinemet IR and faster than that observed for other registered modified release formulations, i.e. Sinemet CR and Stalevo. At 3.9-fold higher dose as compared to Sinemet IR, Sinemet CR and Stalevo, levodopa concentrations above 50% of Cmax were maintained longer with Numient, i.e. 4.9 hrs for Numient as compared to 1.5, 2.1, and 2.1 hrs for Sinemet IR, Sinemet CR, and Stalevo, respectively. This observation can be explained by the modified released characteristics of the Numient but also due to higher dose of Levodopa in this new formulation. This observation would also explain thrice daily dosing for this new Numient formulation, which is comparable to Sinemet CR (every 4 to 12 hrs during the waking day), and is lower than for IR Sinemet (even every 2 hrs).

Numient had a lower peak-to-trough fluctuation than IR levodopa-carbidopa (approximately 1.5 versus 3.2). Based on these, it can be concluded that the development goals of Numient have been reached from the pharmacokinetic point of view.

Additional biopharmaceutical performance of Numient has been assessed to be satisfactory. In vivo co-administration with up to 40 % v/v alcohol did not result in a dose dumping. High-fat, high-calorie meal did not affect the overall extent of absorption of Levodopa, but it significantly slowed the rate of absorption of Levodopa, by delaying the absorption of Levodopa by 2 hours and delaying peak plasma concentrations from 1.5 to 7 hrs. However, since the phase 2 and phase 3 studies were not standardized with regard to the concomitant food intake, the administration of Numient with or without food, as indicated in the SmPC, is considered acceptable.

Considering that Numient is a multiphasic formulation, additional parameters were included in the evaluation of bioequivalence between Numient manufactured at the Taiwan and US sites and in the evaluation of the food effect, i.e. partial AUC. Bioequivalence between the products manufactured at the Taiwan and US manufacturing site has been sufficiently demonstrated.

The applicant claims that the established IVIVC model adequately described the Levodopa and Carbidopa concentration-time data and therefore can be considered as a Level A. It can be concluded that IVIVC model reasonably predicts C_{max} and AUC_{inf}. However, it cannot be considered as a Level A model since it does not accurately predict the whole concentration-time curve for all formulations, i.e. the point-to-point relationship is not established, and high mean prediction errors were obtained for the partial AUCs. Further optimisation in order to obtain a more firm point-to-point relationship is needed.

Pharmacodynamics

The aforementioned results with respect to functional testing (including finger tapping, and walk time) demonstrate that the onset of action of Numient is similar to IR L-dopa+ treatment, but that its effects last longer. Between 3 and 6-7 hours post dosing the results of these functional tests indicated a better motor function for Numient compared to IR L-dopa+ treatment.

Association between pharmacokinetic and pharmacodynamic effects

The initial rate of absorption of Numient was similar to that of IR Levodopa-Carbidopa. This is logical, as the IR Levodopa-Carbidopa component is the first component of Numient to be released. The modified release Levodopa-Carbidopa components are released subsequently at later times. These facts could clarify why the number of taps per minute within about the first hour after dosing was comparable between Numient and IR L-dopa+ treatment. Levodopa concentrations above 50% of Cmax maintained 4.9 hours for Numient compared to 1.5 hours for IR Levodopa-Carbidopa. These sustained Levodopa concentrations allow a longer duration of therapeutic effects for Numient compared to IR L-dopa+. This was demonstrated: between 3 and 6-7 hours post dosing the results of functional tests were superior for Numient compared to IR L-dopa+. Hence, the performance on tapping over time seems to be congruent with the plasma concentration curve.

Since the effects of Numient treatment lasts for about 6-7 hours, dosing 3-4 times per day would be sufficient. The recommended dosing frequency of Numient (3-4 times per day) is indeed lower than that of IR L-dopa+, which needs to be dosed approximately every 2 hours.

2.4.5. Conclusions on clinical pharmacology

It can be concluded that the biopharmaceutical claims, i.e. faster initial absorption of Levodopa from Numient than from Sinemet CR and comparable to IR Levodopa-Carbidopa, and stable Levodopa concentrations with reduced maximum plasma concentration/minimum plasma concentration (Cmax/Cmin) fluctuation as compared to Sinemet IR, have been reached from the pharmacokinetic point of view. This appears to be due to the release of IR Levodopa-Carbidopa ahead of the subsequent release of 2 modified release Levodopa-Carbidopa components within Numient. In line with this mechanism, Levodopa concentrations above 50% of Cmax were maintained longer with Numient, i.e. 4.9 hrs for Numient as compared to 1.5, 2.1, and 2.1 hrs for Sinemet IR, Sinemet CR, and Stalevo, respectively. The conducted pharmacodynamic investigations over time, in terms of finger tapping, waking time and UPDRS III score, seem to be congruent with the plasma concentration curve.

These observations explain thrice daily dosing for this new Numient formulation, which is lower as compared to IR Sinemet (even every 2 hrs), but comparable to Sinemet CR (every 4 to 12 hrs during the waking day).

2.5. Clinical efficacy

Numient, a modified release Levodopa-Carbidopa product, has been developed for symptomatic treatment of idiopathic Parkinson's disease in adults.

The efficacy of Numient in patients with Parkinson's disease was investigated in three, double-blind, randomized controlled Phase 3 studies:

- Levodopa-naïve patients with early stage Parkinson's disease (ESPD):

Study IPX066-B08-05 (381 patients)

- Patients with advanced stage Parkinson's disease (ASPD):

Study IPX066-B09-02 (393 patients)

Study IPX066-B09-06 Part 1 (91 patients)

In addition, the efficacy of Numient has been investigated in four open-label studies:

Study IPX066-B08-11 (27 patients)

Study IPX066-B09-03 (open-label extension of studies IPX066-B08-05, IPX066-B08-11, and IPX066-B09-02; 617 patients)

Study IPX066-B09-06 Part 2 (open-label extension of study IPX066-B09-06 Part 1; 74 patients)

Study IPX066-B11-01 (43 patients)

Main features of study design of these are summarized in Table 5

Table 5 Summary of main features of pivotal studies

Dose response and main efficacy study(ies)

EARLY STAGE PARKINSON'S DISEASE (ESPD)

2.5.1.1. Study IPX066-B08-05 Dose-response study and main efficacy study

This was a randomized, double-blind, placebo-controlled, parallel group, 30-week, fixed-dose study in patients with early stage Parkinson's disease naïve to dopaminergic treatment. A 4-week titration period was followed by a 26 week maintenance period. 381 Patients were randomized to a daily dose of L-dopa 435, 735, 1170 mg (Numient) or placebo.

Methods

Main inclusion criteria were: Levodopa-naïve, idiopathic Parkinson's disease not being treated with dopaminergic agents, stable doses of anti-cholinergic therapy, amantadine, or MAO-inhibitor for at least 4 weeks before baseline were allowed during the study. Patients with gastro-intestinal pathology interfering with Levodopa absorption (i.e. peptic ulcers, surgical bowel procedure), narrow angle glaucoma, (potential) melanoma, myocardial infarction with residual arrhythmias were excluded.

Subjects were equally randomized into one of four treatment groups (i.e. 3 Numient treatment groups with a total daily dose of 435, 735, or 1170mg Levodopa– and one placebo treatment group). Total doses were administered in three equal doses (i.e. 145mg, 245mg, and 390mg TID).

Outcomes

Primary endpoint was the change from baseline in the sum of UPDRS ADL and motor score (UPDRS II-III) at end of study. The change in scores from baseline was determined at week 4, 9, 16, 23 and 30. Main secondary endpoints were the PGI and CGI scores and PDQ-39 score.

Treatment compliance was determined by counting the number of residual capsules after completion of the study period. Compliance was defined as a drug intake of 80-120% of the required amount.

Statistical methods

The primary analysis set included all treated study patients with at least one efficacy measurement post-dosing. Study patients were analyzed according to the dose to which they were randomized. Data of subjects not completing the 30 weeks of study treatment were included in the analyses at study endpoint using a last observation carried forward (LOCF) approach. A sensitivity analysis was performed using a mixed-model repeated measures (MMRM) analysis.

The analysis method was based on an ANCOVA approach with baseline values as covariate. All possible interactions between treatment, region (Europe/North America) and strata (prior dopaminergic treatment) were examined and those that were significant at the 0.10 level were kept in the model. The only significant interactions that were found, were treatment by region interactions. The model therefore included main effects for treatment, region and strata, and an interaction effect for region by treatment.

Provided there was an overall significant treatment effect ($p<0.05$), subsequently pairwise comparisons were performed i.e. 145mg Levodopa in Numient vs. placebo, 245mg Levodopa in Numient vs. placebo, and 390mg Levodopa in Numient vs. placebo. In order to control for multiplicity, the Fisher LSD was used. Since this procedure does not provide a closed testing procedure, Dunnett's procedure was used as well as a sensitivity procedure.

Similar analyses were conducted for the secondary endpoints including the total UPDRS scores and the quality of life endpoint PDQ-39.

For categorical variables, a generalized Cochran Mantel Haenszel (CMH) approach was used at the end of study with the combinations of region (Europe/North America) and any previous dopaminergic treatment as strata. Provided the Generalized CMH statistic was significant ($P\leq0.05$), each of the active treatments was compared to placebo.

Sensitivity analysis

Sensitivity analyses for the responders' analyses were conducted for an improvement in UPDRS II-III scores of 20, 30, or 40%.

Results

The number of study patients at randomisation and at the end of study and reasons for dropout are presented in Table 10. Most of the study treatment discontinuations occurred within the first 9 weeks of the study. Most of the premature study treatment discontinuations were due to adverse events. Lack of efficacy was the most important reason for premature study discontinuation in the placebo group.

Table 8 Number of study patients/participant flow

Time window	13-4-2009; 05-10-2010			
n-screened	427			
Study arm	**Numient 145 mg*TID**	**Numient 245 mg TID**	**Numient 390 mg TID**	**Placebo**
n-randomised	87	104	98	92
n-completed	72	83	74	71
n-early discontinuation due to	15	21	24	21
Adverse events	5	15	15	4
Lack of efficacy	4	0	1	12
Withdrawal by subject	3	1	3	4
Protocol violation	1	0	2	0
Noncompliance	0	1	1	0
Lost to follow-up	1	1	0	0
Death	0	1	0	0
Other**	1	2	2	1

* Numient is a fixed combination product of Levodopa and Carbidopa. Since the ratio of these compounds within the product is fixed (4:1) and Carbidopa only contributes to the effects of Levodopa, only the amount of Levodopa within the product has been represented here.

**Six study patients at site 202 were removed from the study by the Sponsor because the UPDRS ratings performed at this site indicated that the procedures differed significantly from both the Sponsor's expectations of how these ratings were to be performed and how these ratings were performed at other sites participating in the study.

The baseline data are presented in

Table 11. The majority of patients were about 65 years of age, male (about 55%), and had a diagnosis of Parkinson's disease for about 2 years. The mean sum of UPDRS II and III scores at baseline varied between 36 and 38 across different treatment groups. More than 80% of patients used concomitant medications for Parkinson's disease. Usage of such medication tended to be higher for 145 mg TID Numient treatment (16%) as compared to other treatment groups (7-8%). Treatment compliance was >95% in all patients.

Table 9 Baseline features by study treatment

Study arm	Numient 145 mg*TID (n=87)	Numient 245 mg TID (n=104)	Numient 390 mg TID (n=98)	Placebo (n=92)
Mean age (SD)	63.8 (9.8)	65.2 (9.7)	64.8 (9.3)	65.4 (9.4)
Male (%)	54%	57%	55%	57%
Duration Parkinson's disease (years), mean (SD)	2.3 (3.1)	1.8 (1.9)	2.0 (2.33)	1.8 (2.0)
UPDRSII -III score				
mean (SD)	36.1 (13.6)	38.2 (15.6)	36.3 (13.0)	36.5 (11.89)
range	19 -78	18 - 89	18 - 65	20-90
Total PDQ-39 score, mean (SD)	26.0 (16.9)	25.2 (18.6)	25.1 (17.1)	24.0 (15.5)
Concomitant medications for Parkinson's disease				
None	16.1%	8.7%	7.1%	8.7%
Dopamine agonists	0	1.0%	0	0
MAO-inhibitors	26.4%	33.7%	27.6%	28.3%
Anticholinergics	6.9%	4.8%	5.1%	4.3%
Amantadine	16.1%	18.3%	26.5%	20.7%
Compliance**	100%	100%	99.0%	97.8%

* Numient is a fixed combination product of Levodopa and Carbidopa. Since the ratio of these compounds within the product is fixed (4:1) and Carbidopa only contributes to the effects of Levodopa, only the amount of Levodopa within the product has been represented here.
**Proportion of patients who had taken 80-120% of the provided capsules.

Primary endpoint: "Change in UPDRS II-III score"

The improvement from baseline in UPDRS II-III score is presented in Table 12. The UPDRS score decreased by more than 10 points compared to baseline in all Numient treatment groups, compared to -0.6 points in the placebo group. The changes from baseline tended to be higher for increasing Numient dosages -11.7 points for Numient 145mg, -12.9 points for Numient 245 mg, and -14.9 points for Numient 390mg Numient TID. Changes from baseline in UPDRSII-III scores for each Numient regime differed statistically significantly from placebo treatment ($p<0.0001$).

Table 10 Change in UPDRS II-III score at end of study compared to baseline

UPDRS II-III score	Numient 145 mg TID (n=87)	Numient 245 mg TID (n=104)	Numient 390 mg TID (n=98)	Placebo (n=92)
Baseline, mean	36.1	38.2	36.3	36.5
Change from baseline, mean				
End of study	**-11.7**	**-12.9**	**-14.9**	**-0.6**
Δ with placebo p-value	-11.1 <0.0001	-12.3 <0.0001	-14.3 <0.0001	-
By week				
Change from baseline, mean				
Week 4	- 8.0	- 8.4	- 9.6	-2.9
Week 9	-11.5	-10.8	-12.7	-3.3

Table 10 Change in UPDRS II-III score at end of study compared to baseline

UPDRS II-III score	Numient 145 mg TID (n=87)	Numient 245 mg TID (n=104)	Numient 390 mg TID (n=98)	Placebo (n=92)
Week 16	-13.0	-12.9	-14.7	-3.1
Week 23	-13.3	-13.9	-16.6	-3.1
Week 30	-13.0	-13.7	-16.6	-1.4

Responder analysis

A summary of the responder analysis is presented in Table 13. Regarding the UPDRS II-III scores responders were defined as patients who improved at least 5 units from baseline. Responders were also defined based on the different percentage improvement from baseline in the UPDRS II-III scores. More than half of Numient-treated patients experienced ≥30% improvement in summed UPDRS II-III score, compared to 12% of placebo-treated patients.

Table 11 Responder analysis with respect to change from baseline in summed UPDRS II-III score

Treatment	Number (%) of Subjects Who Responded with an Improvement of at Least				
	5 Units	20%	25%	30%	40%
Placebo (N = 92)	28 (30.4)	21 (22.8)	13 (14.1)	11 (12.0)	7 (7.6)
IPX066					
145 mg LD (N = 87)	61 (70.1)	54 (62.1)	50 (57.5)	44 (50.6)	30 (34.5)
245 mg LD (N = 104)	83 (79.8)	75 (72.1)	70 (67.3)	56 (53.8)	39 (37.5)
390 mg LD (N = 98)	71 (72.4)	69 (70.4)	64 (65.3)	57 (58.2)	50 (51.0)

Abbreviations: LD = levodopa.

Notes:

Responder was defined as a subject whose UPDRS Part II plus Part III score improved at least 5 units from Baseline. Additional analyses were performed using 25% improvement as the definition of response with sensitivity analyses at 20%, 30%, and 40% improvements.

For all definitions of responder and for each active treatment versus placebo, $P < 0.0001$, Cochran-Mantel-Haenszel test.

Secondary endpoints

Results for the main secondary endpoints are presented in Table 14. Mean total UPDRS-scores of L-dopa+-treated patients decreased by 12 points or more, while respective scores in placebo-treated patients remained similar (p<0.0001). Absolute changes were higher for patients treated with 390mg compared to 145mg TID Numient (-14.6 vs. -12.2). 70% or more patients experienced clinical improvement upon Numient treatment compared to one-fourth to one-third of placebo-treated patients (p<0.0001).

Table 12 Results of secondary endpoints by study treatment

Secondary endpoint	Numient 145 mg TID (n=87)		Numient 245 mg TID (n=104)		Numient 390 mg TID (n=98)		Placebo (n=92)	
PGI at end of study								
Very much worse	0		1.0%		2.0%		1.1%	
Much worse	0		4.9%		4.1%		8.7%	
Minimally worse	8.3%		5.8%		7.1%		23.9%	
No change	21.4%		17.5%		13.3%		32.6%	
Minimally improved	31.0%		30.1%		29.6%		25.0%	
Much improved	34.5%	**39.3%**	31.1%	**40.8%**	29.6%	**43.9%**	6.5%	**8.7%**
Very much improved	4.8%		9.7%		14.3%		2.2%	
PGI-responder, %*	70.3%		70.9%		73.5%		33.7%	
p-value vs. placebo	<0.0001		<0.0001		<0.0001			

Table 12 Results of secondary endpoints by study treatment

Secondary endpoint	Numient 145 mg TID (n=87)	Numient 245 mg TID (n=104)	Numient 390 mg TID (n=98)	Placebo (n=92)
CGI at end of study				
Very much worse	0	0	0	1.1%
Much worse	0	2.9%	2.0%	4.3%
Minimally worse	6.0%	2.9%	5.1%	23.9%
No change	21.4%	23.3%	20.4%	43.5%
Minimally improved	32.1%	32.0%	26.5%	18.5%
Much improved	36.9%	33.0%	35.7%	7.6%
Very much improved	3.6% **40.3%**	5.8% **38.8%**	10.2% **45.9%**	1.1% **8.7%**
CGI-responder, %*	72.6%	70.8%	72.4%	27.2%
p-value vs. placebo	<0.0001	<0.0001	<0.0001	
Total PDQ-39, mean				
Baseline	25.6	25.5	25.6	24.0
Change from baseline at end of study	-4.4	-3.8	-6.0	+0.6
Δ with placebo	-5.0	-4.4	-6.6	
p-value	0.02	0.03	0.0008	

* Defined as a patient experiencing **any** improvement upon study treatment

ADVANCED STAGE PARKINSON'S DISEASE (ASPD)

2.5.1.2. Study IPX066-B09-02

Study IPX066-B09-02 concerns a randomized, double-blind, double-dummy, active-control, parallel-group superiority study planned to compare the efficacy and safety of Numient to that of IR L-dopa+ in patients with advanced Parkinson's disease with insufficient control of motor symptoms i.e. motor fluctuations.

Methods

Main inclusion criteria were: idiopathic Parkinson's disease with at least 2.5 cumulative hours per day 'OFF' time, stable regime of a total daily dose of at least 400mg L-dopa+ dosed four times daily for at least 4 weeks before screening. Concomitant treatment (i.e. for at least 4 weeks prior to screening) with Amantadine, anticholinergics, selective MAO B inhibitors or dopamine agonists was allowed when kept constant.

Exclusion criteria involved: prior or active psychosis, prior medical conditions or prior surgical procedures that would interfere with Levodopa absorption, prior or current narrow-angle glaucoma, arrhythmias after myocardial infarction, previous or suspected melanoma.

Three different treatment regimens have been applied in the study:

1. open label IR L-dopa+ in the IR dose-adjustment period of 3 weeks. IR L-dopa+ dosage was determined on an individual basis.
2. open label Numient in the dose-conversion period of 6 weeks. Numient dosage was determined on an individual basis.
3. randomised double-blind maintenance period of 13 weeks. Patient completing the conversion period randomised either to continue Numient or to the L-dopa+ immediate release dose determined at the end the IR L-dopa+ dose-adjustment period.

IR L-dopa+ dose adjustment

During this period, the patients were to initially take IR L-dopa+ on their pre-study IR Levodopa regimen. Dose adjustment, if necessary, was allowed during the IR L-dopa+ period. Suggested time between dosage adjustments was approximately every 3 days. The dosing regimen was to be finalized at least 5 days prior to the end of week 3.

Dose-conversion from IR L-dopa+ into Numient

During the 6-week Numient dose-conversion period, the investigators were to establish a dosing regimen using one strength of Numient that minimized "OFF" time without causing troublesome dyskinesia. The recommended dosing frequency was 3 times a day during waking hours (approximately every 6 hours).

The suggested dose conversion from IR L-dopa+ into Numient is presented in Table 15 Total daily doses of Numient were nearly twice as high compared to IR L-dopa+ treatment. The recommended Numient doses reflect the bioavailability and peak concentration (Cmax) of Levodopa from Numient of approximately 70% and 30%, respectively, relative to Sinemet, in study patients with advanced Parkinson's disease with motor fluctuations (Hauser 2011).

Table 13 Suggested dose conversion from IR L-dopa+ into Numient

Total Daily IR LD Dose (mg)	Suggested Initial IPX066 Dosage (LD in mg) Each Dose Approximately 6 Hours Apart During Waking Hours		
	Morning Dose	Midday Dose	Evening Dose
400 - 550	3 capsules x 95	3 capsules x 95	3 capsules x 95
551 - 750	4 capsules x 95	4 capsules x 95	4 capsules x 95
751 - 950	3 capsules x 145	3 capsules x 145	3 capsules x 145
951 - 1250	3 capsules x 195	3 capsules x 195	3 capsules x 195
1251 - 1650	4 capsules x 195 OR 3 capsules x 245	4 capsules x 195 OR 3 capsules x 245	4 capsules x 195 OR 3 capsules x 245
>1650	4 capsules x 245	4 capsules x 245	4 capsules x 245

LD= Levodopa

Study patients were to be maintained on only one dose strength of Numient, administered not more frequently than five times a day to prevent accumulation. A bedtime dose of Numient was allowed.

Outcomes

The primary efficacy variable was the baseline-adjusted 'OFF' time expressed as a percentage of waking hours at the end of study. The percent of 'OFF' time was defined as the total 'OFF' time divided by the total waking time from the Parkinson's disease diaries completed for the 3 days immediately prior to the visit. Additionally, 'ON' times with and without troublesome dyskinesias were evaluated as endpoints.

Secondary outcomes included UPDRS scores at week 12, 17 and 22. At end of study, PGI and CGI were determined, as well as the baseline-adjusted (sub) scores of the PDQ-39, SCOPA-S, mRS, EQ-5D and SF-36 scales.

Statistical methods

The primary efficacy analysis was an ANCOVA model with treatment and centers as factors and the percent of 'OFF' time during waking hours at baseline as a covariate. The baseline measurement of 'OFF' time was the last non-missing-valued 'OFF' time measurement that was made prior to first administration of IR Levodopa-Carbidopa at the initiation of the dose-adjustment period. A baseline-adjusted measurement was defined as any measurement that was made after the first dose of study drug. If one or more days of reporting of 'OFF' time, 'ON' time with or without (non)-troublesome dyskinesia in the diaries was/were missing, the diaries from the available days were used.

Prior to carrying out the main factor ANCOVA model, the full model, including the interactions of treatment by center was tested. If the treatment by center interaction was significant at the 0.10 level, then the full model was to be used. Additionally, in the case of interaction, the effect of region (North America or Europe) was to be investigated. If the treatment by center interaction was not significant, then the analysis was to be conducted on a two-factor main effects model. Additional analyses examined the interactions of treatment with region and with country.

All randomized patients were included in the primary analysis. Missing data were imputed using the last observation carried forward method for patients who dropped out after visit 6 and the substitution of the average end of study value for the two groups combined, for those who dropped out before Visit 6. A sensitivity analysis for imputing missing data was performed by using a Mixed Model Repeated Measure (MMRM) approach.

Results

Of the 567 study patients screened for this study, 471 were enrolled and received at least one dose of study treatment. A total of 450 study patients completed the 3-week IR L-dopa+ dose-adjustment period and entered the Numient dose-conversion period. 57 Of these patients (12.7%) discontinued early. Adverse events (23 patients) and lack of efficacy (13 patients) constituted the most common reasons for discontinuation during the dose conversion phase.

A total of 393 study patients were randomized at the end of the dose conversion period of whom 368 study patients completed the 13-week double-blind treatment period.

The number of study patients at randomisation and end of study is presented in Table 16

Table 14 Number of study patients/participant flow

Time window	29-9-2009; 19-01-2011	
n-screened	**567**	
IR L-dopa+ adjustment (3 weeks)	**471**	
n-early discontinuation due to	**21**	
Adverse events	3	
Lack of efficacy	0	
Withdrawal by subject	7	
Protocol violation	1	
Noncompliance	1	
Lost to follow-up	0	
Death	0	
Other	9	
Numient dose conversion (6 weeks)	**450**	
n-early discontinuation due to	**57**	
Adverse events	23	
Lack of efficacy	13	
Withdrawal by subject	12	
Protocol violation	4	
Noncompliance	0	
Lost to follow-up	0	
Death	2	
Other	3	
Randomized, double blind treatment (13 weeks)	**393**	
	Numient	**IR L-dopa+**
Randomized	**201**	**192**

Completed	**186**	**182**
n-early discontinuation due to	15	10
Adverse events	3	3
Lack of efficacy	2	2
Withdrawal by subject	5	2
Protocol violation	1	1
Noncompliance	0	1
Lost to follow-up	0	1
Death	0	0
Other	4	0

The demographic data of the two randomized treatment groups are presented in Table 17. The mean age of subjects enrolled in the study was 63.5 years, with a range of 40 to 90 years. More males (62.0%) than females (38.0%) were enrolled in the study.

Table 15 Characteristics at baseline of randomized patients in study IPX066-B09-02

	Numient (n=201)	**IR L-dopa+ (n=192)**	**All randomized study patients (n=393)**
Age, mean (SD)	63.1 (10.0)	63.4 (8.8)	63.2 (9.4)
Male (%)	64%	65%	65%
Duration Parkinson's disease (years), mean (SD)	7.5 (4.8)	7.3 (4.2)	7.4 (4.5)
Total daily IR L-dopa+ dose in mg at baseline, mean (SD)			794.3 (364.2)
Dosing frequency, mean (SD)			5.1 (1.7)
OFF/ ON in hours (X, SD)			
'OFF' time	6.05 (2.26)	5.89 (1.97)	5.97 (2.12)
'ON' time without dyskinesia	8.41 (3.31)	8.51 (3.01)	8.46 (3.16)

	Numient (n=201)	**IR L-dopa+ (n=192)**	**All randomized study patients (n=393)**
'ON' time with non-troublesome dyskinesia	1.56 (2.30)	1.59 (2.39)	1.57 (2.34)
'ON' time with troublesome dyskinesia	0.37 (0.93)	0.35 (1.00)	0.36 (0.96)
Compliance*	100%	99.5%	99.7%

* Proportion of patients without any protocol deviation

Outcome

The study patients' functional status at baseline and end of study for randomized patients is presented in Table 18. The mean 'OFF' time by study visit for randomized study patients (n=393) has been presented in Figure 8.

Table 16 Summary of randomized study patients' diary data

	Numient (n= 201)	IR L-dopa+ (n= 192)
'OFF' time (hours), mean		
Baseline randomization period	**6.1**	**5.9**
End of IR L-dopa+ adjustment	5.6	5.6
End of Numient dose conversion period/randomization	3.9	3.9
End of randomized study period	**3.9**	**4.9**
Change end of study compared to baseline	**-2.2**	**-1.0**
Δ with IR L-dopa+ p-value	-1.2 < 0.0001	
'OFF' time as a percentage of waking hours Baseline randomization period Change end of study compared to baseline	 36.9% -13.1%	 36.0% -6.2%
Δ with IR L-dopa+ p-value	-6.9 < 0.0001	

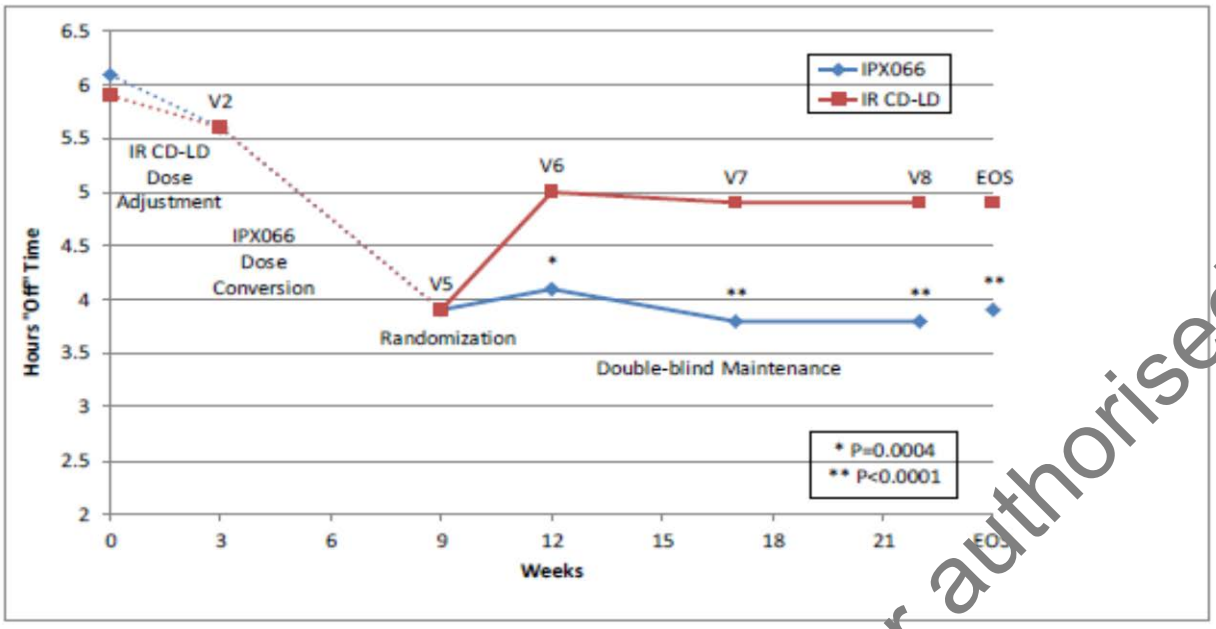


Figure 6 Mean 'OFF' time by visit for randomized study patients

Abbreviations:

V = Visit; EOS = End of Study; IR CD-LD= IR L-dopa+

N values (Numient/IR L-dopa+): V1, V2, V5 = 201/192, V6 = 188/186, V7 = 188/183, V8 = 185/181, EOS = 201/192

The mean 'OFF' time decreases by about 0.4 hours upon IR L-dopa+ treatment. There was no evidence of stabilization of 'OFF' time over the 3 week IR adjustment period. In the conversions period 'OFF' time decreased further with 1.7 hours in the average. See figure above. After randomization the mean 'OFF' time remained similar for the Numient-treated patients but worsened in the IR CD-LD group up to 1 hour. See figure above. However the OFF time did not return to the level at the end of the IR CD-LD adjustment period. The mean change in 'OFF' time at end of study compared to baseline was larger for Numient treatment (-2.2 hours) than for IR L-dopa+ treatment (-1.0 hours; p<0.0001). In line with this, the decrease in 'OFF' time as a percentage of waking hours was larger for Numient treatment than for IR L-dopa+ treatment (-13.1 vs. -6.2%; p<0.0001).

An alternative way of examining 'OFF' time is to select a level of improvement to define a responder. By definition, anyone who did not complete the trial was considered a non-responder from the point at which they dropped out. Using levels of improvement of at least 0.5 hours, 1 hour, 1.5 hours, 2 hours, and 3 hours, the percent of responders at end of study is shown in Table 19. The decrease in 'OFF' time was larger for Numient treatment compared to IR L-dopa+ treatment at any unit of improvement (p≤ 0.0034).

Table 17 Improvement in 'OFF' time at the end of study compared to baseline for randomized patients

Treatment Group	Number (%) of Responders[a]				
	Improvement in "Off" Time From Baseline to End of Study				
	≥0.5 Hours	≥1 Hour	≥1.5 Hours	≥2 Hours	≥3 Hours
IPX066 (N = 201)	140 (69.7%)	127 (63.2%)	111 (55.2%)	95 (47.3%)	69 (34.3%)
IR CD-LD (N = 192)	101 (52.6%)	87 (45.3%)	74 (38.5%)	61 (31.8%)	42 (21.9%)
P value	<0.0001	<0.0001	0.0003	0.0007	0.0034

[a] Anyone who did not complete the trial was considered a non-responder from the point at which they dropped out.

Secondary endpoints

The main secondary endpoints with respect to study IPX066-B09-02 are presented in Table 20. Upon Numient treatment, the mean UPDRS II-III score in the 'ON' state was decreased by about 6 points at end of study compared to baseline. For IR L-dopa+ treatment this decrease was lower (-2.2; p<0.0001). In line with this, the PGI and CGI responder rate (defined as any improvement upon study treatment) was higher for Numient (67.5 and 66% respectively) compared to IR L-dopa+ (42.3 and 44.2% respectively, p<0.0001 for both outcome measures). Decreases in PDQ-39 scores were higher upon Numient treatment (-3.4) compared to IR L-dopa+ treatment (-1.9; p=0.03).

Table 18 Results of main secondary endpoints by study treatment

Secondary endpoint	**Numient (n= 201)**		**IR L-dopa+ (n= 192)**	
UPDRS II-III in 'ON' state, mean				
Baseline	32.3		32.4	
End of study	-5.7		-2.1	
Δ with IR L-dopa+	4.0			
p-value	<0.0001			
PGI at end of study				
Very much worse	0		0	
Much worse	6.5%		11.6%	
Minimally worse	12.5%		25.4%	
No change	13.5%		20.6%	
Minimally improved	29.0%		24.9%	
Much improved	30.0%	**38.5%**	15.3%	**17.4%**
Very much improved	8.5%		2.1%	
PGI-responder, %*	67.5%		42.3%	
p-value vs. IR L-dopa+	<0.0001			

Secondary endpoint	Numient (n= 201)		IR L-dopa+ (n= 192)	
CGI at end of study				
Very much worse	0		0	
Much worse	2.5%		4.2%	
Minimally worse	11.0%		20.0%	
No change	20.5%		31.6%	
Minimally improved	26.0%		30.5%	
Much improved	35.5%	**40.%**	12.1%	**13.7%**
Very much improved	4.5%		1.6%	
CGI-responder, %*	66.0%		44.2%	
p-value vs. IR L-dopa+	<0.0001			
Total PDQ-39, mean				
Baseline	30.6		31.3	
Change from baseline at end of study	-3.7		-1.9	
Δ with IR L-dopa+	-1.5			
p-value	0.03			

* A defined as a study patient experiencing any improvement upon study treatment

Changes from baseline at end of study with respect to the SCOPA-S sleeping scale, and some general scales with respect to health-related quality of life (EQ5D, SF-36) did not differ statistical significantly between Numient and IR L-dopa+ treatment (p> 0.05).

Dosing and dosing frequency of Numient and IR L-dopa+

At screening, enrolled study patients took a mean total daily L-dopa+ dose of 794.3±364.2 mg (Table 21). The mean dosing frequency was 5.1±1.7 times per day at baseline. During the first 3 weeks of the trial, investigators could adjust the IR L-dopa+ dosage if needed to attain maximum clinical benefit. At the end of dose adjustment (week 3/Visit 2), the mean total daily dose of IR L-dopa+ was 815 mg. There was no change from baseline in daily IR L-dopa+ dose for 60.4% of study patients, while the daily IR L-dopa+ dose was adjusted upward by more than 100 mg per day for 15.8% of subjects. At the end of dose adjustment, the mean dosing frequency was 5.2±1.7 times per day. The frequency decreased from baseline for 3.4% of study patients and increased for 14.1% of study patients.

For each individual the Numient dose was adjusted during the 6-week dose-conversion period to reach maximum clinical benefit. The median daily dose of Numient at the end of dose conversion period was 1365 mg

(mean 1621.7mg) for all randomized study patients, with 88% of the study patients receiving less than 2400 mg of Numient.

Table 19 Dosing

	Numient	IR L-dopa+
N	201	192
IR L-dopa+ dose adjustment (3 weeks)*		
Mean dose (SD) at start period	**794.3 mg (364.2)**	
Median dose	750.0 mg	
Range	400 - 3000 mg	
Mean dose (SD) at end period	**814.6 mg (371.4)**	**814.5 mg (341.2)**
Median dose	750 mg	800 mg
Range	400 - 2550 mg	400 – 2000 mg
Numient dose conversion (6 weeks)**		
Mean dose (SD) at start period	According to conversion table	
Median dose	Mean, median and range values not specified	
Range		
Mean dose (SD) at end period	**1630.0 mg (760.4)**	**1613.0 mg (729.1)**
Median dose	1330 mg	1450 mg
Range	570 – 5390 mg	570 – 4900 mg
Randomised treatment phase (13 weeks)		
Mean dose (SD) at start period	**1630.0 mg (760.4)**	**814.5 mg (341.2)**
Median dose	1330 mg	800 mg
Range	570 – 5390 mg	400 – 2000 mg
Mean dose (SD) at end period	**1621.7 mg (744.3)**	**814.5 mg (356.5)**
Median dose	1365 mg	750 mg
Range	570 – 5390 mg	400 – 2550 mg

*All patients received IR L-dopa+ treatment in this study phase

**All patients received Numient treatment in this study phase

The final dosing frequency at the end of dose conversion phase for all randomized study patients averaged 3.6±0.7 (median 3.0) for Numient and 5.1±1.5 (median 5.0) for IR L-dopa+ at the end of dose adjustment (Table 22). The most common dosing frequency for Numient was 3 doses per day (52.2% of subjects), with over 90% of study patients taking 4 or fewer doses per day. In comparison, the most common dosing frequency for IR L-dopa+ was 4 times per day (43.8% of subjects), with 56.0% taking IR L-dopa+ 5 or more times per day.

Table 20 Dosing frequency

	Numient	IR L-dopa+
N	393	393
Number of doses per day		
< 3	0	0
3	52.2%	0.3%
4	39.7%	43.8%
5	7.9%	26.7%
6	0	16.3%
>6	0.3%	13.0%
Mean (SD)	3.6 (0.7)	5.1 (1.5)
Median	3	5
Range	3 - 7	3 - 18

Dosing of IR L-dopa+ compared to Numient

The observed median dose of Numient was approximately 1.8 times that of IR L-dopa+ for all randomized study patients, based on the 74.5% bioavailability relative to IR L-dopa+, the estimated systemic exposure to Levodopa with Numient is approximately 36% higher than that with IR L-dopa+.

There was a trend for dose related conversion ratios although the differences were small. For subjects with an adjusted daily dose IR L-dopa between 400-600 mg the Numient conversion ratio was 2.3 (SD 0.7). For subjects receiving IR L-dopa between 800-1200 mg, 1200-1600 mg, or > 1600 mg conversion rates were 2.0 (SD 0.5) , 2.0 (SD 0.5), 1.9 (SD 0.6), and 1.7 (SD 0.4) respectively.

2.5.2. Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 21 Summary of main studies in early Parkinson's disease patients

Title: Study IPX066-B08-05					
Design	A Phase III, randomized, double-blind, placebo-controlled, parallel 30-week study to determine the effects of 145, 245, and 390 mg thrice daily L-dopa+ treatment in Levodopa-naïve patients with early stage Parkinson's disease				
	Duration run-in phase: 4 weeks Duration double-blind phase: 26 weeks Duration of extension phase: 9 months (Study IPX066-B09-03)				
Hypothesis	Superiority				
Treatments groups	IPX066 145mg TID**, $n_{randomized}$=87				
	IPX066 245mg TID, $n_{randomized}$=104				
	IPX066 390mg TID, $n_{randomized}$=98				
	Placebo TID, $n_{randomized}$=92				
Endpoints and definitions	Primary endpoint	Change from baseline in UPDRS Parts II-III score at end of study			
	Secondary endpoint	Change from baseline in PDQ-39			
	Secondary endpoint	PGI at end of study			
	Secondary endpoint	CGI at end of study			
Database lock	Study ran from 13 April 2009 until 5 October 2010				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Modified intention to treat, LOCF End of study				
Effect estimate per comparison	Treatment group	IPX066 145mg TID	IPX066 245mg TID	IPX066 390mg TID	Placebo
	$n_{Randomised}$ $n_{Completed}$	87 72	104 83	98 74	92 71
	UPDRS II-III score, mean Baseline Change from baseline at end of study Proportion of patients with ≥5 points improvement	 36.1 -11.7 70.1%	 38.2 -12.9 79.8%	 36.3 -14.9 72.4%	 36.5 -0.6 30.4%
	Total PDQ-39, mean Baseline Change from baseline at end of study	 25.6 -4.4	 25.5 -3.8	 25.6 -6.0	 24.0 +0.6
	Δ with placebo p-value	-5.0 0.02	-4.4 0.03	-6.6 0.0008	
	PGI at end of study Very much worse Much worse Minimally worse No change	 0 0 8.3% 21.4%	 1.0% 4.9% 5.8% 17.5%	 2.0% 4.1% 7.1% 13.3%	 1.1% 8.7% 23.9% 32.6%

Title: Study IPX066-B08-05					
	Minimally improved	31.0%	30.1%	29.6%	25.0%
	Much improved	34.5%	31.1%	29.6%	6.5%
	Very much improved	4.8%	9.7%	14.3%	2.2%
	PGI-responder,%*	70.3%	70.9%	73.5%	33.7%
	p-value vs. placebo	<0.0001	<0.0001	<0.0001	
	CGI at end of study				
	Very much worse	0	0	0	1.1%
	Much worse	0	2.9%	2.0%	4.3%
	Minimally worse	6.0%	2.9%	5.1%	23.9%
	No change	21.4%	23.3%	20.4%	43.5%
	Minimally improved	32.1%	32.0%	26.5%	18.5%
	Much improved	36.9%	33.0%	35.7%	7.6%
	Very much improved	3.6%	5.8%	10.2%	1.1%
	CGI-responder,%*	72.6%	70.8%	72.4%	27.2%
	p-value vs. placebo	<0.0001	<0.0001	<0.0001	
Notes	*A responder was defined as any patient who experienced any improvement upon study treatment. **In this table only the amount of Levodopa within the L-dopa+ product has been specified. This is because Carbidopa exerts no clinically relevant pharmacological effects except from enhancing the effects of Levodopa.				

Table 22 Summary of main studies in advanced stage Parkinson's disease

Title: Study IPX066-B09-02		
Design	Randomized, double-blind, double-dummy, active-control, parallel-group study planned to compare the efficacy and safety of IPX066 to that of IR L-dopa+ in study patients with advanced stage Parkinson's disease with insufficient control of motor symptoms or motor fluctuations.	
	Run-in: 3 weeks Conversion to IPX066: 6 wks Double-blind treatment: 13 weeks Extension phase: 9 months	IR L-dopa+ dose optimalisation Titration to IPX066 IPX066 versus IR L-dopa+ Study IPX066-B09-03
Hypothesis	Superiority	
Treatments groups	IPX066 mean dose 1622 mg/day, $n_{randomized}$= 201	
	IR L-dopa+ mean dose 825 mg/day, $n_{randomized}$= 192	
Endpoints and definitions	Primary endpoint	'OFF' time as a percentage of waking hours, change from baseline
	Co-primary endpoint	Decrease in 'OFF' time at the end of study compared to baseline
	Secondary endpoint	summed UPDRS II-III score, change from baseline
	Secondary endpoint	PDQ-39, change from baseline
	Secondary endpoint	PGI score at end of study
	Secondary endpoint	CGI score at end of study
Database lock	Study ran from 29 September 2009 until 19 January 2011	
Results and Analysis		
Analysis description	**Primary Analysis**	

Title: Study IPX066-B09-02			
Analysis population and time point description	Modified intention to treat, LOCF End of study		
Effect estimate per comparison	**Treatment group**	**IPX066**	**IR L-dopa+**
	$n_{Randomised}$ $n_{Completed}$	201 186	192 182
	'OFF' time as percent of waking hours Baseline End of study	36.9% -13.1%	36.0% -6.2%
	Δ with IR L-dopa+ p-value	-5.8% < 0.0001	
	Decrease in 'off' time compared to baseline ≥0.5 hour ≥ 1 hour ≥1.5 hours ≥2 hours ≥3 hours	 69.7% 63.2% 55.2% 47.3% 34.3%	 52.6% 45.3% 38.5% 31.8% 21.9%
	Overall p-value	≤0.0034	
	UPDRS II-III in 'ON' state, mean Baseline End of study	 32.3 -5.7	 32.4 -2.1
	Δ with IR L-dopa+ p-value	-3.5 <0.0001	
	Total PDQ-39, mean Baseline Change from baseline at end of study	 30.6 -3.4	 31.3 -1.9
	Δ with IR L-dopa+ p-value	-1.5 0.03	
	PGI at end of study Very much worse Much worse Minimally worse No change Minimally improved Much improved Very much improved PGI-responder, %* p-value vs. IR L-dopa+	 0 6.5% 12.5% 13.5% 29.0% 30.0% 8.5% 67.5% <0.0001	 0 11.6% 25.4% 20.6% 24.9% 15.3% 2.1% 42.3%
	CGI at end of study Very much worse Much worse Minimally worse No change Minimally improved Much improved Very much improved CGI-responder, %* p-value vs. IR L-dopa+	 0 2.5% 11.0% 20.5% 26.0% 35.5% 4.5% 66.0% <0.0001	 0 4.2% 20.0% 31.6% 30.5% 12.1% 1.6% 44.2%

*A responder was defined as any patient who experienced any improvement upon administration of study treatment.

2.5.2.1. Supportive study(ies)

Study IPX066-B09-06 Part 1

Study IPX066-B09-06 Part 1 concerns a randomized, double-blind, double-dummy, switching and cross-over study in patients with advanced stage PD (ASPD). Patients were converted from stable Carbidopa/Levodopa/Entacapoen (CLE) doses to Numient over a 6-week period. The design of study IPX066-B09-06 Part 1 is comparable to that of study IPX066-B09-02, but there was no CLE adjustment period in study IPX066-B09-06 Part 1. At study entry in study IPX066-B09-06 Part 1, patients were converted from stable CLE doses to open-label Numient over a 6-week period. Following dose conversion, 91 study patients were randomized in a 1:1 ratio to one of two treatment sequences and treated with either Numient or CLE under double-blind conditions for 2 weeks (period 1). In between the study treatment periods, study patients received open-label Numient for 1 week. After this, patients received treatment with the alternate study medication (CLE or Numient) for 2 weeks (period 2) under double-blind conditions.

91/110 Study patients (83%) completed the dose conversion period and were randomized. During the dose conversion period, one study patient (0.9%) withdrew due to adverse events, 7 study patients withdrew consent (6.4%), 7 study patients withdrew for lack of efficacy (6.4%), 3 subjects discontinued due to protocol violations (2.7%), and 1 study patient withdrew for other reasons (0.9%).

Percentage 'OFF' time during walking hours was 36.1% at baseline. The decrease in 'OFF' time was higher upon Numient treatment compared to CLE treatment (24.0±16.2% vs. 32.5±21.9%;p<0.001). 60% OF IPX066-treated and 44% of CLE-treated ASPD patients experienced a decrease in 'OFF' time of at least 1.5 hours.

Study IPX066-B11-01

Study IPX066-B1-01 concerned an uncontrolled study in 43 ASPD patients previous CR L-dopa+ treatment. This treatment was converted to Numient treatment within a 6-week period After this period the effects of Numient treatment was evaluated during 2 consecutive follow-up periods of 6 months.

33/43 (76.7%) subjects completed the dose conversion period of CR L-dopa+ treatment into Numient. The reasons for premature treatment discontinuation were: adverse events (3), lack of efficacy (3), withdrawal by study patient (2), non-compliance (1), and other reasons (1).

32 Study patients proceeded to the first 6-month extension of study IPX066-B11-01. 7 Patients discontinued study treatment, mainly (4/7) because of adverse events. 12 Patients received Numient treatment in the second 6-month extension of study IPX066-B11-01. All these patients completed this study part.

For 12 patients the functional status has been determined after a single dose of CR L-dopa+ and Numient treatment at inclusion Mean 'OFF' time upon CR L-dopa+ treatment was 3.2 hours compared to 1.7 hours upon Numient treatment (p<0.0001).

80% of all study patients in study IPX066-B11-01 experienced improvement upon dose conversion of CR L-dopa+ into Numient. The same rate has been observed in the first 6-month study extension. No assessment has been conducted in the second 6-month study extension. 80% Of patients preferred Numient treatment above CR L-dopa+ treatment.

Open label extension studies IPX066-B09-03 and study IPX066-B09-06 Part 2

Study IPX066-B09-09-03 and study IPX066-B09-06 Part 2 both concern open-label extension studies of original studies in which all patients received individualized Numient treatment.

Study IPX066-B09-03 (617 patients) concerns a 9-month open-label extension study of Numient treatment in patients who successfully completed studies IPX066-B08-05 (early stage Parkinson's disease), IPX066-B08-11 and IPX066-B09-02 (both concern ASPD). Respectively 97%, 96% and 95% of 617 patients entered in long-term extension study were still in study at month 1 ,5 and 9 respectively.

The median Numient total daily dose at month 9 was 720 mg (mean = 727 mg). UPDRS Total score at inclusion was 26.7 for ESPD patients and 34.5 for ASPD patients. UPDRS scores remained relatively stable for both ESPD patients (decrease between 0 and -1 compared to baseline during 9 months of follow-up) and ASPD patients (decrease between 0 and -2 compared to baseline during 9 months of follow-up). 84.6% of ASPD patients and 82.7% of ASPD patients were satisfied with Numient treatment at month 9. At month 9, PDQ-39 scores were increased by about 2 points for both ESPD and ASPD patients from baseline scores of 21.4 and 27.5 respectively.

83.3% Of all ESPD study patients included in study IPX066-B09-03 used Numient doses within the dose range of 435 through 1170 mg. With respect to ASPD study patients, the median (mean) daily dose of Numient at month 9 in this extension study was 1450 (1618) mg in the ASPD study patients originally enrolled in study IPX066-B09-02. This dose is comparable to that established during dose conversion period in the antecedent Study B09-02. The median (mean) daily dose of Numient utilized at month 9, 2518 (2313) mg, by the 12 ASPD patients from phase 2 Study B08-11 is also similar to the Numient dose utilized during the antecedent study. The dosing frequency established during the antecedent studies generally was maintained throughout the long-term study. Specifically, 80%, 82%, and 83% of study patients who took Numient 3 or fewer, 4, or 5 times daily in the antecedent studies still took Numient 3 or fewer, 4, or 5 times daily after exposure to Numient for up to an additional 9 months.

Study IPX066-B09-6 Part 2 (74 patients) concerns 6-month open-label extension study in patients who completed study IPX066-B09-06 Part 1. Retention rate at month 3 and 6 were 93% and 89.2%, respectively. UPDRS II-III scores remained relatively stable during this open-label extension study (an increase of up to 1.4 points compared to a baseline score of 28.6). The median Numient dose for the 74 study patients at entry in study part 2 (end of part 1) of study IPX066-B09-06 was 1495 mg (mean ± SD: 1696 mg ± 678 mg) and 68/74 study patients (91.9%) took Numient 4 times or less at end of part 1. At the end of part 1, 66/71 subjects (93%) with dosing data took Numient 4 times or less per day. A total of 51/71 subjects (72%) maintained the same dosing frequency as they had used during part 1.

In summary, in both open-label extension study IPX066-B09-03 and study IPX066-B09-06 Part 2 all patients received open-label Numient treatment. Numient -dosing and dosing frequency of Numient remained stable compared to the original studies. UPDRS Scores remained relatively stable over study periods. Both at month 1 and 9, most patients (>60%) were satisfied with Numient treatment in study IPX066-B09-03.

2.5.3. Discussion on clinical efficacy

Early stage Parkinson's disease (ESPD)

Design and conduct of clinical studies, efficacy data and additional analyses

ESPD Patients have been included in study **IPX066-B08-05**. In this double-blind, placebo-controlled, 30-week study 381 patients were randomized to receive thrice daily Numient treatment according one of the following Levodopa strengths (145mg, 245 mg, and 390 mg) or thrice daily placebo treatment. Primary outcome was the change from baseline with respect to the UPDRS II-III score. Six patients were removed from study site 202 because the UPDRS ratings performed at this site differed significantly from the sponsor's expectations about

the performance of these ratings. However these patients were included in the statistical analysis. The Applicant demonstrated that treatment effects were consistent for the baseline carried forward approach as well as for the worst observation carried forward approach. For this reason, the exclusion of these 6 patients had no profound impact on overall study results.

The study duration and endpoints comply with the Guideline on clinical investigation of medicinal products in the treatment of Parkinson's disease (EMA/CHMP/330418/2012 rev. 2). The study design of study IPX066-B08-05 however does not comply with this guideline, since this study lacks an active comparator arm (e.g. IR or CR L-dopa+ treatment). Hence, it remains unclear whether the modified release formulation has an advantage with respect to efficacy against comparative treatment for Parkinson's disease in ESPD. This is not considered an objection against the granting of a marketing authorisation as the efficacy of Numient against placebo treatment has been demonstrated in study IPX066-B08-05 (see below). Claims about superiority in comparison to any other L-dopa+ product are however not warranted based on this placebo-controlled study, since such has not been demonstrated.

The change from baseline in UPDRS II-III score (36.1, 38.2, 36.3, and 36.5 respectively) was -11.7, -12.9 and -14.9, and -0.6 for 145 mg, 245 mg, and 390 mg Levodopa within Numient and placebo capsules respectively. Differences were statistically significant as compared to placebo. UPDRS II-III scores increased by ≥5 points in at least 70% of Numient-treated patients compared to 30.4% of placebo treated patients. The proportions of patients with at least 30% improvement from baseline with respect to the $UPDRS_{II-III}$ score were 51%, 54%, 58%, and 12% for 145 mg, 245 mg, and 390 mg Levodopa within Numient and placebo capsules respectively. Mean total PDQ-39 scores decreased from 25.6, 25.5, 25.6, and 24.0 at baseline with 4.4, 3.8, and 6.0 points upon 145mg, 245mg, and 390 mg thrice daily Levodopa within Numient compared to an increase of 0.6 point for thrice daily placebo treatment($p<0.04$). These results show that Numient improves motor function in patients with early stage Parkinson's disease, as assessed by patients and investigators. The improvement in UPDRS score tended to be larger with higher Numient doses. The dose-effect relationship was however not very strong. The difference in UPDRS II-III score from baseline was 3.2 point higher for 390mg compared to 145mg Levodopa within Numient. This is not considered an issue, as Numient treatment is titrated based on individual patient's clinical response. An improvement of at least 30% from baseline with respect to the UPDRS II-III score was experienced by at least 51% of Numient treated patients compared to 12% of placebo-treated patients (difference 39%). This difference in response is considered large enough to be clinically meaningful.

The clinical relevance of these outcomes is confirmed by the CGI and PGI responder analysis. At end of study, PGI-scores were either much improved or very much improved in respectively 39.3%, 40.8%, and 43.9% of patients treated with 145mg, 245mg, and 390mg Levodopa in Numient. PGI-scores were much or very much improved in 8.7% of placebo-treated patients. Similar observations have been obtained with respect to the CGI-scores for the 145 mg (40.3%), 245mg (38.8%), 390mg (45.9%) Levodopa in Numient treatment groups and placebo treatment group (8.7%). For both PGI and CGI scores the difference between each Numient -treatment dose and placebo was statistically significant ($p< 0.0001$).

Study **IPX066-B09-03** is the 9-month open-label extension study of study IPX066-B08-05 and some studies in ASPD patients (IPX066-B08-11 and IPX066-B09-02). In this study, 268 ESPD patients received open-label treatment with a total daily dose of 435-1170 mg Numient. Slight decreases in UPDRS total scores (-0.5 to -0.8) compared to baseline (26.7) have been observed during this trial. These small changes indicate that over the duration of the trial the improvement in UPDRS score did not differ from the main study. PDQ-39 scores tended to increase with time: +0.4 at month 1, +1.7-1.8 at month 5 and 9 compared to 21.4 at baseline.

The open label and uncontrolled design of the long term extension phase do not allow for a formal conclusion of maintenance of efficacy as in principle patients who benefit will continue. However the higher retention rates (95% of the study patients included in study IPX066-B09-03 completed the extension study) and stable scores may allow the conclusion that the effects of Numient remain relatively constant with time in ESPD patients. In addition, there was no indication that increasing doses were needed to maintain clinical effects, since 83.3% of all ESPD study patients included in study IPX066-B09-03 used Numient doses within the dose range of 435 through 1170 mg. Moreover as the long term efficacy of L-dopa is not a subject of discussion (based on the long experience with it) these data are considered sufficient in support of long term efficacy of Numient.

Advanced stage Parkinson's disease (ASPD)

Design and conduct of clinical studies, efficacy data and additional analyses

In the randomized, double-blind, double dummy study **IPX066-B09-02** the efficacy of Numient has been compared with IR L-dopa+ treatment during 13 weeks in patients with ASPD. This main study phase was preceded by an IR L-dopa+ dose adjustment period of 3 weeks and a Numient dose conversion period of 6 weeks respectively. 201 Patients were randomized to receive Numient treatment, 192 patients were randomized to receive IR L-dopa+ treatment. At baseline, the 'OFF' time as percent of waking hours was 36-37% (i.e. approximately 6 hours) for both treatment groups. At end of study, this percentage was decreased with 13% (i.e. -2.2 hours) and 6.2% (i.e. -1.0 hour) upon Numient treatment and IR L-dopa+ treatment respectively. 55.2% of Numient-treated ASPD patients experienced a decrease of at least 1.5 hours in 'OFF' time compared to 38.5% of IR L-dopa+ treated patients. The decrease in PDQ-39 score from a baseline of 31 was larger for Numient-treated patients (-3.4) compared to IR L-dopa+-treated patients (-1.9;p=0.03). The clinical relevance of these findings is supported by the fact that PGI-scores in 38.5% of Numient-treated patients compared to 17.4% of IR L-dopa+ treated patients were much or very much improved (p< 0.0001). Much or very much improved CGI-scores have been obtained in 40% of Numient -treated patients and 13.7% of IR L-dopa+ treated patients.

As presented in Figure 8 above, 'OFF' time decreased during 3 weeks of IR L-dopa+ adjustment and there was no tendency of forming a plateau. It is therefore likely that the reduction in 'OFF' time would have continued if IR L-dopa+ had been further optimised. Instead, after these three weeks patients were converted into Numient treatment.

A total of 57 out of the 450 (12.7%) ASPD patients discontinued Numient treatment during the 6-week dose conversion period of IR L-dopa+ into Numient and optimisation period of Numient. The main reasons for premature study discontinuation in these 57 patients were: adverse events (40.4%), lack of efficacy (22.8%), and subject withdrawal (21.1%). Only patients who tolerated Numient were randomized.

Hence, the treatment comparison with IR L-dopa may not be fair considering the IR L-dopa+ optimisation was incomplete where as in the conversion into Numient patients where titrated up to the maximum. It was unclear why the baseline values at study entry have been used as a reference instead of values at randomization or values at end of IR L-dopa+ optimization. In additional analyses, the Applicant demonstrated that treatment effects remained consistent irrespective whether baseline was chosen at study entry, at IR L-dopa+ dose optimization, or at randomization.

Study **IPX066-B09-06 Part 1** concerns a randomized, double-blind, 2x2 week cross-over study. In this study, the effects of Numient have been compared with those of Carbidopa/Levodopa/Entacapone (CLE). CLE treatment was converted into Numient treatment. There was no CLE dose adjustment. 19 out of 110 study patients (17.3%) discontinued Numient T in the dose conversion period. The most important reasons for study

discontinuation in these 19 patients were: lack of efficacy and withdrawal by subject (both 36.8%). The Applicant demonstrated in additional analyses that these patients were not underexposed to Numient treatment. Hence, the dose conversion scheme of CLE treatment into Numient appears appropriate.

After treatment conversion into Numient, the effects of Numient treatment were compared with those of CLE treatment. Percentage 'OFF' time during waking hours was 36.1% (5.9 hour) at baseline. The decrease in 'OFF' time was higher upon Numient treatment (-2.1 hour) as compared to CLE treatment (-0.7 hour). 60% of Numient-treated and 44% of CLE-treated ASPD patients experienced a decrease in 'OFF' time of at least 1.5 hours. Effects remained similar at similar doses of Numient within the open-label extension phase of study IPX066-B09-06 Part 1 (study part 2). 89.2% (66/74) of the included 74 patients were still in this study at month 6 of the open-label extension phase.

Study **IPX066-B11-01** is an open-label conversion study of CR L-dopa+ alone or in combination with IR L-dopa+ to Numient, followed by an open-label extension study of Numient in ASPD patients. 43 Patients have been included in this study. Ten study patients (23.3%) discontinued study participation within the conversion period of CR L-dopa+ into Numient. The most important reasons for this premature study discontinuation in these 10 patients were: adverse events (30%), lack of efficacy (30%), and subject withdrawal (20%). 'OFF' time was shorter for Numient treatment compared to CR L-dopa+ treatment during a 6-hour observation period after administration of a single dose of Numient and CR L-dopa+ in 12 study patients (1.7 hours for Numient treatment compared to 3.2 hours for CR L-dopa+ treatment; $p<0.0001$).

Study **IPX066-B09-09-03** concerns an open-label extension study of original studies (both ESPD and ASPD) in which all patients received individualized Numient treatment. UPDRS Total scores remained relatively stable over study periods (up to -2 point decrease). Also Numient dosing and dosing frequency remained stable. At month 9, 83% of ASPD patients were satisfied with Numient treatment. These findings demonstrate that the effects of Numient treatment remain relatively stable over time in ASPD patients.

Dose conversion into Numient

The proposed dose conversion tables in the SmPC are based upon the conversion schedule applied in the clinical studies. However, up to 23% of study patients(n= 158 patients) discontinued study participation upon conversion of pre-study L-dopa+ treatment into the modified release L-dopa+ product Numient within studies IPX066-B09-02, IPX066-B11-01, IPX066-B09-06 Part 1. Adverse events were the reason for premature study discontinuation upon treatment conversion in 23 patients out of 57 discontinuing patients (= 40.4%) in study IPX066-B09-02. In study IPX066-B11-01, adverse events were the reason for premature study discontinuation upon treatment conversion in three out of ten patients (i.e. 30%). % . Lack of efficacy (n= 7) and withdrawal by subject (n=7) were the most important reasons for premature study dropout upon treatment conversion of CLE treatment into Numient (n=19).

Separate conversion tables have been proposed for the conversion of dose ranges of IR L-dopa+, and CLE treatment into single doses of Numient. The Applicant demonstrated that the bioavailability of Levodopa of the proposed Numient doses is in between that of respective IR L-dopa+ or CLE dose ranges. The Applicant also demonstrated that patients who discontinued Numient treatment due to adverse events after treatment conversion from IR L-dopa+ in study IPX066-B09-02 were not overexposed. Moreover, patients who discontinued Numient treatment due to lack of efficacy or withdrawal by subject after treatment conversion from CLE treatment were not underexposed. Hence the conversion tables into Numient were considered acceptable.

Both by using the baseline observation carried forward and the worst observation carried forward approach with respect to missing values, it was demonstrated that treatment effects were consistent in both studies IPX066-B08-05 and IPX066-B09-02.

2.5.4. Conclusions on the clinical efficacy

Pharmacodynamics

As demonstrated in the pharmacodynamic studies, the onset of action of the modified release product Numient, as measured by finger tapping, is similar to that of IR L-dopa+. Compared to IR L-dopa+ the duration of action of Numient is however longer as measured by UPDRS and tapping and there is a larger decrease in OFF time, allowing a less frequent dosing of Numient (thrice daily versus every 2 hours). This is considered an advantage of Numient.

Early stage Parkinson's disease (ESPD)

Numient treatment was found to be more effective than placebo for the treatment of ESPD with respect to combined motor and ADL functioning and global improvement. Due to the lack of an active control arm it is not possible to conclude whether in ESPD Numient is superior to IR L-dopa+. The results of a 9-month open-label extension study indicate that the effects of Numient are maintained.

Advanced stage Parkinson's disease (ASPD)

There were uncertainties regarding the IR L-dopa optimisation phase within study IPX066-B09-02, as UPDRS scores did not reach a plateau phase, and this could imply that the obtained effect sizes may be exaggerated. However, the Applicant demonstrated that treatment effects in general were consistent irrespective of the choice of baseline at study entry, dose conversion or baseline at randomization.

Ultimately, the results of the studies in ASPD patients indicated that the effects of Numient with respect to decreasing 'OFF' time are superior to those of IR L-dopa+ treatment and that these effects remain relatively stable with time in ASPD patients.

2.6. Clinical safety

The analysis of the safety of Numient in this report includes all subjects who received at least one dose of study treatment (Numient, active comparator, or placebo). Results of 17 trials, comprising 6 Phase III studies in study patients with early and advanced stage Parkinson's disease (ESPD and ASPD respectively), one Phase 2 study in patients with advanced stage Parkinson's disease (ASPD), and 9 Phase 1 studies in healthy subjects have been included in this safety analysis. There are no ongoing trials.

The following evaluations have been performed in nearly all trials: laboratory evaluations, physical examination, vital signs assessment, ECG, analysis of concomitant medications, ECG, and recording of adverse events.

Patient exposure

350 Patients with early stage Parkinson's disease (ESPD) and 628 patients with advanced stage Parkinson's disease (ASPD) have been included in the conducted Phase 2 and 3 studies (Table 25).

Table 23 Exposure to Numient and other treatments in Phase 2 and 3 trials

	Numient	IR L-dopa+	CR L-dopa+	Carbidopa/Levodopa/Entacapone (CLE)	Placebo
Phase 2 study					
ESPD patients	0	0	0	0	0
ASPD patients	27	27	0	0	0
Controlled Phase 3 studies					
ESPD patients	289	0	0	0	92
ASPD patients	558	471	0	88	0
Uncontrolled Phase 3 studies					
ESPD patients**	61	0	0	0	0
ASPD patients***	43	0	12*	0	0
Total ESPD patients	**350**	**0**	**0**	**0**	**92**
Total ASPD patients	**628**	**498**	**12***	**88**	**0**
Total ESPD+ ASPD patients	**978**	**498**	**12***	**88**	**92**

***** In a substudy of open-label study, 12 of 43 included patients in study IPX066-B11-01 received a single dose of CR L-dopa+ at visit 0, prior to dose conversion to Numient.

****** Only the 61 ESPD patients from controlled study IPX066-B08-05 who received Numient treatment for the first time in uncontrolled study IPX066-B09-03 have been represented here. 207 of the patients received Numient treatment in both study IPX066-B08-05 and IPX066-B09-03. These numbers have been represented with respect to the controlled Phase 3 studies only. No other study treatment has been investigated in ESPD patients in uncontrolled Phase 3 studies.

******* All ASPD patients who completed any controlled Phase 2 and 3 studies were eligible to receive Numient treatment in a Phase 3 uncontrolled study. 336 patients from study IPX066-B09-02 and 13 ASPD patients from study IPX066-B08-11 have been included in uncontrolled Phase 3 study IPX066-B09-03. 74 Patients from study IPX066-B06-02 Part 1 have been enrolled in uncontrolled Phase 3 study IPX066-B06-02 Part 1. Since all these ASPD patients have received Numient treatment within the original Phase 2 and 3 controlled studies (IPX066-B08-11, IPX066-B09-02, and IPX066-B06-02 Part 1), these patient numbers have not been repeated within this row.

Numient exposure, dosing and dosing frequency in ESPD and ASPD patients

The total cumulative exposure of ESPD(n=350) and ASPD patients(n=628) to Numient has been represented in Table 26. Total cumulative exposure was defined as the total number of days during which subjects were on Numient treatment throughout all the studies in which they were enrolled. If there were time gaps between studies or differing treatments within a study, only the number of days the subject was on Numient were counted. Over 50% of ESPD patients were exposed to Numient for 365 days or more compared to 27% of ASPD patients. Trials with Numient in healthy volunteers all lasted shorter than 30 days.

Table 24 Patients with Parkinson's disease exposed to Numient in clinical trials

	Any	≥30 days	≥90 days	≥180 days	≥ 365 days
ESPD patients	350 (100%)	321 (92%)	295 (84%)	288 (82%)	200 (57%)
ASPD patients	628 (100%)	564 (90%)	461 (73%)	424 (68%)	170 (27%)
Total	**978**	**885**	**756**	**712**	**370**

Mean exposure time for all 978 patients included in Phase 2 and 3 Phase trials who received Numient treatment was 40.2 weeks (Table 27). Mean(SD) exposure time to Numient was 49.5 (24.6) weeks for ESPD patients (n=350) compared to 34.9 (20.7) weeks for ASPD patients(n=628). Median exposure time for ESPD and ASPD patients were 66 and 42 weeks respectively. ESPD patients received a mean total daily dose of 743 mg Numient in on average 3 administrations. ASPD patients received a mean total daily dose of 1737 mg Numient in on average 3.6 administrations.

Table 25 Exposure to Numient: exposure time, dosing and dosing frequency in ESPD and ASPD patients

	ESPD (n=350)	ASPD (n=628)	Total (n=978)
Mean exposure time (weeks), mean (SD)	49.5 (24.6)	34.9 (20.7)	40.2 (23.2)
Median exposure time (weeks)	66.3	42.1	46.9
Final total daily Numient dose, %			
<1600 mg	99.4%	53.5%	69.9%
≥1600 mg	0.6%	46.5%	30.1%
Mean (SD) total daily Numient dose (mg)	742.6 (320.4)	1737.2 (817.2)	1381.3 (832.3)
Median total daily Numient dose (mg)	735	1560	1170
Range	190-3120	285-5880	190-5880
Mean daily frequency of dosing	3.0	3.6	3.4

Adverse events

summarizes treatment-emergent adverse events with respect to Phase 3 controlled studies. An adverse event was any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that did not necessarily have a causal relationship with this treatment.

EPSD

Adverse events in the ESPD study IPX066-B08-05 are summarized by dose group. The adverse event rate in the Numient 145 mg group (56.3%) was lower than that of the placebo group (72.8%) and the 245 mg (72.1%) and 390 mg (71.4%) groups.

ASPD

293 ASPD patients (52.5%) reported at least one adverse event upon Numient treatment. 36.2% Of these were treatment related. 4.8% of ASPD patients reported a serious adverse event upon Numient treatment, of which 0.9% were assessed as treatment-related. A total of 28 ASPD patients (5.0%) discontinued Numient treatment early because of at least one adverse event.

Table 26 Overview of adverse events in ESPD and ASPD patients in Phase 3 controlled studies

	ESPD (n=381)					ASPD (n= 1117)		
	Numient			Placebo		Numient	IR L-dopa+	CLE
	145mg*	245mg	390mg					
Number of patients	**87**	**104**	**98**	**92**		**558**	**471**	**88**
Any adverse event	56.3%	72.1%	71.4%	72.8%		52.5%	29.3%	13.6%
Treatment-related adverse event	43.7%	54.8%	59.2%	47.8%		36.2%	15.1%	5.7%
Serious adverse event	4.6%	4.8%	2.0%	3.3%		4.8%	1.5%	0
Treatment-related serious adverse event	0	0	0	0		0.9%	0.4%	0
Adverse event leading to early discontinuation	5.7%	14.4%	15.3%	4.3%		5.0%	1.3%	0
Death	0	1.0%	0	0		0.4%	0	0

*The Numient dosages are abbreviated by the amount of Levodopa within each Numient capsule. Patients received 3 Numient or placebo capsules per day.

The occurrence of adverse events by system organ class for ESPD and ASPD patients included within Phase 3 controlled studies is presented within Table 29. ESPD patients have been included in a double-blind Phase 3 study Particular adverse events with an incidence of 2% or higher have also been represented within this table.

The most frequently observed adverse events with respect to Numient treatment in ESPD patients concerned adverse events with respect to the following system organ classes: nervous system disorders (35%), gastrointestinal events (28%), psychiatric disorders (19%), musculoskeletal and connective tissue disorders (13%), and infections and infestations (12%). Absolute proportions were higher Numient compared to placebo treatment for all these organ classes, except for infections and infestations (11.4 vs. 19.6%), and musculoskeletal and connective tissue disorders (12.8 vs. 13.0%).

Table 27 Summary of adverse events within Phase 3 controlled trials

	ESPD-double blind			ASPD-double blind			ASPD-open label	
	Numient	Placebo		Numient	IR L-dopa+	CLE	Numient	IR L-dopa+
Number of patients exposed	**289**	**92**		**290**	**192**	**88**	**558**	**471**
Any adverse event	67.1%	72.8%		36.2%	39.6%	13.6%	43.9%	17.0%
Blood and lymphatic system	**0**	**2.2%**		**0.3%**	**0.5%**	**0**	**0.4%**	**0**
Anemia	0	2.2%		0	0	0	0.4%	0
Cardiac disorders	**4.2%**	**3.3%**		**1.4%**	**1.0%**	**0**	**1.3%**	**0**
Ear and labyrinth disorders	**1.7%**	**0**		**0.3%**	**0.5%**	**0**	**0.9%**	**0**
Endocrine disorders	**0.3%**	**0**		**0.3%**	**0**	**0**	**0.4%**	**0**
Eye disorders	**2.1%**	**4.3%**		**1.4%**	**0.5%**	**0**	**1.1%**	**0**
Gastrointestinal disorders	**28.0%**	**23.9%**		**7.9%**	**8.3%**	**1.1%**	**13.1%**	**3.0%**
Constipation	3.5%	1.1%		1.0%	1.0%	0	1.8%	0.4%
Dry mouth	4.2%	1.1%		0.3%	0	0	2.0%	0.4%
Salivary hypersecretion	0%	2.2%		0.3%	0	0	0	0.2%
Diarrhoea	2.4%	2.2%		1.7%	0.5%	0	1.3%	0.2%

	ESPD-double blind			ASPD-double blind			ASPD-open label	
	Numient	Placebo		Numient	IR L-dopa+	CLE	Numient	IR L-dopa+
Number of patients exposed	**289**	**92**		**290**	**192**	**88**	**558**	**471**
Nausea	18.0%	8.7%		2.4%	1.6%	0	5.7%	0.8%
Vomiting	3.1%	3.3%		0.7%	2.1%	0	1.8%	0.2%
General disorders and administration site conditions	**9.0%**	**9.8%**		**4.1%**	**6.3%**	**2.3%**	**5.6%**	**1.7%**
Asthenia	2.1%	0		0	0.5%	0	0.4%	0
Fatigue	1.0%	2.2%		0.7%	0	0	0.2%	0.4%
Gait disturbance	1.0%	2.2%		0	1.6%	0	0.7%	0
Peripheral oedema	2.1%	2.2%		1.7%	2.1%	1.1%	0.9%	0.6%
Hepatobiliairy disorders	**0.7%**	**0**		**0**	**0**	**0**	**0.2%**	**0.2%**
Immune system disorders	**0**	**0**		**0**	**0**	**0**	**0.2%**	**0**
Infections and infestations	**11.4%**	**19.6%**		**7.2%**	**8.3%**	**0**	**4.8%**	**3.0%**
Gastro-enteritis viral	0	2.2%		0	0.5%	0	0	0
Influenza	1.0%	2.2%		0.3%	0	0	0	0
Nasopharyngitis	3.8%	2.2%		0.3%	1.6%	0	0.4%	0.6%
Rhinitis	0.3%	3.3%		0	0	0	0	0
Tinea infection	0	2.2%		0	0	0	0.2%	0
Upper respiratory tract infection	0.7%	2.2%		1.4%	2.1%	0	1.4%	0
Injury, poisoning and procedural complications	**4.2%**	**7.6%**		**2.8%**	**5.2%**	**3.4%**	**4.1%**	**1.9%**
Fall	1.7%	4.3%		2.4%	2.1%	2.3%	2.7%	0.8%
Investigations	**4.5%**	**5.4%**		**3.4%**	**2.1%**	**1.1%**	**1.3%**	**0.8%**
Metabolism and nutrition disorders	**3.1%**	**5.4%**		**0.7%**	**1.0%**	**0**	**1.1%**	**0.4%**
Hyperglycaemia	0	2.2%		0	0	0	0	0
Hyponatraemia	0	2.2%		0.3%	0	0	0.2%	0
Musculoskeletal and connective tissue disorders	**12.8%**	**13.0%**		**5.5%**	**6.3%**	**2.3%**	**5.9%**	**3.2%**
Arthralgia	2.4%	1.1%		0.7%	2.1%	0	0.7%	0.4%
Back pain	2.4%	3.3%		1.0%	2.1%	0	1.8%	0.8%
Muscle spasms	2.4%	1.1%		0.3%	1.6%	0	0.5%	0.6%
Pain in extremity	2.8%	2.2%		1.0%	0.5%	0	0.4%	0.2%
Neoplasms	**1.0%**	**1.1%**		**0.3%**	**0.5%**	**0**	**0.4%**	**0.2%**
Nervous system disorders	**34.9%**	**30.4%**		**10.3%**	**8.3%**	**5.7%**	**18.1%**	**4.0%**
Dizziness	13.8%	5.4%		2.1%	2.1%	0	3.4%	0.4%
Dizziness postural	1.0%	1.1%		0	0	0	0.2%	0
Dyskinesia	3.8%	0		3.1%	1.0%	0	4.8%	0.6%
Headache	12.5%	10.9%		0.7%	1.6%	0	3.9%	1.3%
Restless legs syndrome	2.1%	0		0	0	0	0	0.2%
Somnolence	3.8%	2.2%		0.3%	0	1.1%	0.9%	0.8%
Psychiatric disorders	**19.4%**	**12.0%**		**9.7%**	**8.3%**	**2.3%**	**9.7%**	**1.9%**
Abnormal dreams	4.5%	0%		0	0.5%	0	0.7%	0.2%
Anxiety	3.5%	0		0.7%	1.6%	0	2.2%	0.2%
Depression	1.7%	5.4%		0.3%	2.6%	1.1%	1.1%	0.6%
Insomnia	5.9%	3.3%		3.4%	1.0%	0	2.2%	0.6%

	ESPD-double blind			ASPD-double blind			ASPD-open label	
	Numient	Placebo		Numient	IR L-dopa+	CLE	Numient	IR L-dopa+
Number of patients exposed	**289**	**92**		**290**	**192**	**88**	**558**	**471**
Initial insomnia	1.0%	2.2%		nd	nd	nd	nd	nd
Sleep disorder	2.1%	0		1.4%	2.1%	0	0.5%	0
Renal and urinary disorders	**2.1%**	**3.3%**		**2.1%**	**1.6%**	**1.1%**	**1.4%**	**0**
Pollakiuria	0	3.3%		0.3%	0	0	0.4%	0
Reproductive system and breast disorders	**0.3%**	**2.2%**		**0.7%**	**0**	**0**	**0.9%**	**0**
Respiratory, thoracic and mediastinal disorders	**6.2%**	**3.3%**		**1.0%**	**2.6%**	**0**	**1.6%**	**0.4%**
Dyspnoea	2.1%	0		0.7%	0	0	0.4%	0
Skin and subcutaneous tissue disorders	**5.9%**	**3.3%**		**2.8%**	**2.1%**	**0**	**2.0%**	**0.4%**
Surgical and medical procedures	**0.7%**	**3.3%**		**0.7%**	**1.6%**	**0**	**0.2%**	**0**
Vascular disorders	**5.5%**	**3.3%**		**2.4%**	**2.6%**	**0**	**2.5%**	**0.6%**
Orthostatic hypotension	2.4%	1.1%		0.7%	1.0%	0	0.4%	0.2%

nd= not determined

Adverse events of special interest

Neurological adverse events

Neurological adverse events occurred in 38% of ESPD patients and 32% of ASPD patients in Phase 2 and 3 studies (Table 30). In ESPD patients, these adverse events were reported by 26% of patients treated with 145mg Numient TID compared to 38% of patients treated with 390mg Numient TID. Headache and dyskinesia were the most frequently reported adverse events.

Dyskinesia occurred in 4.3% of ESPD patients and in 9.4% of ASPD patients receiving Numient treatment. Dyskinesia was reported by 2%, 1%, and 5% of 145 mg, 245 mg, and 390 mg Levodopa within Numient, and 0 study patients in the placebo group in study IPX066-B08-05. The time of occurrence for dyskinesia was after 7 days of exposure.

Hyperkinesia and dystonia occurred in 0 and 0.3% of ESPD patients compared to 0.2 and 1.4% of ASPD patients in Phase 2 and 3 studies.

Table 28 Summary of neurological adverse events

	Phase 3 double blind studies						Phase 2+3 studies	
	ESPD (n= 381)				ASPD (n=290)		Numient treatment (n=978)	
	Numient 145mg TID	Numient 245mg TID	Numient 390mg TID	Placebo TID	Numient		ESPD	ASPD
Number of patients exposed	**87**	**104**	**98**	**92**	**290**		**350**	**628**
Any adverse event	56.3%	72.1%	71.4%	72.8%	36.2%		73.7%	68.9%
Nervous system disorders	**26.4%**	**39.4%**	**37.8%**	**30.4%**	**10.3%**		**37.7%**	**32.0%**
Dyskinesia	2.3%	3.8%	5.1%	0	3.1%		4.3%	9.4%
Hyperkinesia	0	0	0	0	0		0	0.2%
Dystonia	0	1.0%	0	1.1%	0		0.3%	1.4%
Headache	6.9%	12.5%	17.3%	10.9%	0.7%		12.6%	5.3%
Tremor	4.6%	0	0	1.1%	0.3%		3.1%	2.2%
Paraesthesia	0	1.0%	1.0%	0	0.7%		0.6%	1.4%
Hypesthesia	0	1.0%	1.0%	0	0.7%		0.6%	1.1%
Convulsion	0	0	0	0	0		0	0.3%
Cognitive impairment	0	0	0	0	0		0.3%	0.3%

Dyskinesia upon Numient treatment in Phase 2 and 3 studies has been observed in 4.3% of ESPD patients and 9.4% of ASPD patients. The severity of dyskinesia was mild to moderate in all investigated ESPD patients and also in most ASPD patients (Table 31)

Table 29 Summary of dyskinesia by severity

	Phase 3 double blind studies						Phase 2+3 studies	
	ESPD (n= 381)				ASPD (n=290)		Numient treatment (n=978)	
	Numient 145mg TID	Numient 245mg TID	Numient 390mg TID	Placebo TID	Numient		ESPD	ASPD
Number of patients exposed	**87**	**104**	**98**	**92**	**290**		**350**	**628**
Any adverse event	56.3%	72.1%	71.4%	72.8%	36.2%		73.7%	68.9%
Dyskinesia	**2.3%**	**3.8%**	**5.1%**	**0%**	**3.1%**		**4.3%**	**9.4%**
Mild	2.3%	1.9%	3.1%	0	0.7%		2.9%	3.5%
Moderate	0	1.9%	2.0%	0	1.4%		1.4%	4.5%
Severe	0	0	0	0	1.0%		0	1.4%

Psychological adverse events and sleep disorders

Psychiatric symptoms tended to be more common for higher doses of Numient in double blind Phase 3 studies (about 22% for 245mg and 390mg TID Levodopa-containing Numient compared to 13% for the lowest Numient dose)(Table 32).

There were 68 study patients with 87 possibly suicide-associated terms. All narratives and terms were provided blinded to the Center for Suicide Risk Assessment at Columbia University for rational classification utilizing the Columbia-Classification Algorithm for Suicide Assessment. This review did not identify any suicide events, suicide attempts, or suicidal ideation.

Table 30 Summary of psychological adverse events and sleep disorders

	Phase 3 double blind studies						**Phase 2+3 studies**	
	ESPD (n= 381)				**ASPD (n=290)**		**Numient treatment (n=978)**	
	Numient 145mg TID	**Numient 245mg TID**	**Numient 390mg TID**	**Placebo TID**	**Numient**		**ESPD**	**ASPD**
Number of patients exposed	**87**	**104**	**98**	**92**	**290**		**350**	**628**
Any adverse event	56.3%	72.1%	71.4%	72.8%	36.2%		73.7%	68.9%
Psychiatric adverse events	**12.6%**	**22.1%**	**22.4%**	**12.0%**	**9.7%**		**3.1%**	**6.4%**
Acute psychosis	0	0	0	0	0.3%		0	0.3%
Psychotic disorder	0	0	0	0	0		0	0.2%
Hallucination	0	2.9%	1.0%	0	1.0%		1.4%	4.1%
Hallucination, visual	0	1.9%	1.0%	0	0.3%		1.7%	1.6%
Hallucination, auditory	0	0	0	0	0		0	0.5%
Delusion	0	0	0	0	0.3%		0	0.2%
Paranoia	0	0	0	0	0		0	0.3%
Confusional state	0	1.0%	0	0	1.4%		0.9%	1.6%
Anxiety	2.3%	2.9%	5.1%	0	0.7%		3.4%	4.9%
Depression	1.7%	1.9%	2.0%	5.4%	0.3%		2.6%	2.4%
Insomnia	5.9%	8.7%	6.1%	3.3%	3.4%		8.6%	4.8%
Sleep disorder	2.1%	1.9%	2.0%	0	1.4%		2.3%	1.1%
Abnormal dreams	4.5%	8.7%	6.1%	0	0		4.6%	1.1%
Nightmare	0.7%	0	1.0%	0	0.3%		0.6%	0.5%
Somnolence*	3.8%	4.8%	3.1%	2.2%	0.3%		3.7%	1.4%
Hypersomnia	0	1.0%	0	0	0		0.3%	0
Pathological gambling	0	0	0	0	0.3%		0.3%	0.3%
Excessive sexual fantasies	0	0	0	0	0.3%		0	0.2%

	Phase 3 double blind studies						Phase 2+3 studies	
	ESPD (n= 381)				ASPD (n=290)		Numient treatment (n=978)	
	Numient 145mg TID	Numient 245mg TID	Numient 390mg TID	Placebo TID	Numient		ESPD	ASPD
Number of patients exposed	87	104	98	92	290		350	628
Hypersexuality	0	0	0	0	0.3%		0	0.2%
Obsessive compulsive disorder	0	0	0	0	0.3%		0	0.2%
Obsessive thoughts	0	0	0	0	0		0	0.2%
Suicidal ideation	87 suicide-associated terms				0		0.3%	0

*This adverse event has been reported under neurological adverse events, but is reported here due to its close association with other sleep-related psychological symptoms

Cardiovascular or cerebrovascular ischaemic adverse events

ESPD patients included in Phase 3 controlled studies

2.4% of Numient -treated ESPD patients reported cardiovascular or cerebrovascular adverse events in Phase 3 controlled study. For 145mg, 245mg and 390 Levodopa within Numient these rates were 4.6%, 2.9%, and 0% respectively (Table 33).

ASPD patients included in Phase 3 controlled studies

1.0% Of 290 ASPD patients experienced a cardiovascular or cerebrovascular ischaemic adverse event (Table 33). In study IPX066-B09-02 all of the study patients with cardiovascular events had risk factors for ischaemic heard disease.

Upon combining all cardiovascular and cerebrovascular ischaemic adverse events upon double-blind and open-label treatments in this study, rates of these events were higher during Numient treatment (5.09 per 100 study patient years) compared to IR L-dopa+ treatment (0 per 100 study patient years).

The separate rates for cardiac ischemic events in study IPX066-B09-02, were also higher for Numient (2.04 and 3.05 per 100 subject-years for serious adverse events and all adverse events respectively) compared with a rate of 0 events per 100 subject-years for both serious adverse events and adverse events for IR L-dopa+ treatment. None of the study patients discontinued early due to cardiovascular or cerebrovascular ischaemic adverse events.

Cardiac arrhythmias have been observed in two ASPD patients treated with Numient in double-blind Phase 3 studies. None of these were severe, serious, or prompted premature treatment discontinuation. No episodes of serious ventricular arrhythmias have been observed in the ASPD population treated with Numient.

During the double-blind Numient -treatment, one patient experienced cerebral infarction, and one patient experienced deep vein thrombosis.

Applicant's conclusion

The applicant concludes that there is no evidence of an increased risk of cardiovascular or cerebrovascular, cardiac arrhythmic, or thromboembolic adverse events upon Numient treatment compared to placebo or standard L-dopa+ treatment.

The presence of pre-existing cardiovascular risk factors makes it difficult to identify any risks specific to Numient in terms of cardiovascular ischaemic events. The number of events was so low that it most likely was due to random occurrence.

Table 31 Summary of cardiovascular or cerebrovascular ischaemic adverse events

	Phase 3 double blind studies						**Phase 2+3 studies**	
	ESPD (n= 381)				**ASPD (n=290)**		**Numient treatment (n=978)**	
	Numient 145mg TID	**Numient 245mg TID**	**Numient 390mg TID**	**Placebo TID**	**Numient**		**ESPD**	**ASPD**
Number of patients exposed	**87**	**104**	**98**	**92**	**29**		**350**	**628**
Any adverse event	56.3%	72.1%	71.4%	72.8%	36.2%		73.7%	68.9%
Cardiovascular or cerebrovascular ischaemic adverse event	**4.6%**	**2.9%**	**0**	**3.3%**	**1.0%**		**3.4%**	**1.8%**
(Sudden) death	0	0	0	0	0		0	0.4%
Myocardial infarction	2.3%	0	0	0	0.3%		0.3%	0
Coronary artery disease or occlusion	1.1%	1.0%	0	0	0		0.6%	0.2%
Coronary artery bypass	0	1.0%	0	0	0		0.3%	0
Arteriosclerosis coronary artery	0	0	0	0	0		0.3%	0
Ischaemic cardiomyopathy	0	0	0	1.1%	0		0	0
Angina pectoris	1.1%	1.0%	0	0	0.3%		0.9%	0.5%
ECG signs of myocardial ischaemia	0	1.0%	0	0	0		0.3%	0
Cerebrovascular accident	0	0	0	1.1%	0.3%		0	0.3%
Haemorrhagic stroke	0	0	0	0	0		0.3%	0
Transient ischaemic attack	0	0	0	0	0.3%		0	0.2%
Carotid artery stenosis	0	0	0	1.1%	0		0	0
Cardiac arrhythmia adverse event	**0%**	**1.0%**	**5.0%**	**2.2%**	**0.7%**		**4.0%**	**1.9%**
Atrial fibrillation	0	0	1.0%	0	0		1.4%	0.6%
Atrial flutter	0	0	0	0	0		0	0.2%
Sick sinus syndrome	0	0	0	0	0		0.6%	0
Atrioventricular	0	1.0%	1.0%	0	0.3%		0	0.6%

	Phase 3 double blind studies						Phase 2+3 studies	
	ESPD (n= 381)				ASPD (n=290)		Numient treatment (n=978)	
	Numient 145mg TID	Numient 245mg TID	Numient 390mg TID	Placebo TID	Numient		ESPD	ASPD
Number of patients exposed	**87**	**104**	**98**	**92**	**290**		**350**	**628**
block								
Bundle branch block	0	0	0	0	0		0.3%	0.4%
Tachycardia			1.0%	1.1%	0.3%		0.3%	0.3%
Extrasystoles	0	0	0	0	0		0	0.2%
Ventricular extrasystoles	0	0	1.0%	0	0		0.3%	0
Supraventricular extrasystoles	0	0	1.0%	1.1%	0		0.3%	0
Sinus bradycardia	0	0	0	0	0		0.6%	0
Thromboembolic adverse events	**0**	**0**	**0**	**1.1%**	**0.7%**		**0**	**0.8%**
Cerebral infarction	0	0	0	0	0.3%		0	0.2%
Cerebrovascular accident	0	0	0	1.1%	0		0	0.3%
Pulmonary embolism	0	0	0	0	0		0	0.3%
Deep vein thrombosis	0	0	0	0	0.3%		0	0.3%

Gastro-intestinal disorders

The reported frequencies of gastrointestinal disorders tended to be lower for ASPD patients compared to ESPD patients in Phase 2 and 3 studies (21.5% vs. 28.9%)(

Table 34).

Nausea was the most frequently observed adverse event, occurring in 18% of Numient -treated compared to 8.7% of placebo-treated ESPD patients in Phase 3 controlled studies. The reporting rates for ESPD patients with respect to 145, 245, and 390 mg Levodopa in Numient treatment were 13.8%, 19.2%, and 20.4% respectively.

Other adverse events that tended to occur more often in Numient -treated patients compared to placebo-treated patients were: constipation (3.5 vs. 1.1%), diarrhoea (2.4 vs. 2.2%), dry mouth (4.2 vs. 1.1%). Salivary hypersecretion has not been observed in ESPD patients in Phase 2 and 3 trials, but occurred in 0.3% of ASPD patients.

Table 32 Summary of gastrointestinal adverse events

	Phase 3 double blind studies						Phase 2+3 studies	
	ESPD (n= 381)				ASPD (n=290)		Numient treatment (n=978)	
	Numient 145mg TID	Numient 245mg TID	Numient 390mg TID	Placebo TID	Numient		ESPD	ASPD
Number of patients exposed	**87**	**104**	**98**	**92**	**290**		**350**	**628**
Any adverse event	56.3%	72.1%	71.4%	72.8%	36.2%		73.7%	68.9%
Gastrointestinal disorders	**21.8%**	**28.8%**	**32.7%**	**23.9%**	**7.9%**		**28.9%**	**21.5%**
Nausea	13.8%	19.2%	20.4%	8.7%	2.4%		17.7%	8.1%
Vomiting	2.3%	1.9%	5.1%	3.3%	0.7%		2.9%	2.7%
Constipation	2.3%	5.8%	2.0%	1.1%	1.0%		4.6%	3.7%
Diarrhoea	1.1%	2.9%	3.1%	2.2%	1.7%		2.0%	2.7%
Dry mouth	3.4%	1.9%	7.1%	1.1%	0.3%		4.6%	2.9%
Salivary hypersecretion	0	0	0	2.2%	0.3%		0	0.3%

Melanoma

Study patients with a history of malignant melanoma or suspicious undiagnosed skin lesion, which, in the opinion of the investigator, could have been melanoma, were excluded from the Phase 3 controlled studies.

Malignant melanoma was reported by a single study patient (0.1%) in the Numient studies. One study patient in the ESPD population (from study IPX066-B08-05) was diagnosed with lentigomaligna (verbatim term: Lentigo malignant melanoma) on day 10 of Numient 390 mg Levodopa treatment.

Serious adverse event / deaths / other significant events

Serious adverse events

In the Numient clinical development program, a serious adverse event was defined as any adverse event occurring at any dose that resulting in a congenital anomaly/birth defect, a persistent or significant disability/incapacity, inpatient hospitalization or prolongation of existing hospitalisation, a life-threatening adverse event, or death. In addition, important medical events that may not result in death, be life-threatening, or require hospitalization may have been assessed as serious adverse events when, based upon appropriate medical judgment, they may have jeopardized the subject and may have required medical or surgical intervention to prevent one of the outcomes listed in this definition.

In study IPX066-B08-05, serious adverse events were reported by 3.8% of ESPD patients in the Numient group and 3.3% of patients in the placebo group. All serious adverse events have been reported by single study patients, and none were considered to be treatment-related by the investigator. The number of study patients experiencing serious adverse events were comparable across the 145, 245, and 390mg Levodopa in Numient treatment groups and placebo group: 4.6%, 4.8%, and 2.0% for Numient, and 3.3% for placebo treatment.

In the ASPD population, 4.1% of patients experienced a serious adverse event during double-blind Numient treatment, compared to 2.6% of IR L-dopa+ treated patients. With respect to all combined Phase 2 and 3 studies, 9.4% of patients experienced serious adverse events upon Numient treatment, 6.3% of ESPD patients

and 11.1% of ASPD patients. The most frequently observed serious adverse event in ESPD patients was urinary tract infection (0.6%). The most frequently observed serious adverse events in ASPD patients were: atrial fibrillation (0.6%), non-cardiac chest pain (0.6%), dyskinesia (0.5%), and anxiety (0.5%). The occurrence rate of all other serious adverse events was 0.3% or lower.

None of the healthy volunteers has experienced serious adverse events.

Table 33 Summary of common serious adverse events

	Phase 3 double blind studies						Phase 2+3 studies	
	ESPD (n= 381)				ASPD (n=482)		NUMIENT treatment (n=978)	
	NUMIENT 145mg TID	NUMIENT 245mg TID	NUMIENT 390mg TID	Placebo TID	NUMIENT	IR L-dopa+	ESPD	ASPD
Number of patients exposed	87	104	98	92	290	192	350	628
Any adverse event	56.3%	72.1%	71.4%	72.8%	36.2%	2.6%	73.7%	68.9 %
Any serious adverse event	**4.6%**	**4.8%**	**2.0%**	**3.3%**	**4.1%**	**2.6%**	**6.3%**	**11. %**
Cerebrovascular accident	0	0	0	1.1%	0.3%	0	0	0.3%
Pulmonary embolism	0	0	0	0	0	0	0	0.3%
Deep vein thrombosis	0	0	0	0	0.3%	0	0	0.3%
Hypotension	0	0	0	0	0	0	0	0.3%
Orthostatic hypotension	0	0	0	0	0	0	0	0.3%
Atrial fibrillation	0	0	0	0	0	0.5%	0	0.6%
Atrioventricular block complete	0	1.0%	0	0	0	0	0.3%	0.2%
Coronary artery disease	1.1%	0	0	0	0	0	0.3%	0
Coronary artery bypass	0	1.0%	0	0	0	0	0.3%	0
Myocardial infarction	2.2%	0	0	0	0.3%	0	0.3%	0.3%
Non-cardiac chest pain	0	0	0	0	0.3%	0	0	0.6%
Constipation	0	0	0	0	0	0	0	0.3%
Gastritis	0	0	0	0	0	0	0	0.3%
Small intestinal obstruction	0	0	0	0	0.3%	0	0.3%	0.2%
Volvulus	0	0	0	0	0.3%	0	0	0.3%
Abdominal strangulated hernia	0	1.0%	0	0	0	0	0.3%	0
Dyskinesia	0	0	0	0	0	0	0	0.5%
Gait disturbance	0	0	0	0	0	0	0	0.3%
Fall	0	0	0	0	0	0	0	0.3%
Femoral neck fracture	0	0	0	0	0	0	0.3%	0.3%
Arthritis	0	0	0	0	0.3%	0	0	0.3%
Prostatectomy	0	0	0	1.1%	0	0	0.3%	0
Renal failure	0	0	0	0	0	0	0.3%	0.2%
Urinary tract infection	1.1%	0	1.0%	0	0	0	0.6%	0
Sepsis	0	0	0	0	0	0	0	0.3%
Urosepsis	0	0	0	1.1%	0	0	0.3%	0
Osteoarthritis	0	1.0%	0	0	0	0	0.3%	0
Back pain	0	0	0	0	0	0	0.3%	0.2%
Spinal column stenosis	0	0	0	0	0	0	0.3%	0.2%
Spinal osteoarthritis	0	0	0	0	0	0	0	0.3%
Spondylolisthesis	0	0	0	0	0.3%	0	0	0.3%

Non-Hodgkin lymphoma	0	1.0%	0	0	0	0	0.3%	0
COPD	0	0	1.0%	0	0	0	0.3%	0
Acute psychosis	0	0	0	0	0.3%	0	0	0.3%
Anxiety	0	0	0	0	0.3%	0	0	0.5%
Hyponatreaemia	0	0	0	0	0	0	0.3%	0.2%

Deaths

11 Deaths have been reported in the 978 patients exposed to Numient treatment (1.1%). Of the 11 deaths, 4 were considered to be due to cardiovascular or cerebrovascular events (acute myocardial infarction, sudden death, and death, haemorrhagic stroke and hypertension), 3 were due to infections (pneumonia, aspiration, haemorrhagic pancreatitis), and 2 were due to malignancies (non-Hodgkin's lymphoma and prostate cancer). Of the remaining 2 deaths, one was due to renal failure and the other due to Parkinson's disease.

10 of the dead patients received Numient treatment at the time of the adverse event that led to death, and one death occurred post treatment, 8 days after the last dose of Numient. Nine deaths occurred in patients aged ≥65 years. The applicant stated that deaths were due to a variety of causes and no unexpected pattern was observed.

No deaths occurred in any of the studies with healthy volunteers.

Table 34 Summary of deaths within Phase 2 and 3 studies

	Phase 3 double blind studies			**Phase 2+3 studies**	
	ESPD (n= 381)		**ASPD (n=482)**	**Numient treatment (n=978)**	
	Numient TID	**Placebo TID**	**Numient**	**ESPD**	**ASPD**
Number of patients exposed	289	92	290	350	628
Death	**0.3%**	**0**	**0**	**0.6%**	**1.3%**
Cardiovascular or cerebrovascular events	**0**	**0**	**0**	**0.3%**	**0.5%**
(Sudden) death	0	0	0	0	0.3%
Hemorrhagic stroke and hypertension	0	0	0	0.3%	0
Acute myocardial infarction	0	0	0	0	0.2%
Infections	**0**	**0**	**0**	**0**	**0.5%**

Pneumonia	0	0	0	0	0.2%
Aspiration	0	0	0	0	0.2%
Hemorrhagic pancreatitis	0	0	0	0	0.2%
Neoplasmata	**0.3%**	**0**	**0**	**0.3%**	**0.2%**
Non-Hodgkin's lymphoma	0.3%	0	0	0.3%	0
Prostate cancer	0	0	0	0	0.2%
Renal failure	0	0	0	0	0.2%
Parkinson's disease	0	0	0	0	0.2%

Note: the percentages in this table have been rounded off

Laboratory findings and ECG

Haematology

The occurrence of abnormal haematology parameters at end of study or premature study termination in patients with normal haematology parameters at baseline were comparable for Numient and placebo treatment in ESPD patients and Numient treatment and IR L-dopa+ treatment in ASPD patients. The proportion of patients with low haemoglobin and haematocrit values under Numient treatment tended to increase with time during the Phase 2 and 3 studies. An association between Numient treatment and anaemia can therefore not be excluded.

Chemistry

Hyperglycaemia was the most frequently observed abnormal chemistry parameter at the end of study/premature study termination, occurring in approximately 30% of ESPD and ASPD patients. Rates were similar for Numient, IR L-dopa+, and placebo-treated patients within Phase 3 double-blind studies. No other clinically relevant changes with respect to chemistry parameters have been observed.

Urinalysis has been conducted in both ESPD and ASPD patients. No clinical relevant abnormalities have been observed.

ECG

The proportions of study patients with any changes from baseline with respect to ventricular rate, PR-, QRS-, QT-, RR- and QTcF-interval within Phase 3 double blind studies and open label extension studies have been summarized within the table below.

Changes from baseline with respect to most investigated ECG characteristics were comparable between treatments. The PR-interval changed by 5 msec or more in 36-43% of Numient-treated patients across different Phase 2 and 3 studies compared to 33% of placebo-treated patients in ESPD patients. 24% Of placebo-treated patients experienced an increase in QRS interval compared to >30% of Numient -treated patients in different Phase 2 and 3 studies.

Table 35 ECG abnormalities

	Phase 3 double blind studies				Phase 2+3 studies	
	ESPD (n= 381)		ASPD (n=290)		Open label extension Numient treatment (n=703)	
	Numient TID	Placebo TID	Numient		ESPD	ASPD
Number of patients exposed	289	92	290		268	435
Ventricular rate, bpm, change from baseline						
< -10	11.7%	9.2%	9.2%		8.4%	12.0%
-10 to 0	36.5%	33.3%	35.4%		33.1%	31.5%
0 to 10	39.0%	40.2%	38.3%		43.7%	43.0%
≥ 10	12.8%	17.2%	17.1%		14.8%	13.5%
PR-interval, msec, change from baseline						
< -1	38.1%	43.0%	46.4%		36.2%	45.1%
-1 to <5	21.2%	24.4%	17.3%		20.4%	18.1%
≥ 5	39.9%	32.6%	36.3%		43.1%	36.9%
QRS-interval, msec, change from baseline						
< 0	34.0%	50.6%	46.7%		36.9%	45.7%
0 to <3	31.2%	25.3%	21.3%		31.6%	18.0%
≥ 3	34.8%	24.1%	32.1%		31.6%	36.3%
QT-interval, msec, change from baseline						
≤30	90.1%	80.5%	92.1%		92.0%	89.9%
>30 to 60	8.5%	14.9%	5.0%		7.6%	8.7%
>60	1.4%	4.6%	2.9%		0.4%	1.4%

RR-interval, msec, change from baseline						
< -33	38.2%	42.5%	38.3%		43.7%	40.4%
-33 to <12	16.1%	18.4%	17.5%		16.7%	17.3%
≥ 12	45.4%	39.1%	44.2%		39.5%	42.3%
QTcF-interval, msec, change from baseline						
≤30	92.6%	87.4%	92.9%		92.0%	93.0%
>30 to 60	5.3%	8.0%	5.0%		7.2%	5.3%
>60	2.1%	4.6%	2.1%		0.8%	1.7%

QTcF= QT-interval corrected for heart rate

Safety in special populations

Age

Safety data with respect to Numient treatment have been analysed in different subgroups according to age: <65 years, 65-74 years, 75-84 years, 85+ years. This analysis has been conducted for ESPD patients and ASPD patients separately.

ESPD

The occurrence of adverse events in ESPD patients in the conducted Phase 3 controlled studies has been represented within the table below. The occurrence of adverse events in the age groups <65 years, 65-74 years, 75-84 years, and 85+ were 65%, 67%, 71%, and 100% respectively. The occurrence of serious adverse events tended to increase with age (1.5% for patients aged < 65 years compared to 6.8% of patients aged 75-84 years).

Table 36 Adverse events and premature discontinuation upon Numient in ESPD by age

	Numient treatment			
MedDRA Terms	Age <65	Age 65-74	Age 75-84	Age 85+
Number of patients	135	107	44	3
Any adverse event	65.2%	67.3%	70.5%	100%
Any serious adverse event	1.5%	5.6%	6.8%	0
Premature study discontinuation	16.3%	24.7%		
Adverse event as reason for premature study discontinuation	8.1%	15.6%		
Organ system adverse event				
Blood and lymphatic system	0	0	0	0
Cardiac disorders	3.7%	5.6%	2.3%	0
Ear and labyrinth disorders	2.2%	0.9%	2.3%	0
Endocrine disorders	0.7%	0	0	0
Eye disorders	3.0%	0.9%	2.3%	0

Gastrointestinal disorders	26.7%	29.0%	27.3%	66.7%
General disorders and administration site conditions	5.9%	12.1%	9.1%	33.3%
Hepatobiliary disorders	0.7%	0.9%	0	0
Infections and infestations	13.3%	12.1%	4.5%	0
Injury, poisoning and procedural complications	4.4%	2.8%	6.8%	0
Investigations	5.2%	4.7%	2.3%	0
Metabolism and nutrition disorders	3.0%	2.8%	4.5%	0
Musculoskeletal and connective tissue disorders	20.0%	5.6%	9.1%	0
Neoplasms	0	0.9%	4.5%	0
Nervous system disorders	34.1%	40.2%	27.3%	0
Psychiatric disorders	19.3%	20.6%	15.9%	33.3%
Renal and urinary disorders	3.0%	0.9%	2.3%	0
Reproductive system and breast disorders	0.7%	0	0	0
Respiratory, thoracic and mediastinal disorders	9.6%	1.9%	6.8%	0
Skin and subcutaneous tissue disorders	7.4%	2.8%	9.1%	0
Surgical and medical procedures	0	1.9%	0	0
Vascular disorders	3.0%	7.5%	9.1%	0

ASPD

The occurrence of adverse events in ASPD patients in the conducted Phase 3 controlled studies has been represented within the table below. The occurrence of adverse events in the age groups <65 years, 65-74 years, 75-84 years, and 85+ were 49%, 56%, 57%, and 80% respectively. The occurrence of serious adverse events tended to increase with age (2.7% for patients aged < 65 years compared to 8.9% of patients aged 75-84 years; 20% in patients (n=5) 85 years and above).

Table 37 Adverse events upon Numient treatment in ASPD patients by age

	Numient treatment			
MedDRA Terms	Age <65	Age 65-74	Age 75-84	Age 85+
Number of patients	296	201	56	5
Any adverse event	49.0%	55.7%	57.1%	80.0%
Organ system adverse event				
Blood and lymphatic system	0	0.5%	1.8%	0
Cardiac disorders	0.7%	3.0%	3.6%	20.0%
Ear and labyrinth disorders	0.7%	1.5%	1.8%	0
Endocrine disorders	1.0%	0	0	0
Eye disorders	1.4%	2.0%	1.8%	20.0%
Gastrointestinal disorders	14.9%	15.9%	17.9%	60.0%
General disorders and administration site conditions	8.1%	7.0%	8.9%	0
Hepatobiliary disorders	0	0	1.8%	0
Immune system disorders	0	0.5%	0	0
Infections and infestations	9.5%	6.5%	7.1%	20.0%
Injury, poisoning and procedural complications	4.7%	6.0%	3.6%	0
Investigations	3.0%	4.0%	0	0
Metabolism and nutrition disorders	1.0%	2.5%	0	0
Musculoskeletal and connective tissue disorders	8.4%	8.5%	8.9%	20.0%
Neoplasms	0	1.0%	1.8%	0
Nervous system disorders	20.3%	24.4%	23.2%	40.0%

Psychiatric disorders	14.5%	14.4%	8.9%	0
Renal and urinary disorders	1.7%	3.5%	3.6%	0
Reproductive system and breast disorders	0.3%	2.5%	1.8%	0
Respiratory, thoracic and mediastinal disorders	2.4%	1.0%	5.4%	0
Skin and subcutaneous tissue disorders	2.7%	4.5%	3.6%	0
Surgical and medical procedures	0	1.0%	0	20.0%
Vascular disorders	3.0%	5.0%	1.8%	20.0%

Renal impairment

Study patients with abnormal kidney function (e.g. serum creatinine level ≥1.5x upper limit of normal) or requiring dialysis were excluded from all Numient studies. According to the applicant, renal impairment is considered unlikely to affect the PK of Levodopa, since renal excretion accounts for less than 10% of the overall clearance of Levodopa. In clinical practice, the Levodopa dose generally does not have to be adjusted in patients with renal failure (LeWitt 2008). The applicant recommends that Numient is administered cautiously to patients with severe renal disease.

Hepatic impairment

Study patients with abnormal hepatic function (e.g. liver enzyme values ≥2x upper limit of normal) were excluded from all Numient studies. The applicant does not expect that Levodopa affects the PK of Levodopa, since Levodopa is predominantly cleared peripherally. Levodopa use in case of hepatic disease has not been found to be associated with safety concerns, and Levodopa has been used in patients with hepatic disease (Als-Nielsen et al. 2004).

The applicant recommends that Numient is administered cautiously to patients with biliary obstruction or severe hepatic disease.

Pregnancy and lactation

There are no adequate or well-controlled studies with Numient in pregnant women. One pregnancy was reported in the Numient Clinical Development Program. In the Phase 1 healthy volunteer study IPX066-B10-01, there was a positive pregnancy test reported for a 22-year-old subject 1 week after a single dose of Numient (245 mg) was administered. Twin boys were delivered at term via Caesarean section. No abnormalities were noted at birth. The Apgar score was 9 for both infants. No further information was available regarding the pregnancy or outcome.

Safety related to drug-drug interactions and other interactions

No formal drug-drug and drug-disease interaction studies with Numient were conducted. It was assumed that drug interactions with Numient would be consistent with these of other Levodopa-Carbidopa products.

The occurrence of adverse events by any concomitant use of dopamine agonists, amantadine, and type B monoamine oxidase inhibitors was analysed. Only concomitant use of type B MAO- inhibitors was associated with a changed occurrence of adverse events (see Table 40).

Table 38 Adverse events reported by ≥3% of IPX066 study patients whether or not using MAO inhibitors – type B in Phase 3 controlled studies

	Number (%) of Subjects					
	IPX066 Total Exposed					
	Early PD (N = 289)		Advanced PD (N = 558)		Overall PD (N = 847)	
	MAOI-B Use		MAOI-B Use		MAOI-B Use	
Adverse Event Preferred Term	No (N = 204)	Yes (N = 85)	No (N = 401)	Yes (N = 157)	No (N = 605)	Yes (N = 242)
At least 1 AE	129 (63.2)	65 (76.5)	202 (50.4)	91 (58.0)	331 (54.7)	156 (64.5)
AE Rates Higher Without MAOI-B Use (Overall PD)						
Headache	27 (13.2)	9 (10.6)	20 (5.0)	4 (2.5)	47 (7.8)	13 (5.4)
AE Rates Higher With MAOI-B Use (Overall PD)						
Nausea	31 (15.2)	21 (24.7)	23 (5.7)	13 (8.3)	54 (8.9)	34 (14.0)
Dizziness	22 (10.8)	18 (21.2)	14 (3.5)	10 (6.4)	36 (6.0)	28 (11.6)
Dyskinesia	5 (2.5)	6 (7.1)	22 (5.5)	13 (8.3)	27 (4.5)	19 (7.9)
Dry Mouth	2 (1.0)	10 (11.8)	9 (2.2)	3 (1.9)	11 (1.8)	13 (5.4)
Insomnia	9 (4.4)	8 (9.4)	16 (4.0)	[illegible]	25 (4.1)	13 (5.4)
Fall	3 (1.5)	2 (2.4)	9 (2.2)	10 (6.4)	12 (2.0)	12 (5.0)
Hallucination	1 (0.5)	3 (3.5)	5 (1.2)	8 (5.1)	6 (1.0)	11 (4.5)
Diarrhoea	3 (1.5)	4 (4.7)	6 (1.5)	6 (3.8)	9 (1.5)	10 (4.1)
Vomiting	4 (2.0)	5 (5.9)	5 (1.2)	5 (3.2)	9 (1.5)	10 (4.1)
Constipation	6 (2.9)	4 (4.7)	8 (2.0)	5 (3.2)	14 (2.3)	9 (3.7)
Somnolence	5 (2.5)	6 (7.1)	3 (0.7)	3 (1.9)	8 (1.3)	9 (3.7)
Pain in extremity	2 (1.0)	6 (7.1)	3 (0.7)	2 (1.3)	5 (0.8)	8 (3.3)
Anxiety	4 (2.0)	6 (7.1)	12 (3.0)	2 (1.3)	16 (2.6)	8 (3.3)

Abbreviations: AE = adverse event, PD = Parkinson's disease; MAOI-B = Monoamine Oxidase Inhibitor – Type B.

Discontinuation due to adverse events

76.4% Of patients with Parkinson's disease treated with Numient completed this treatment in Phase 2 and 3 studies. In early stage and advanced stage Parkinson's disease these percentages were 79% and 75% respectively. The most frequent reasons for discontinuation during Numient treatment were: adverse events (11% in ESPD and 8.1% in ASPD), withdrawal by subject (4.3% in ESPD; 7.6% in ASPD), and lack of efficacy (1.4% for ESPD and 4.8% for ASPD).

Regarding ESPD patients in Phase 3 double blind studies, the predominant reason study patients discontinued in the 2 higher Numient dose groups was due to an adverse event (245 mg Levodopa in Numient, 14.4%, and 390 mg Levodopa in Numient, 15.3%); whereas the predominant reason in the placebo group was lack of efficacy (13.0%). Other reasons for premature study discontinuation were comparable for the investigated Numient and placebo treatment.

Premature study discontinuation upon double blind study treatment was 6.6% for Numient and 5.2% for IR L-dopa+ treatment.

Table 39 Overview of patient disposition in clinical studies with Numient

	Phase 3 double blind studies						Phase 2+3 studies	
	ESPD (n= 381)				ASPD (n=290)		Numient treatment (n=978)	
	Numient 145mg TID	Numient 245mg TID	Numient 390mg TID	Placebo TID	Numient	IR L-dopa+	ESPD	ASPD
Number of patients exposed	87	104	98	92	290	192	350	628
Premature study treatment discontinuation	17.2%	20.2%	24.5%	22.8%	6.6%	5.2%	21.1%	25.0%
Reason								
Adverse event	5.7%	14.4%	15.3%	4.3%	1.0%	1.6%	10.9%	8.1%
Death	0	1.0%	0	0	0	0	0.6%	0.8%
Protocol violation	1.1%	0	2.0%	0	0.7%	0.5%	0.9%	1.4%
Non-compliance with study drug	0	1.0%	1.0%	0	0.3%	0.5%	0.6%	0.6%
Lack of efficacy	4.6%	0	1.0%	13.0%	1.0%	1.0%	1.4%	4.8%
Lost to follow-up	1.1%	1.0%	0	0	0	0.5%	0.9%	0.2%
Withdrawal by study patient	3.4%	1.0%	3.1%	4.3%	2.1%	1.0%	4.3%	7.6%
Other	1.1%	1.9%	2.0%	1.1%	1.4%	0	1.7%	1.4%

2.6.1. Discussion on clinical safety

Safety of Numient treatment has been determined in different randomized, double-blinded clinical studies as well as open label studies, with a maximum duration of 15 months. Within different studies the effects of Numient treatment have been compared to other drug treatment for Parkinson's disease, such as IR and CR L-dopa+, and CLE. Effects of Numient treatment have been compared to placebo treatment in ESPD patients but not in ASPD patients.

350 ESPD and 628 ASPD patients have been included. 74% of ESPD patients and 69% of ASPD patients experienced any adverse events.

The occurrence of adverse events increases with increasing doses of Numient. In a placebo-controlled Phase 3 study in ESPD patients (study IPX066-B08-05) the occurrence of any adverse event was 56%, 72%, and 71% for respectively thrice daily 145, 245, and 390 mg Levodopa in Numient treatment. Whether this also applies to ASPD patients was unclear. The maximum tolerated Numient dose in clinical studies in ASPD is also unclear. In additional analyses, no clear pattern was demonstrated between the occurrence of adverse events and Numient dosage in ASPD patients. The Applicant demonstrated that premature study dropout in patients who received >1,960mg Levodopa per day is within the same range as observed in the overall study population. Premature study dropout due to adverse events was also comparable. The occurrence of adverse events also tended to increase with advancing age. With respect to ESPD 65% of patients under 65 years of age (n=135) experienced adverse events compared to 67% of patients aged 65-74 years of age (n=107), and 71% of patients of patients aged 75-84 years of age (n=44). 49% Of ASPD patients under 65 years of age (n=296) experienced adverse events compared to 56-57% in patients aged 65-84 years of age (n=257) and 80% of patients aged 85 years and above (n=5).

The most frequently observed adverse events in Phase 3 controlled studies among ESPD and ASPD patients concerned nervous system disorders (ESPD: 30-35%; ASPD: 10%), gastrointestinal disorders (ESPD: 24-28%; ASPD: 7.9%), psychiatric disorders (ESPD: 12-19%; ASPD: 10%), infections and infestations (ESPD: 11-20%; ASPD: 7%), and musculoskeletal and connective tissue disorders (ESPD: 13%; ASPD: 6%). Differences in occurrence of adverse events between ESPD and ASPD patients is likely to be partially due to differences in exposure time between these patients: 57% of ESPD patients were exposed to Numient for at least one year compared to 27% of ASPD patients.

Because of the prolonged action of Numient compared to IR L-Dopa+, adverse events are also expected to persist for a prolonged time. Dyskinesia is a common adverse event of all L-dopa+ products. Within the Numient studies, 4% of ESPD patients and 9% of ASPD patients experienced dyskinesia. In ESPD patients dyskinesia tended to occur more frequently upon higher Numient doses (2%, 4%, and 5% for 145, 245, and 390 mg Levodopa in Numient thrice daily). None of the placebo-treated patients experienced dyskinesia, indicating that the dyskinesia are related to Levodopa-Carbidopa treatment. Most dyskinesias were mild to moderate. Because of this and the fact that Numient treatment was associated with a decrease in 'OFF' time with improved motor function (see clinical efficacy), the occurrence of dyskinesia is not considered detrimental for this application.

Headache was the most frequently observed neurological adverse event (13% of ESPD patients and 5% of ASPD patients) in Phase 2 and 3 studies. Headache is also considered a common adverse event within the SmPC of CR L-dopa+ product Sinemet CR®.

Psychological adverse events have been reported by 3% of ESPD patients and 6% of ASPD patients in Phase 2 and 3 studies. The most frequently observed psychiatric adverse events in these studies were insomnia (ESPD 9%; ASPD 5%), anxiety (ESPD 3%; ASPD 5%), somnolence (ESPD: 4%; ASPD: 1%), hallucination (ESPD: 1%; ASPD: 4%), and depression (ESPD: 3%; ASPD: 2%). The occurrence of sleeping disorders is relevant with respect to driving and the use of machines.

Cardiovascular and cerebrovascular ischaemic adverse events were experienced by 3% of ESPD patients and 2% of ASPD patients. These events tended to occur less frequently upon higher Numient doses (5% for 145 mg Levodopa in Numient TID, compared to 3% and 0% for 245 mg and 390 mg Levodopa in Numient). Within the Numient development program, there appeared to be no direct association between Numient treatment and the occurrence of these adverse events. It is however remarked that patients with any arrhythmia after a myocardial infarction were excluded from study participation. In the SmPCs of other L-dopa products registered by a centralized procedure (e.g. Stalevo®) or non-centralized procedures (e.g. Madopar®, Sinemet) it has been indicated that caution is needed in patients with a positive cardiovascular history. Despite the findings within the

Numient development program, cardiovascular risk is considered to be increased in patients treated with Numient.

Melanoma prevalence was found to be higher in patients with Parkinson's disease than in the general population (Bertoni et al. 2010; Paisán-Ruiz 2010). Probably for this reason, patients with malignant melanoma or a suspicious undiagnosed skin lesion have been excluded from clinical studies with respect to Numient. One ESPD patient treated with thrice daily 390mg Levodopa in Numient was diagnosed with a melanoma at study day 10. Though it is unknown whether the development of this melanoma was due to Numient treatment, this seems unlikely.

Haematological and chemical parameters, ECGs, and vital signs were in general comparable between different treatments. There was noclinically important safety risk of Numient with respect to these outcomes. However an increased occurrence of anaemia upon prolonged Numient treatment cannot be excluded. As the incidence of anaemia under Levodopa is well-known for other L-dopa+ products this may be mentioned in the SPC.

The effects of Numient have not been investigated in patients with renal/hepatic impairment or pregnancy and lactation. For this reason, a cautious approach is recommended when Numient is administered to patients with these conditions.

The occurrence of adverse events increased if Numient treatment was associated with treatment with type B MAO inhibitors. For this reason, combination of Numient with selective type B MAO-inhibitors should be monitored for potentiation of the effects of L-dopa and orthostatic hypertension and the dose may need to be adapted accordingly.

Serious adverse events have been observed in 6% of ESPD patients and in 11% of ASPD patients upon Numient treatment in Phase 2 and 3 studies. Twice as many ASPD patients compared to ESPD patients died upon Numient treatment in these studies (1.3% vs. 0.6%).

Numient doses and dosing frequency remained relatively stable in the open-label extension studies (see clinical efficacy section). This finding indicates that Numient treatment –once tolerated- continued to be tolerated with time.

With respect to ESPD, 4.3%, 5.7%, 11.4%, and 15.3%, of patients treated with placebo, Numient 145mg (n=87), , Numient 245mg (n=104) and , Numient 390mg (n=98) discontinued study treatment prematurely because of adverse events. These results show that premature study discontinuation because of adverse events tended to be higher for Numient treatment compared to placebo treatment (6-15% vs. 4%). Premature study discontinuation also tended to be higher for higher doses of Numient treatment.

Up to 23% of patients discontinued the study upon conversion of pre-study L-dopa+ treatment to Numient and further optimisation of Numient treatment. The precise reasons of this premature study discontinuation were unclear. In additional analyses, the Applicant demonstrated that the 3 most common reasons for discontinuation during treatment conversion into Numient were: adverse events (4.5%), lack of efficacy (3.8%), and withdrawal by subject (3.5%).

Within studies IPX066-B09-02, IPX066-B09-06 Part 1, and IPX066-B11-01, Numient dose was back-titrated in only one patient who discontinued prematurely during the dose conversion phase. Hence, back-titration of Numient dose was not a major reason for premature study discontinuation during the dose conversion phase into Numient. In additional clinical dosing and PK analyses, the Applicant demonstrated that premature study discontinuations were not due to under- or overdosage of Numient.

General measures to avoid premature study discontinuation were initially unclear. The Applicant explained that such measures involved: selecting and training of experienced study staff, providing protocol-specific dosing guidelines to the clinical sites, allowing Numient dosing to be individualized during dose conversion, and frequent and regular communication with study patients by clinical site staff via the telephone between clinic visits.

The occurrence of adverse events upon Numient treatment appears to be comparable to that of other L-dopa+ products. This is supported by additional safety analyses with respect to the occurrence of adverse events for different L-dopa+ formulations. It was initially unclear to what extent the nature and frequency of adverse events upon Numient treatment differs from that of other CR L-dopa+ products such as Sinemet CR®. In additional analyses, the Applicant demonstrated that insomnia appeared to be reported more frequently on Numient treatment, whereas dyskinesia, confusion, and dystonia were reported more frequently on CR L-dopa+ treatment. Differences in occurrence of insomnia were minor (Numient: 3.4%; Sinemet CR®: 1.2%; difference: 2.2%). Considering this, and also that 'OFF' time was reduced by 1 hour or more in clinical studies, and the occurrence of several other adverse events was lower for Numient treatment compared to Sinemet CR®, minor differences in occurrence of insomnia are considered acceptable. Moreover, a warning about somnolence and episodes of sudden sleep onset have been proposed in the SmPC.

2.6.2. Conclusions on the clinical safety

In general, the safety profile of Numient is in line with that of other registered L-dopa+ products. The occurrence of adverse events increased with age.

In ESPD patients it has been shown that the occurrence of adverse events increases with higher doses of Numient (dose dependency). Whether this also applies to ASPD patients was not clarified. The maximum tolerated Numient dose in clinical studies was also not clarified. In additional analyses, no clear pattern was demonstrated between the occurrence of adverse events and Numient dosage in ASPD patients. The Applicant demonstrated that premature study dropout in ASPD patients who received >1,960 mg Levodopa per day is within the same range as observed in the overall study population. Premature study dropout due to adverse events was also comparable. Premature study discontinuation in ASPD patients was found to occur more often with higher Numient doses upon dose conversion and during treatment.The fact that up to 23% of ASPD patients discontinued their study participation upon treatment conversion of their previous L-dopa+ treatment into Numient demonstrates that this treatment conversion is problematic in a considerable proportion of patients. In additional analyses, the Applicant demonstrated that the 3 most common reasons for discontinuation during treatment conversion into Numient were: adverse events(4.5%), lack of efficacy (3.8%), and withdrawal by subject (3.5%). One might argue that Numient doses were not adequate. However, the Applicant demonstrated in some additional analyses that patients who discontinued study treatment during treatment conversion had neither received too high or too low Numient doses.

Despite that an increased cardiovascular risk was not observed in the clinical studies within the Numient development program the warning with respect to the use of L-dopa+ in cardiovascular compromised study patients still applies considering this is a class effect. Moreover cardiovascular compromised patients have been excluded from the trials.

The Numient doses in the open-label extension studies indicated that treatment with Numient–once tolerated-continued to be tolerated with time.

The occurrence of adverse events upon Numient treatment is comparable to that of other L-dopa+ products. This is supported by additional safety analyses with respect to the occurrence of adverse events for different L-dopa+ formulations.

An increased incidence of anaemia upon prolonged Numient treatment cannot be excluded. As the occurrence of anaemia under L-dopa is well known this is included in the SmPC.

2.7. Pharmacovigilance system

The Rapporteur considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.2 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 1.2 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks (Recognised class effects with LD)	• Dyskinesias • Psychosis associated events • Impulsive control disorders (ICDs) • Orthostatic hypotension • Sudden onset of sleep/somnolence • Neuroleptic malignant syndrome (NMS)
Important potential risks (Potential class effects with LD)	• Melanoma
Important potential risks (with Numient)	• None
Missing information	• None

Pharmacovigilance plan

The pharmacovigilance regarding the risks associated with the treatment of Numient will be addressed through routine pharmacovigilance activities. No post-authorisation study is planned.

Risk minimisation measures

Safety concerns	Routine risk minimisation measures	Additional risk minimisation measures
Dyskinesias	Section 4.8 of the SPC identifies dyskinesias as a common Undesirable effect of LD-CD treatment. Sections 4.2, 4.4 and 4.5 of the SPC recommend careful dose titration with close monitoring during the dose adjustment period for the appearance or worsening of dyskinesia, and the PIL will reflect this under Section 2.	None
Psychosis associated events	Psychosis associated events are recognized to occur in PD patients on LD-CD. Available data have not highlighted an increased frequency or severity of hallucinations or related events with Numient compared with other LD-CD preparations. There is a warning in Section 4.4 of the SPC recommending monitoring patients for new or worsening mental status and behavioural changes and monitoring concomitant medications for worsening of Parkinson's motor symptoms. Guidance is provided in Section 4.8 of the SPC noting confusional state and hallucintations are common and psychotic episode and agitation are uncommon.	None
Impulse control disorders (ICDs)	Impulse control disorders are uncommon in PD patients treated with dopaminergic agents including LD-CD medicinal products (see Section 4.8 of the SPC). A very small number of this type of event have been reported in subjects taking Numient. Current data do not indicate that Numient is associated with an increased risk compared with other LD-CD medicinal products. There is a warning in Section 4.4 of the SPC recommending monitoring of patients for the development of impulse control disorders. Section 2 of the PIL recommends patients inform their physician of the development of urges to behave in a way unusal to himself. A warning in Section 4 of the PIL details the manifestations of the impulse control disorder.	None
Orthostatic hypotension	Section 4.5 of the SPC warns of a drug-drug interaction of levodopa with concomitant use of type B monoamine oxidase inhibitors resulting in severe orthostatic hypotension. Orthostatic hypotension is a common effect of LD-CD, which is referenced in Section 4.8 of the SPC and Section 4 of the PIL.	None
Sleep disturbances (sudden onset of sleep/somnolence)	Levodopa has been associated with somnolence and episodes of sudden sleep onset which are common and referred to in Section 4.8 of the SPC and Section 4 of the PIL. A small number of cases have been reported with Numient but current data do not indicate that Numient is associated with an increased risk compared with other LD-CD products. Warnings in Sections 4.4 and 4.7 of the SPC recommend patients refrain from driving or engaging in activities where impaired alertness may put themselves at risk of serious injury. The PIL will also reflect these warnings in Section 2.	None
Neuroleptic malignant- syndrome (NMS)	Although no cases of neuroleptic malignant syndrome (NMS) have been reported with Numient, this is a recognised, albeit uncommon, class effect of LD and dopamine agonists. A warning in section 4.4 of the SPC recommends monitoring patients when LD-CD medicinal product dosing is reduced abruptly or discontinued. These side effects are detailed in Section 4 of the PIL.	None

Safety concerns	Routine risk minimisation measures	Additional risk minimisation measures
Melanoma	While melanoma is uncommon (see Section 4.8 of the SPC and Section 4 of the PIL), a warning in Section 4.4 of the SPC recommends periodic skin examinations to identify melanoma in Parkinson's patients. Section 2 of the PIL directs patients to inform their physician if they have had a history of melanoma.	None

2.9. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Numient provides an onset of action which is similar to the one of IR L-dopa+ formulations, but at the same time offers a prolonged duration of the effect which allows for less frequent dosing. These benefits are considered important advantages of the product for the patients.

Pharmacokinetic studies demonstrated that the initial rate of absorption of the modified release Levodopa-Carbidopa product Numient was similar to that of IR Levodopa-Carbidopa (see Figure 4). This is logical, as the IR Levodopa-Carbidopa component is the first component of Numient to be released. The two modified release Levodopa-Carbidopa components of Numient are released subsequently in different parts of the gastrointestinal tract. In line with this mechanism, Levodopa concentrations above 50% of Cmax were maintained longer with Numient (4.9 hrs) as compared to IR L-dopa+, CR L-dopa+, and CLE (1.5, 2.1, and 2.1 hrs respectively). Following multiple dosing of Numient in patients, levodopa had lower peak-to-trough fluctuations as compared to IR L-dopa+ (1.5 versus 3.2), while the accumulation of levodopa was minimal after both Numient and IR L-dopa+. These findings support the claim that levodopa has a more uniform plasma level after use of Numient compared to IR L-dopa+ which translates into the benefit of improved functioning of the patients, because of improved symptom control.

The pharmacodynamic results of study IPX066-B08-11 support the claim that the onset of effect in time of Numient was similar to that of IR L-dopa+ and that Numient has a longer duration of effect as compared to IR L-dopa+ treatment. Between 3 and 6-7 hours post-dosing of a single administration of Numient the number of alternative finger taps was higher for Numient compared to IR L-dopa+ treatment (see Table 6). Since the effects of Numient treatment lasts for about 6-7 hours, dosing 3-4 times per day would be sufficient. Within the Numient development program, all ESPD patients received thrice daily Numient treatment and less than 10% of ASPD patients received Numient treatment more than 4 times a day. Thus the recommended dosing frequency of Numient (3-4 times per day) is lower than that of IR L-dopa+ (which needs to be dosed approximately every 2 hours) and this is an important benefit of the product.

Early stage Parkinson's disease (ESPD)

The clinical effects of Numient in ESPD patients have been investigated in one placebo-controlled study (study IPX066-B08-05) and in an open-label study (study IPX066-B09-03). The beneficial effects of Numient as well as the most important study outcomes within these studies are stated below.

Change in UPDRS II-III score
Numienthas shown benefits in improving both the self-assessed activities of daily life (UPDRS part II) and the clinician-scored monitored motor evaluation (UPDRS part III) of ESPD patients. This was demonstrated by the clinically meaningful and statistically significant differences in the decrease in UPDRS II-III scores, measured for each of the three evaluated doses of Numient, as compared to placebo (Table 12).

Positive results in two other relevant endpoints support the benefits of Numient in this population. These were the percentage of patients with decrease of at least 5 points in UPDRS II-III score and proportion of patients with an improvement in UPDRS II-III score of at least 30%. The proportions (51-58% for Numient) of patients with an improvement of at least 30% tended to be higher than that for placebo treatment (12%). In the open-label extension phase of study IPX066-B08-05, study IPX066-B09-03, mean UPDRS II-III scores at baseline (24.7) remained relatively constant on Numient treatment (-0.5 after 9 months of follow-up) confirming the observed effect.

PDQ-39 score
Numient improves the quality of life of ESPD patients as confirmed by the results on PDQ-39 scores at the end of the study period as compared to the baseline. All three doses of Numient caused a statistically significant decrease of the PDQ-39 score by 4.4 to 6 points while the score of the patients on placebo increased by 0.6 points. These results were confirmed in the open-label extension phase of study IPX066-B08-05, study IPX066-B09-03, where the mean PDQ-39 scores at baseline (21.4) remained relatively constant after 9 months of Numient treatment (+1.7 after 9 months of follow-up).

PGI- and CGI-scores
Results of the secondary outcomes PGI-scores, CGI-scores were consistent with that of the primary endpoint (change in UPDRS II-III score). As observed with respect to the primary endpoint, changes from baseline for each secondary endpoint were larger for each Numient treatment group compared to placebo treatment. A dose effect was not observed.

In summary, as expected for an L-dopa+ formulation, Numient is effective in EPSD. Treatment effects of Numient persisted over time during the 9-month open-label extension study.

Advanced stage Parkinson's disease (ASPD)

Treatment conversion into Numient

The dose conversion schemes proposed by the Applicant with respect to the conversion of IR L-dopa+ and CLE treatment into Numient were agreed. These were justified by additional PK analyses, demonstrating that the bioavailability of Levodopa regarding the proposed Numient doses is between the lower and upper limit of Levodopa bioavailability of the respective IR L-dopa+ or CLE dose ranges. Additionally, in the clinical studies with a treatment conversion phase it was demonstrated that premature study dropout during treatment conversion into Numient was neither due to overdosing nor due to under-dosing.

- *Numient versus IR L-dopa+*

Changes in 'OFF' time
The beneficial effect of Numienton 'OFF' time as a percentage of waking hours at baseline was greater to the one observed for the IR L-dopa+ treatment group. In the comparative treatment phase, the reduction in 'OFF' time as a percentage of waking hours was larger, and clinically and statistically significant for Numient treatment compared to IR L-dopa+ treatment (13.1% vs. 6.2%; p< 0.0001 - see Table 24.

At baseline, the 'OFF' time as percent of waking hours was 36-37% (i.e. approximately 6 hours) for both treatment groups. After dose adjustment of IR L-dopa+ and subsequent dose conversion into Numient, the effects of adjusted IR L-dopa+ treatment were compared with those of optimised Numient treatment during a comparative treatment phase of 13 weeks. At the end of the study, 'OFF' time was reduced by 2.2 hours on Numient treatment and by 1 hour upon IR L-dopa+ treatment. This difference was statistically significant (p< 0.0001). A reduction in 'OFF' time of at least 1.5 hours has been observed in 55.2% of Numient treated patients compared to 38.5% of IR L-dopa+ treated patients (p= 0.0003) (see Table 24).

In line with the observed reductions in 'OFF' time, the increases in 'ON' time without dyskinesia from a baseline value of 8.4-8.5 hours were larger for Numient treatment (+1.6 hours) compared to IR L-dopa+ treatment (+0.8 hours; p=0.0478).

Change in UPDRS II-III scores
The benefits of Numient in ASPD patients, expressed in an improvement of ADL and clinician-scored monitored motor evaluation, were shown by a clinically and statistically significant decrease in UPDRS II-III score, which was larger for Numient treatment compared to IR L-dopa+ treatment (mean difference -3.5; p< 0.0001) (see Table 24.

PDQ-39 score
Similarly to ESPD patients, in ASPD the positive effect on quality of life as measured by PDQ-39 scores was statistically significantly larger for Numient treatment compared to IR L-dopa+ treatment (see Table 24).

PGI- and CGI-scores
For the endpoints capturing the patients' and clinicians' global impression there was a positive effect of Numient as compared to IR L-Dopa+ treatment. Much to very much improved PGI-scores were reported by 38.5% of the patients on Numient treatment compared to 17.4% of the patients on IR L-dopa+ treatment. Similarly, much to very much improved CGI-scores were reported by 40.0% of patients on Numient treatment compared to 13.7% of patients on IR L-dopa+ treatment.

In summary, the benefits of Numient in ASPD patients were demonstrated by the greater reduction in 'OFF' time, and the more substantial improvement of UPDRS II-III and PDQ-39 scores as compared to IR L-dopa+ treatment. The clinical relevance of these observations was confirmed by the fact that much to very much improved PGI-scores were reported by 38.5% of the patients on Numient treatment compared to 17.4% of the patients upon IR L-dopa+ treatment. Similar results were obtained with respect to CGI-scores.

After dose conversion of CLE into Numient treatment, similar results have been obtained with respect to the reduction in 'OFF' time and UPDRS II-III score for Numient compared to CLE treatment. 'OFF' time was also found to be significantly reduced on Numient treatment compared to pre-study CR L-dopa+ treatment.

- Open-label extension studies with Numient treatment

313 Patients of the 349 ASPD patients enrolled in study IPX066-B09-03 (89.7%) completed this study. 66 of the 74 patients enrolled in open label extension study IPX066-B09-06 Part 2 (89.2%) completed this study. Hence, Numient treatment discontinuation rate was <15% in these studies, supporting the claim of efficacy in this population. UPDRS II-III scores remained stable for ASPD patients in study IPX066-B09-03 (+0.1 at month 9 compared to a baseline score of 28.1) and study IPX066-B09-06 Part 2 (+1.4 at month 6 compared to a baseline score of 28.6) which also confirms the benefits of the treatment with Numient.

Uncertainty in the knowledge about the beneficial effects.

Early stage Parkinson's disease (ESPD)

The comparative efficacy of Numient to IR L-dopa+ could not be concluded upon because of the lack of an active comparator in the ESPD development plan.

Six study patients were removed from study site 202 within study IPX066-B08-05 because the UPDRS ratings performed at this site differed significantly from the sponsor's expectations about the performance of these ratings. The Applicant indicated that these 6 study patients were included in the statistical analyses. Sensitivity analysis indicated that the inclusion or exclusion of these patients did not impact on the overall results.

Advanced stage Parkinson's disease (ASPD)

During the 3-week IR L-dopa+ dose adjustment period within study IPX066-B09-02, 'OFF' time decreased with 0.3-0.5 hours. The reduction in 'OFF' time did not plateau. Because of this it could be assumed that 'OFF' time could have decreased further after additional dose adjustment of IR L-dopa+ treatment.

Following dose conversion of pre-study L-dopa+ treatment into Numient treatment, beneficial effects have been observed such as reductions in 'OFF' time. It cannot be concluded whether the 6-week dose conversion period is long enough to optimize Numient treatment in patients.

The study design of the ASPD studies may have led to an unfair comparison considering that the IR L-dopa+ optimization appears incomplete whereas during the conversion from IR L-Dopa+ to Numient patients where titrated up to the maximum Numient dose. Moreover only patients who tolerated Numient were selected for randomization. It appears that that efficacy of a maximum dose of Numient was compared to a non-optimized dose of IR L-dopa+ instead of comparing equivalent doses of IR L-dopa+ and Numient. The Applicant however, demonstrated that treatment effects in general were consistent irrespective of the choice of baseline at study entry, dose conversion or baseline at randomization.The open-label switching study IPX066-B11-01 converting from CR L-dopa+ to Numient was a small study: only 43 ASPD patients were included. Exploratory PK-pharmacodynamic analyses have been conducted in 12 patients. Because of the limited amount of study participants, confidence intervals around effect estimators will be wider than if it were the case to include more ASPD patients. The design of the study and the limited number of included patients did not allow for firm conclusions to be made about the efficacy of Numient as compared to CR L-dopa+.

No dose conversion table for the conversion of CR L-dopa+ treatment into Numient was proposed in the SmPC, because of the limited data available. It is indicated that initial doses from the conversion table of IR L-dopa+ into Numient may be used. These initial doses may need to be decreased by about 30% for the conversion of CR L-dopa+ treatment into Numient. Though some more guidance with respect to the conversion of CR L-dopa+

into Numient would have been desirable, Numient dosing in clinical practice is ultimately determined by the patient's clinical response. Because of this, the guidance currently provided in combination with clinical surveillance is considered sufficient with respect to the conversion of CR L-dopa+ into Numient.The effects of missing values on the outcomes of studies IPX066-B08-05 and IPX066-B09-02 were unclear. However, both by using the baseline observation carried forward approach and the worst observation carried forward approach the applicant demonstrated that differences in treatment effects between the proposed L-dopa+ and placebo treatment remained statistically significant in ESPD patients (study IPX066-B08-05). This also applies to 'ON'/'OFF' time outcomes in study IPX066-B09-02 (ASPD patients) in which the effects of Numient treatment have been compared with IR L-dopa+ treatment. Hence, treatment effects were consistent irrespective of the imputation methodology.

Risks

Unfavourable effects

A total of 350 ESPD patients and 628 ASPD patients have been exposed to Numient treatment in the development programme. 57% of ESPD patients have been exposed to Numient treatment for at least one year, compared to 27% of ASPD patients.

Across the different studies (IPX066-B09-02, IPX066-B09-06 Part 1, and IPX066-B11-01), up to 23% (range 13-23%) of the study patients discontinued treatment during the conversion phase. In an additional analysis, the Applicant demonstrated that adverse events (4.5%), lack of efficacy (3.8%), and study withdrawal (3.5%) were the most common reasons for premature study discontinuation.

After dose conversion of pre-study L-dopa+ treatment into Numient, initial Numient doses were allowed to be changed to an optimal dose. It was clarified that during treatment conversion, Numient dose was back-titrated in only one patient who discontinued prematurely during the dose conversion phase. Hence, back-titration of Numient dose was not a major reason for premature study discontinuation during the dose conversion phase into Numient.

In ESPD patients the occurrence of adverse events increased with the increase in dose of Numient in this fixed dose study. Within study IPX066-B08-05, 56.3%, 72.1%, 71.4% of ESPD patients experienced adverse events on 145mg (n=87), 245mg (n=104), and 390mg (n=98) of Levodopa in Numient thrice daily. Similarly, 72.8% of placebo-treated ESPD patients (n=92) experienced adverse events.

The Applicant demonstrated in an additional analysis that there was no clear pattern between the occurrence of adverse events and Numient dosage in ASPD patients.

The occurrence of adverse events also tended to increase with advance in age. 65.2%(n= 135) of the ESPD patients aged up to 64 years experienced adverse events, compared to 67.3% (n=107) of the patients aged 65-74 years, 70.5% (n=44) of the patients aged 75-84 years and 100%(n=3) of the patients aged 85 years or above. With respect to ASPD patients, 49.0% of the patients aged up to 64 years (n= 296) experienced adverse events, compared to 55.7% of the patients aged 65-74 years (n=201), 57.1% of patients aged 75-84 years (n=56), and 80.0% of the patients aged 85 years or above (n=5).

Up to 23% of the patients discontinued their study participation upon conversion of pre-study L-dopa+ treatment into Numient treatment. 12.7% of the ASPD patients discontinued prematurely in study IPX066-B09-02 prematurely during treatment conversion of IR L-dopa+ to Numient. In 23/57 cases (40.4%) this was because of adverse events.

Study discontinuation because of adverse events tended to be higher for higher dosages of Numient treatment compared to placebo treatment. 5.7% of the patients treated with 145 mg Levodopa discontinued study treatment because of adverse events. Respective proportions of the ESPD patients discontinued study treatment who received 245 mg and 390 mg Levodopa within Numient thrice daily were 14.4% and 15.3% respectively. 4.3% of the placebo-treated ESPD patients discontinued study treatment because of adverse events. The percentage of the ESPD patients discontinuing study treatment because of an adverse event was 14.7% (19/129) in female patients compared to 10% (16/160) in male patients. 7% of female ASPD patients and 3.9% of male ASPD patients discontinued Numient treatment prematurely because of an adverse event.

Serious adverse events have been observed in 6% of the ESPD patients and in 11% of the ASPD patients on Numient treatment in Phase 2 and 3 studies. 3% Of ESPD patients on placebo treatment experienced serious adverse events. None of the ASPD patients received placebo treatment.

The most frequently observed adverse events in Phase 3 controlled studies among ESPD and ASPD patients concerned nervous system disorders (ESPD: 30-35%; ASPD: 10%), gastrointestinal disorders (ESPD: 24-28%; ASPD: 7.9%), psychiatric disorders (ESPD: 12-19%; ASPD: 10%), infections and infestations (ESPD: 11-20%; ASPD: 7%), and musculoskeletal and connective tissue disorders (ESPD: 13%; ASPD: 6%).

Dyskinesia is a common adverse event of all L-dopa+ products. Within the Numient studies, 4% of ESPD patients and 9% of ASPD patients experienced dyskinesia. In ESPD patients dyskinesia tended to occur more frequently upon higher Numient doses (2%, 4%, and 5% for 145, 245, and 390 mg Levodopa in Numient thrice daily). None of the placebo-treated patients experienced dyskinesia. Most dyskinesias were mild to moderate.

Headache was the most frequently observed neurological adverse event (13% of ESPD patients and 5% of ASPD patients) in Phase 2 and 3 studies.

Dizziness was experienced by 13% of ESPD patients compared to 6% of ASPD patients included in Phase 2 and 3 studies. Orthostatic hypotension occurred in 2% of ESPD patients compared to 1% of ASPD patients.

Psychological adverse events have been reported in 3% of ESPD patients and 6% of ASPD patients in Phase 2 and 3 studies. The most frequently observed psychiatric adverse events in these studies were insomnia (ESPD 9%; ASPD 5%), anxiety (ESPD 3%; ASPD 5%), somnolence (ESPD: 4%; ASPD: 1%), hallucination (ESPD: 1%; ASPD: 4%), and depression (ESPD: 3%; ASPD: 2%).

Haematological and chemical parameters, ECGs, and vital signs were in general comparable between different treatments. However, the proportion of patients with low haemoglobin and haematocrit values under Numient treatment tended to increase with time during Phase 2 and 3 studies.

Uncertainty in the knowledge about the unfavourable effects

The occurrence of adverse events has been evaluated in different studies in which different conversion schemes for treatment conversion of pre-study L-dopa+ treatment into Numient treatment have been used. The duration of follow up also differed in these studies. It therefore remains unclear whether the occurrence of adverse events in different studies is comparable.

Cardiovascular and cerebrovascular ischemic adverse events were experienced by 3% of ESPD patients and 2% of ASPD patients. These events occurred less frequently upon higher Numient doses (5% for 145 mg Levodopa in Numient TID, compared to 3% and 0% for 245 mg and 390 mg Levodopa in Numient). Within the Numient development program, there appeared to be no direct association between Numient treatment and the occurrence of these adverse events. It is however remarked that patients with any arrhythmia after a

myocardial infarction were excluded from study participation. Because of this, the precise cardiovascular risk profile of Numient is considered unknown.

Table 40 Effects Table for Numient for the treatment of Parkinson's disease.

Effect	Short Description	Unit	Numient Treatment	Control	Uncertainties / Strength of evidence	Refs
Favourable Effects						
PK / PD						
Tapping	Duration of tapping after administration of a single treatment dose	hours	7.6	5.6 (1)	Time to onset is similar for Numient and IR L-dopa+ (0.33 vs. 0.36 hours) Levodopa concentrations above 50% of Cmax were maintained longer for Numient compared to IR L-dopa+ (4.9 vs. 1.5 hours)	(4)
Dosing	Dosing frequency per day	Times/day	3-4	0-12 (1)	Numient is a multiphasic formulation. A level A In vitro-in vivo correlation model has not been established	(4)
Early stage Parkinson's disease (ESPD)						
$UPDRS_{II-III}$	Change in $UPDRS_{II-III}$ score from baseline	points	Overall BL: 36.7 145mg: -11.7 245mg: -12.9 390mg: -14.9 (TID(3))	Overall BL: 36.7 -0.6 (TID(2))	P<0.0001 for separate treatment comparisons with placebo. Changes from baseline in PDQ-39, PGI, and CGI scores in line with primary outcome ($UPDRS_{II-III}$). Lack of an active comparator	(5)
Advanced stage Parkinson's disease (ASPD)						
'OFF' time	Change in 'OFF' time end of study compared to baseline	hour	BL: 6.1 -2.2	BL: 5.9 -1.0 (1)	Difference between treatment groups: -1.2 hour (p<0.0001)	(6)

Effect	Short Description	Unit	Numient Treatment	Control	Uncertainties / Strength of evidence	Refs
CGI	Clinical Global Impression: much and very much improved	%	40.0	13.7 (1)	Study dropout upon conversion of pre-study L-dopa+ treatment into Numient not due to over- or underdosing of Numient Comparison may have been done to suboptimal IR L-dopa+ regimen	(6)
PGI	Patient Global Impression: much and very much improved	%	38.5	17.4 (1)	Treatment effects consistent irrespective of imputation technique for missing values	(6)
Unfavourable Effects						
Adverse events	Adverse events in ESPD patients	%	145mg: 56.3 245mg: 72.1 390mg: 71.4 (TID(3))	72.8 (2)	Dose effect relationship in ESPD, but not in ASPD	
Dyskinesia	Occurrence of dyskinesia in ESPD patients	%	145mg: 2 245mg: 4 390mg: 5 (TID(3))	0(2)		
Nausea	Gastro-intestinal adverse events (nausea)	%	145mg: 21.8(13.8) 245mg: 28.8(19.2) 390mg: 32.7(20.4) (TID(3))	8.7(3.3)(placebo)	Time-dependent relationship cannot be excluded.	

Abbreviations: ASPD: advanced stage Parkinson's disease, BL: baseline, ESPD: early stage Parkinson's disease, IR: immediate release, L-dopa+: Levodopa + any other active substance, PD: pharmacodynamics, PK: pharmacokinetics, TID: thrice daily

Notes: (1) IR L-dopa+, (2) placebo, (3) Levodopa dose within Numient capsule has been specified. Each capsule is administered thrice daily, (4) study IPX066-B08-11, (5) study IPX066-B08-05, (6) study IPX066-B09-02

Benefit-risk balance

Importance of favourable and unfavourable effects

Numient is a modified release L-dopa+ product, consisting of one IR L-dopa+ component and 2modified release L-dopa+ components. Pharmacokinetic studies have shown that Numient plasma levels remain stable for a longer period of time as compared to IR L-dopa+. Physical functioning tests in pharmacodynamic studies

demonstrated that the onset of action of Numient is similar to that of IR L-dopa+ and the effect was maintained for a longer period as compared to IR L-dopa+. The postulated advantage of Numient as compared to IR L-dopa+ has therefore been demonstrated - the prolonged duration of action and reduced 'OFF' time with fewer fluctuations in plasma levels allows for less frequent dosing of Numient (3-4 times per day) compared to IR L-dopa+ treatment (up to every 2 hours). Since it is difficult to control motor function adequately with oral tablets, the observed reduction in 'OFF' time and in dosing frequency is considered an advantage of the treatment with Numient.

In ESPD patients Numient has shown benefits in improving both the self-assessed activities of daily life (UPDRS part II) and the clinician-scored monitored motor evaluation (UPDRS part III), demonstrated by the clinically meaningful and statistically significant differences in the decrease in UPDRS II-III scores. The positive results in two other relevant endpoints (percentage of patients with decrease of at least 5 points in UPDRS II-III score and proportion of patients with an improvement in UPDRS II-III score of at least 30%) support the benefits in this population. Numient has also shown an improvement in the quality of life of ESPD patients as confirmed by the results on PDQ-39, and has demonstrated an improved PGI and CGI scores in this population.

In ASPD patients the beneficial effect of Numient was demonstrated by an increase in 'OFF' time as a percentage of waking hours at baseline and in 'ON' time without dyskinesia. Additionally the benefits of Numient in ASPD patients were expressed in an improvement of ADL and clinician-scored monitored motor evaluation, as shown by a clinically and statistically significant decrease in UPDRS II-III score - larger for Numient compared to IR L-dopa+ treatment. Similarly to ESPD patients, in ASPD the positive effect on quality of life as measured by PDQ-39 scores was statistically significantly larger for Numient treatment as were the PGI- and CGI-scores.

The most frequently observed adverse events in Phase 3 controlled studies among ESPD and ASPD patients were nervous system disorders (ESPD: 30-35%; ASPD: 10%), gastrointestinal disorders (ESPD: 24-28%; ASPD: 7.9%), psychiatric disorders (ESPD: 12-19%; ASPD: 10%), infections and infestations (ESPD: 11-20%; ASPD: 7%), and musculoskeletal and connective tissue disorders (ESPD: 13%; ASPD: 6%).

In ESPD, the occurrence of adverse events increased with Numient dose increase. There was insufficient evidence for such a dose-effect relationship in ASPD patients. The Applicant demonstrated in additional analyses that treatment effects were consistent for different baselines and for different imputation techniques for missing values.

Benefit-risk balance

Discussion on the benefit-risk balance

The initial release of the immediate release Levodopa-Carbidopa component of Numient allows an onset of action similar to that of IR L-dopa+ studies. In line with the subsequent pH-dependent release of 2 modified release Levodopa-Carbidopa components of Numient at different sites along the gastro-intestinal tract, stable Levodopa concentrations with reduced maximum plasma concentration/minimum plasma concentration (Cmax/Cmin) are maintained for a longer period as compared to IR Levodopa formulations. The prolonged duration of action of Numient compared to IR L-dopa+ allows for less frequent dosing of Numient. Due to the shorter duration of action of IR L-dopa+ compared to Numient, Levodopa plasma concentrations will fluctuate more upon IR L-dopa+ treatment compared to Numient treatment. This makes it difficult to achieve optimal motor functioning with IR L-dopa+ treatment. Because of this, the reduced dosing frequency of Numient compared to IR L-dopa+ products is therefore not only convenient for daily clinical practice; it also improves physical functioning in patients with Parkinson's disease.

The dosing frequency of Numient is comparable with that of other registered modified release L-dopa+ products, which are dosed two up to eight times per day. Hence, the benefit with respect to dosing of Numient compared to other registered modified release L-dopa+ products is less evident.Separate conversion tables have been proposed for the conversion of dose ranges of IR L-dopa+ and CLE treatment into single doses of Numient. The Applicant demonstrated that the bioavailability of Levodopa of the proposed Numient doses is in between the Levodopa bioavailability of respective IR L-dopa+ or CLE dose ranges. Premature study discontinuations during treatment conversion were not due to over- or underexposure to Numient. Hence, the proposed conversion tables are acceptable.

The data from the presented studies have shown that Numient provides a clinically relevant improvement of the symptoms in both early and advanced stage Parkinson's disease patients, supported by an improvement of their quality of life and physical functioning.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Numient is not similar to Duodopa within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Numient in the treatment of Parkinson's disease is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.