EU Risk Management Plan for
Onerji(levodopa/carbidopa)

RMP version to be assessed as part of this application:

RMP Version number:	1.0
Data lock point for this RMP:	03 May 2024
Date of final sign-off:	11 March 2026
Rationale for submitting an updated RMP:	Not applicable.
Summary of significant changes in this RMP:	No significant changes
Details of the currently approved RMP:	Not applicable as this section is not required for initial marketing authorisation applications.

Approved by:	Name	Date and signature
EU-QPPV, Tanabe Pharma GmbH	[redacted]	

Note: NeuroDerm Ltd. is the developer of ND0612 drug product, while the Marketing Authorisation Applicant is Tanabe Pharma GmbH. Both are subsidiaries of Tanabe Pharma Corporation.

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Part I: Product(s) Overview

Table 1. Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Levodopa (60mg/mL) and carbidopa (7.5mg/mL)
Pharmacotherapeutic group(s) (ATC Code)	Anti-Parkinson drugs, levodopa and decarboxylase inhibitor (ATC: N04BA02)
Marketing Authorisation Applicant	Tanabe Pharma GmbH
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Onerji
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Dopaminergic combination
	Onerji® is a solution of levodopa (60 mg/mL) and carbidopa (7.5 mg/mL) (levodopa: carbidopa ratio of 8:1) for continuous subcutaneous (SC) infusion. *Mechanism of action of levodopa (60mg/mL) and carbidopa (7.5mg/mL):* Levodopa (LD), the metabolic precursor of dopamine, does cross the blood-brain barrier, and presumably is converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa treats the symptoms of Parkinson's disease. When levodopa is administered orally, it 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 (CD) is a decarboxylase inhibitor. Because its decarboxylase inhibiting activity is limited to extracerebral tissues, administration of carbidopa with levodopa makes more levodopa available to the brain. The addition of carbidopa to levodopa reduces the peripheral effects (e.g., nausea and vomiting) due to decarboxylation of levodopa; however, carbidopa does not decrease the adverse reactions due to the central effects of levodopa. Preliminary clinical studies demonstrated that Onerji® is associated with more stable plasma LD levels (lower fluctuation index values and reduced peak-to-through ratio) than intermittent doses of standard oral levodopa/carbidopa (LD/CD). The pivotal efficacy trial ND0612-317 demonstrated that Onerji® is associated with significant benefits

	in both "ON" time without troublesome dyskinesia and "OFF" time, without worsening of dyskinesia in patients with Parkinson's disease experiencing motor fluctuations.
	Important information about its composition: levodopa/carbidopa is an organic molecular entity.
Hyperlink to the Product Information	See the Product Information for Onerji®.
Indication(s) in the EEA	Current: Onerji® is indicated for the treatment of motor fluctuations in patients with advanced Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medicinal products.
	Proposed: Not applicable
Dosage in the EEA	Current: The maximum recommended daily dose of Onerji® is 720 mg of the levodopa component and 90 mg of the carbidopa component. Daily treatment includes an individualised daytime dose delivered over 18 hours which starts about 3 hours before the anticipated patient's wake-up time and a nighttime fixed dose (30 mg of the levodopa component) delivered over 6 hours. Onerji® is administered via two infusion sites, at a fixed rate of 0.08 mL/hour during the night (6 hours) and at an individualised rate ranging between 0.32-0.64 mL/hour during the day (18 hours), for a total duration of 24 hours and a total daily dose of 370-720 mg levodopa and 46-90 mg carbidopa, respectively. Onerji® is administered subcutaneously, and should only be used with one of the following drug delivery systems: - YURWAY® Delivery System, which includes a rechargeable pump, sterile single-use medication cartridge (reservoirs) with attached vial adapters. The Yurway delivery system is used with sterile, single-use infusion sets. - CRONO Twin ND pump, which uses sterile single-use syringes (reservoirs), vial adapters and infusion sets. Onerji® is administered with a levodopa oral morning dose. Additional oral levodopa can be prescribed as needed. If required, other classes of medicinal products for Parkinson's disease can be taken concomitantly with it and adjusted as needed. *Initiation and Titration Instructions*: *Step 1*: Calculate the daily total oral levodopa equivalent dose by utilizing the appropriate levodopa conversion factors *Step 2*: Initiate Onerji® with the full dose (720 mg of levodopa) along with a morning oral dose of levodopa. If patients were on

<table>
<tr><td></td><td>more than 720 mg of daily total oral levodopa equivalent dose before initiating Onerji®, add adjunct oral levodopa throughout the day to make up the difference between their daily total oral levodopa equivalent dose minus the 720 mg of levodopa provided by Onerji® and the morning oral levodopa dose. If a catechol-O-methyltransferase (COMT) inhibitor is co-administered with Onerji®, apply also the COMT-inhibitor multiplication factor to the levodopa Onerji® component.

Step 3: Adjust adjunct oral levodopa, if needed. If patients need to reduce their total daily levodopa dose, adjust adjunct oral levodopa dose prior to reducing Onerji® dose based on Table 2.

Table 2: Onerji® Levodopa daily dose
<table>
<tr><th colspan="2">Daytime – 18 hours</th><th colspan="2">Nighttime – 6 hours</th><th>Total Daily</th></tr>
<tr><th>Flow rate (mL/h)</th><th>Levodopa dose (mg)</th><th>Flow rate (mL/h)</th><th>Levodopa dose (mg)</th><th>Levodopa dose (mg)</th></tr>
<tr><td>0.64</td><td>690</td><td>0.08</td><td>30</td><td>720</td></tr>
<tr><td>0.59</td><td>640</td><td>0.08</td><td>30</td><td>670</td></tr>
<tr><td>0.55</td><td>590</td><td>0.08</td><td>30</td><td>620</td></tr>
<tr><td>0.50</td><td>540</td><td>0.08</td><td>30</td><td>570</td></tr>
<tr><td>0.45</td><td>490</td><td>0.08</td><td>30</td><td>520</td></tr>
<tr><td>0.41</td><td>440</td><td>0.08</td><td>30</td><td>470</td></tr>
<tr><td>0.36</td><td>390</td><td>0.08</td><td>30</td><td>420</td></tr>
<tr><td>0.32</td><td>340</td><td>0.08</td><td>30</td><td>370</td></tr>
</table>
</td></tr>
<tr><td></td><td>Proposed: Not applicable</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td>Current:

- Pharmaceutical form: Solution for infusion

- Strength: levodopa 60mg/mL and carbidopa 7.5mg/mL</td></tr>
<tr><td></td><td>Proposed: Not applicable</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>No</td></tr>
</table>

Note: ND0612 drug product (DP) was the name during development, while the brand name for the product in Europe is Onerji®

Part II: Safety specification

The aforementioned product is under authorisation according to the conditions of a full-mixed application based on Article 8(3) of Directive 2001/83/EC.

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication: **Treatment of motor fluctuations in patients with advanced Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medicinal products.**

Incidence: Parkinson's disease is a progressive neurodegenerative disorder characterized clinically by the presence of cardinal motor features (including bradykinesia and at least one of rest tremor or rigidity) and characterized pathologically by degeneration of dopaminergic neurons in the substantia nigra pars compacta, with consequent striatal dopamine deficiency (Hauser, 2009; Olanow et al., 2009; Poewe et al., 2017). Parkinson disease is the second most common neurodegenerative disorder after Alzheimer's disease and is a major and increasing burden on patients, families, carers and on healthcare systems. Parkinson's disease gets worse slowly. Severe disability or death may be expected in 25% of the patients within 5 years (Findley, 2007). Globally, the incident number of Parkinson's Disease was ~1.1 million in 2019, with an overall age-standardized incidence rate of 13.43/100,000. Among the age groups, the high incident numbers of Parkinson's Disease were observed in patients aged over 65 years (Ou, 2021). The combination of levodopa (LD) and a dopa decarboxylase (DDC) inhibitor (typically carbidopa) is the standard therapy for PD and continues to be the most effective treatment for the motor symptoms of the disease (Fahn, 2006; Olanow et al., 2004). Most patient with Parkinson disease experience satisfactory control with intermittent doses of oral LD/DDC inhibitor therapy, particularly during the early stages of the disease. At these early stages, patients typically experience a long-lasting response following each dose of LD despite the drug having a relatively short half-life of only 45-90 minutes. However, chronic LD treatment and disease progression are associated with the development of motor complications in the form of motor fluctuations (wearing OFF, ON-OFF phenomenon) and dyskinesia, which can be severe and disabling (Olanow et al., 2009). In the extreme, patients cycle between "OFF" periods (in which they experience severe PD features), and "ON" periods which are complicated by disabling dyskinesias. Motor complications affect approximately 20% of Parkinson disease patients within 1 year of treatment, 25-75% of patients after 3-4 years, and virtually all patients over the course of the disease (Fahn et al., 2004; Hely et al., 2005; Kim et al., 2020; Mizuno et al., 2018; Olanow et al., 2013).

Prevalence: Parkinson's disease (all stages) affects more than 6 million people worldwide, including approximately 1 million persons in the US and ranging from 1.4 million to 1.75 million persons in Europe (Ou, 2021). A more recent Parkinson's disease is very rare in individuals under the age of 40 years, and symptoms generally appear in people between 55 and 65 years of age. It is estimated to affect 1% of people over the age of 60 years and 3% over the age of 80 years. From 1990 to 2015, the number of people with PD doubled, driven principally by aging. The Global Burden of Disease Study estimates that the number of PD cases will further increase to about 13 million persons in 2040. Other risk factors for Parkinson's disease include a family history, male gender, head injury, exposure to pesticides, consumption of well water and rural living. The prevalence of dyskinesias and motor fluctuations, and the factors determining their occurrence, was investigated in a community-based population of patients with Parkinson's disease. Among 124 patients with Parkinson's disease, 87 (70%) had received a levodopa-preparation. Among these 87 patients, 40% were experiencing response fluctuations. The prevalence of motor fluctuations was best predicted by disease duration and dose of levodopa (Schrag et al.; 2000).

Demographics of the population in the authorized indication (age, gender, racial and/or ethnic origin) and risk factors for the disease: Levodopa/carbidopa can be used in adults regardless of sex, race and ethnic origin. There is no relevant use of Onerji® in the paediatric population in the treatment of Parkinson's disease. Of note, a product-specific waiver for studies in paediatric populations was granted by the EMA (in March 2020) for ND0612 drug product (investigational product name of ONERJI®). The impact of age on the levodopa and carbidopa pharmacokinetics following Onerji® infusion was not specifically evaluated. In the popPK analysis (age range 20-84 years), no trends with age were observed for levodopa and carbidopa. Dose adjustment should be conducted with caution in patients of 85 years and older. Moreover, there are no studies on the pharmacokinetics of levodopa and carbidopa in patients with hepatic or renal impairment. Dosing with ND0612 is to be individualized to achieve an optimal clinical effect in terms of efficacy and safety. Therefore, potential effects of hepatic or renal impairment on levodopa and carbidopa exposure are indirectly accounted for in dose titration. As a conservative measure, the proposed label for Onerji® states that periodic evaluation of hepatic and renal function are recommended during extended therapy. The proposed label for Onerji® also states that dose adjustment should be conducted with caution in patients with severe renal or hepatic impairment. A variety of risk factors have been associated with earlier and more severe motor complications in patients with Parkinson's disease. These include younger age at disease onset, longer disease duration, more severe nonmotor symptoms (e.g., anxiety and depression), higher levodopa dose and responsiveness, and overall disease severity (Liang TW, 2024; Aradi SD, 2020).

The main existing treatment options: There are several options for treating motor fluctuations in PD, but no drug has been able to manage the problem satisfactorily in the long-term. Oral therapies fail to provide sufficient control of motor fluctuations in many patients with advancing PD. One option is adjusting the LD dose or frequency; however, increasing the dose can lead to worsening of dyskinesia, while lowering the dose can increase "OFF" time. Extended-release formulations have not proven to be more effective (Hauser et al., 2013). A number of adjunct therapies have been developed to try to reduce "OFF" time. These include dopamine agonists, MAO type B inhibitors, COMT inhibitors, and/or the adenosine antagonist istradefylline (Ferreira et al., 2013; Fox et al., 2018). [Of note, istradefylline has been approved in the United States and in Japan, but not in Europe]. None of these options provides benefits superior to LD. In addition, each has its own set of potentially serious side effects such as sleep disturbances, psychosis, impulse-control disorders, etc. (Fox et al., 2018; Jankovic & Tan, 2020). Surgical therapies such as Deep-Brain Stimulation (DBS) can also be used for the treatment of motor complications in PD patients that are not adequately controlled by oral therapies. Indeed, they may provide benefit for both "OFF" time and dyskinesia (Deep-Brain Stimulation for Parkinson's Disease Study Group, 2001). Nevertheless, they require a brain operation that can be associated with potentially serious complications related to the surgery, such as haemorrhage, infection, or seizure (Lachenmayer et al., 2021; Rughani 2018; Buhmann 2017). In addition, complications may also develop related to the stimulation system or the stimulation itself, such as dysarthria. Further, frequent adjustments are necessary and occasional repeated surgical procedures may be required related to stimulation system or battery replacement. Importantly, no procedure has been shown to provide superior anti-parkinsonian benefits in comparison to LD (perhaps with the exception of tremor). Continuous intrajejunal CD/LD infusion (Duodopa®) showed a benefit in "OFF" time and "ON" time without troublesome dyskinesia of a greater magnitude than has been seen to date with any of the approved LD oral therapies (Olanow et al., 2014, Borgohain et al., 2014; Ferreira et al., 2016; Hauser et al., 2021; Poewe et al., 2007; Rascol et al., 2005; Schapira et al., 2011). However, CD/LD enteral suspension is associated with potentially serious side effects associated with the surgical procedure (e.g., peritonitis, pancreatitis, pain, infection) (Duodopa® SmPC) and with the need to have a permanent intrajejunal tube (e.g., blockage, dislocation, infection) which may require periodic repeat invasive procedures to correct. Additionally, it does not solve the issue of competitive absorption for LD in the jejunum. Foslevodopa/foscarbidopa (a pro-drug of LD/CD for continuous SC administration over 24 h by means of an ambulatory infusion pump through

one infusion site) has been approved in Europe (as Produodopa®), in Canada and Japan (as Vyalev®), and more recently in the US (as Vyalev®). In all countries except the US, the maximum recommended daily dose of foslevodopa is 6000 mg, equivalent to ~4260 mg LD. In the US, the maximum recommended daily dose of foslevodopa is 3525 mg, equivalent to ~2500 mg LD. It is indicated for the "Treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyperkinesia or dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results".

Natural history of the indicated condition in the PD population, including mortality and morbidity: Available studies have shown that compared with healthy controls, patients with PD are accompanied by high rates of premature death. This is usually caused by factors such as pneumonia and cerebrovascular and cardiovascular diseases. In the first 5 years after disease onset, mortality in Parkinson´s disease does not increase but it increases with a relative risk factor of 3.5 after 10 years compared with the general population (Scorza FA, 2022). Specific rates of mortality and morbidity due to motor fluctuations in patients with Parkinson´s disease are not available.

Important co-morbidities: Determinant factors, such as aspiration pneumonia, dementia, advanced age cancer, and cardiovascular disease, typically cause death in patients with Parkinson´s disease. There is a considerable information concerning cardiac dysfunctions that demonstrates the involvement of the heart in Parkinson´s disease, including cardiac autonomic dysfunction, cardiomyopathy, coronary heart disease, and arrhythmias/conduction defects (Scorza FA, 2022).

Part II: Module SII - Non-clinical part of the safety specification

The systemic safety profile of LD, CD and their combination after chronic use is well-established in laboratory animals and in humans. Therefore, single dose toxicity, chronic repeat-dose toxicity, genotoxicity, carcinogenicity, or developmental and reproductive toxicity studies have not been conducted with ND0612 DP. Since ND0612 DP is intended for continuous SC administration, the non-clinical testing strategy was designed to mainly evaluate the local toxicity of ND0612 DP at the infusion sites. Accordingly, a 90-day repeat-dose toxicity study in the minipig (Report 95070) was conducted as the pivotal non-clinical study supporting the clinical development and MAA for ND0612 DP. In addition, a subsequent 28-day GLP toxicity study (Report A2369) examined the tolerability of several dosing regimens and provides further support for the safety of ND0612 DP.

The minipig studies showed that treatment with ND0612 DP was systemically well tolerated. There were no mortalities, no adverse clinical signs or changes in body weight gain, and no treatment-related changes in clinical pathology parameters. The pivotal study (Report 95070) demonstrated the absence of systemic adverse effects at dosing regimens which generated LD exposure levels ~6-8-fold higher than those encountered during the clinical studies.

Lesions at the infusion sites were the only treatment-related adverse effect in all non-clinical studies. These lesions were characterised externally as various degrees of local erythema and/or minimal to mild local oedema/swelling at the infusion site. Microscopic examinations showed subchronic and chronic inflammation with and without evidence for necrosis (with and without cavity formation), mineralization, and pigment-filled macrophages, indicative of a normal phagocytic response to previously present haemorrhage. The severity and incidence of these lesions were dependent on the rate of infusion, frequency of reusing each SC infusion site and on the time that elapsed from infusion to the site until

time of pathological examination. These studies indicated that these lesions undergo repair and tend to recover between successive treatments to the same infusion site.

In ND0612 preclinical Study 95070, infusion sites that were visited every five days showed poor tolerability, whereas sites that were used less frequently (i.e., every 10 to 15 days) showed better tolerability as evidenced by lesions of lower severity. Sites infused at high infusion rate of 0.72 mL/h for 8 hours, showed more severe inflammation and necrosis than those sites infused at a rate of 0.32 mL/h for 16 hours followed by 0.1 mL/h for 8 hours, which is comparable to the maximal flow rate administered to each infusion site in PD patients. At this flow rate of 0.32 mL/h×16h + 0.1 mL/h×8h per infusion site, the infusion site lesions were considered tolerable. These lesions tended to recover and were almost completely resolved after a 30-day recovery period.

Based on the results of the non-clinical studies showing lesions at the infusion sites, additional studies were conducted to further investigate the local safety of the excipients in ND0612 formulation. A GLP-compliant 90-day SC toxicity study in the minipig (Report A3574) evaluated the local toxicity of the ND0612 vehicle (i.e., a ND0612 DP formulation containing only the inactive ingredients in the same proportions as in the ND0612 DP formulation with the active ingredients, CD and LD). This study showed that the vehicle itself produces infusion site reactions similar to those produced by the ND0612 formulation containing the active ingredients, suggesting that the cause of these lesions is related to the excipients rather than to CD or LD. This study also showed that infusion of 6 mL/site for 24 hours was better tolerated than infusion of 9 mL/site for 24 hours.

To identify the irritating component in the formulation, NeuroDerm conducted a GLP-compliant local toxicity study in minipigs using several variations of the vehicle formulation and has identified L-arginine as the irritating component in the formulation (Report A4608). In this study, SC infusions of solutions containing L-arginine induced comparable infusion site reactions as the ND0612 complete formulation, while formulations without L-arginine caused minimal responses, comparable in severity and incidence to saline. The study also indicated that the other formulation components, as well as formulations of high pH or high osmolality (characteristic of ND0612 DP), were not responsible for the lesions. This is also consistent with an investigational study conducted by NeuroDerm (Report ND 2-20-093) which examined the effects of ND0612 DP and its components, particularly L-arginine, on coagulation indices in pigs. While no effect was seen on coagulation indices following in vivo treatment, there was a marked inhibition of clotting time ex vivo, when fresh blood samples were incubated with ND0612 formulations containing L-arginine or with isolated L-arginine solutions at the concentrations present in ND0612 DP.

The overall tolerability of the infusion site lesions in animals supports a tolerable treatment in Parkinson´s disease patients, at the indicated dosing regimen with a daily rotation of the two infusion sites.

Part II: Module SIII - Clinical trial exposure

ND0612 clinical development program includes 13 clinical studies: seven Phase 1 studies in healthy volunteers (HVs), and six studies in subjects with Parkinson´s disease (five Phase 2 studies including a Phase 2b long-term safety study, and one efficacy and safety pivotal Phase 3 study).

As of 3rd May 2024, 744 subjects (146 healthy volunteers (HVs) and 598 Parkinson´s disease patients) had been exposed to at least one dose of ND0612 (Table 3), with a cumulative exposure to ND0612 of approximately 974 subject-years. The majority of the exposure had been accumulated from the Phase 2b long-term open-label safety study (ND0612H-012) and from the Phase 3 pivotal efficacy and safety study (ND0612-317), 517 and 452 subject-years, respectively. The longest exposure for a Parkinson´s disease patient had reached 7.5 years.

Table 3: Total Number of Subjects Exposed to ND0612 by Clinical Trial.

Clinical trial	Healthy Volunteers (HVs)	Parkinson´s Disease Patients
ND0612-001	36	-
ND0612-001b	18	-
ND0612-002	-	8
ND0612-003	-	24
ND0612-004	-	16
ND0612-005	36	-
ND0612H-006	-	38
ND0612H-012	-	214*
ND0612H-114	24	-
ND0612H-115	16	-
ND0612-J01	16	-
ND0612-317	-	322
All studies	**146**	**598**

*Including 24 patients rolled over from ND0612H-006.

Note: Study ND-CD-101 (TQT study in HVs) is an oral carbidopa study and is therefore not included in the table

Of the 598 Parkinson´s disease patients included in ND0612 clinical studies, approximately two thirds were males (which reflects the gender ratio in Parkinson's disease).

Table 4 below presents the number of Parkinson´s disease patients included in the clinical studies, as well as their respective cumulative exposure to ND0612, by gender, age and ethnicity categories.

Table 5 below presents ND0612 Treatment Exposure by Daily Modal Dose and Duration for the 598 PD patients included in ND0612 clinical studies.

Table 4: Number of Parkinson´s disease patients and duration of exposure to ND0612, by gender, age and ethnicity categories

	Number (%) of Parkinson´s disease patients	Cumulative Duration of exposure in the clinical studies (in patient-year)
By gender category:		
Males	382 (63.9%)	650.5
Females	216 (36.1%)	323.7
By age category:		
<65 years	304 (50.8%)	528.8
≥65 to <75 years	251 (42.0%)	368.4

≥75 to <85 years	43 (7.2%)	77
By ethnicity category:		
Hispanic or Latino	44 (7.4%)	70.3
Not Hispanic or Latino	493 (82.4%)	890.1
Not reported	61 (10.2%)	13.7
Cumulative exposure in Parkinson´s disease patients		
TOTAL	**598**	**974.1**

Table 5: ND0612 Treatment Exposure by Daily Modal Dose and Duration for the 598 PD patients included in ND0612 clinical studies

	Modal Dose Category (mg/day)								
Exposure Duration to ND0612	< 370 (N=49) n (%)	>= 370 (N=549) n (%)	>= 420 (N=546) n (%)	>= 470 (N=544) n (%)	>= 520 (N=537) n (%)	>= 570 (N=516) n (%)	>= 620 (N=507) n (%)	>= 670 (N=495) n (%)	= 720 (N=493) n (%)
<= 29 Days	48 (8.0)	88 (14.7)	88 (14.7)	88 (14.7)	86 (14.4)	79 (13.2)	78 (13.0)	74 (12.4)	73 (12.2)
>= 30 Days	1 (0.2)	461 (77.1)	458 (76.6)	456 (76.3)	451 (75.4)	437 (73.1)	429 (71.7)	421 (70.4)	420 (70.2)
>= 90 Days	1 (0.2)	390 (65.2)	388 (64.9)	387 (64.7)	383 (64.0)	376 (62.9)	368 (61.5)	360 (60.2)	360 (60.2)
>= 180 Days	1 (0.2)	332 (55.5)	331 (55.4)	331 (55.4)	327 (54.7)	323 (54.0)	316 (52.8)	309 (51.7)	309 (51.7)
>= 365 Days	1 (0.2)	286 (47.8)	285 (47.7)	285 (47.7)	283 (47.3)	281 (47.0)	275 (46.0)	269 (45.0)	269 (45.0)
>= 2 Years	1 (0.2)	211 (35.3)	211 (35.3)	211 (35.3)	209 (34.9)	208 (34.8)	202 (33.8)	197 (32.9)	197 (32.9)
>= 3 Years	0	106 (17.7)	106 (17.7)	106 (17.7)	105 (17.6)	105 (17.6)	105 (17.6)	105 (17.6)	105 (17.6)
>= 4 Years	0	64 (10.7)	64 (10.7)	64 (10.7)	63 (10.5)	63 (10.5)	63 (10.5)	63 (10.5)	63 (10.5)
>= 5 Years	0	49 (8.2)	49 (8.2)	49 (8.2)	49 (8.2)	49 (8.2)	49 (8.2)	49 (8.2)	49 (8.2)
>= 6 Years	0	30 (5.0)	30 (5.0)	30 (5.0)	30 (5.0)	30 (5.0)	30 (5.0)	30 (5.0)	30 (5.0)
>= 7 Years	0	8 (1.3)	8 (1.3)	8 (1.3)	8 (1.3)	8 (1.3)	8 (1.3)	8 (1.3)	8 (1.3)

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Table 6 below includes the list of key exclusion criteria in ND0612 main clinical studies, reason for these exclusion criteria, and the rationale for not including these criteria as missing information.

Table 6: Exclusion Criteria

Criteria	Reason for Exclusion	Is It Considered to Be Included as Missing Information?	Rationale (for not including as missing information)
Atypical or secondary parkinsonism	Exclusion criterion in clinical studies, as patients with atypical or secondary parkinsonism generally do not respond well to drug treatment with levodopa; as such they would not benefit from Onerji® treatment.	No	Not included as missing information, as the targeted population for Onerji® is patients with Parkinson's disease, not patients with atypical or secondary parkinsonism.

Use of non-selective monoamine oxidase (MAO) inhibitors	Exclusion criterion in clinical studies, as concomitant treatment with non-selective monoamine oxidase (MAO) inhibitors (e.g., Phenelzine, tranylcypromine) and Onerji® could expose patients to a risk of acute hypertensive episode.	No	Not included as missing information, as Onerji® Summary of product characteristics (SmPC) includes concomitant use of non-selective monoamine oxidase (MAO) inhibitors (e.g., Phenelzine, tranylcypromine) as a contraindication. These inhibitors must be discontinued at least two weeks prior to initiating therapy with Onerji®.
Subjects with narrow-angle glaucoma	Exclusion criterion in clinical studies, due to the risk of increased intra-ocular pressure when patients with narrow angle glaucoma are treated with levodopa.	No	Not included as missing information, as Onerji® SmPC includes narrow-angle glaucoma as a contraindication.
Subjects with significant cognitive impairment	Exclusion criterion in clinical studies, as these patients may have had difficulties to follow/be compliant with the study protocols instructions, e.g., to properly complete the patients' diary, that was used to assess the study drug efficacy.	No	Not included as missing information, as Onerji® SmPC includes significant cognitive impairment as a contraindication. Indeed, patients with significant cognitive impairment may have difficulties to understand/adhere to the Instructions for Use of Yurway or CRONO Twin ND, which may have an impact on ONERJI® efficacy and/or safety.
Subjects <18 years	Exclusion criterion in clinical studies, as a waiver for studies in pediatric populations was granted to NeuroDerm from the EMA, on the grounds that pediatric studies would be impossible or highly impracticable as Parkinson´s disease is extremely rare in pediatric patients (Thomsen TR, 2010).	No	Not included as missing information, as Onerji® SmPC states that there is no relevant use of Onerji® in the paediatric population in the treatment of Parkinson's disease.

Use in pregnant or lactating women	Exclusion criterion in clinical studies for safety reason, levodopa safety being insufficiently ascertained in pregnant or lactating women. Moreover, the mean age for Parkinson´s disease being 60 years, it is unlikely to include pregnant or lactating patients.	No	Not included as missing information, as Onerji® SmPC includes the following: -Onerji® is not recommended during pregnancy and in women of childbearing potential not using contraception. - Levodopa and possibly levodopa metabolites are excreted in human milk. There is evidence that lactation is suppressed during treatment with levodopa. It is unknown whether carbidopa or its metabolites are excreted in human milk. Animal studies have shown excretion of carbidopa in breast milk. There is insufficient information on the effects of levodopa/carbidopa or their metabolites in newborns/infants. Breast feeding should be discontinued during Onerji® therapy
Hypersensitivity to levodopa, carbidopa or to any of the excipients in ND0612 solution	Exclusion criterion in clinical studies, as the administration of Onerji® in patients with hypersensitivity to levodopa, carbidopa or to any of the excipients in ND0612 solution could expose patients to a safety risk.	No	Not included as missing information, as Onerji® SmPC includes a contraindication in patients with hypersensitivity to levodopa, carbidopa or to any of the excipients.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical studies conducted to date were unlikely to detect certain types of adverse reactions such as rare adverse reactions.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 7: Exposure of Special Populations Included or Not in the Clinical Trial Development Programs

Type of Special Population		**Exposure**
Paediatric population		Not included in the clinical development program
Pregnant or lactating women		Not included in the clinical development program
	• Patients with hepatic impairment (aspartate aminotransferase (AST) or alanine aminotransferase (ALT)	Exclusion criterion in clinical studies.

Patients with relevant co-morbidities:	> 2×upper limit of normal (ULN), and total bilirubin > 2.5 mg/dL)	
	• Patients with renal impairment (serum levels of creatinine > 1.5 mg/dL)	Exclusion criterion in clinical studies.
	• Patients with clinically significant electrocardiogram (ECG) abnormalities	Exclusion criterion in clinical studies.
	• Patients with narrow-angle glaucoma	Exclusion criterion in clinical studies.
	• Patients with significant cognitive impairment	Not included in the clinical development programme.
Others:	• Patients with acute psychosis or troublesome hallucinations	Exclusion criterion at study entry
	• Patients with significant skin conditions or disorders that could interfere with the infusion of ND0612	Exclusion criterion at study entry

Part II: Module SV - Post-authorisation experience

Not applicable as the product has not been commercialised.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

The risk of misuse of ND0612 DP for illegal purposes is low, as the drug has no addictive potential. ND0612 has not been previously marketed (nor withdrawn from marketing) in any country. There are no data to indicate a potential for misuse of ND0612 for illegal purposes.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

If any new risk(s) or a change to the pre-existing risk(s) emerge based on any new relevant safety-related information, those new risks can be either added to the list of safety concerns or to the list of risks not considered important for inclusion, based on their medical assessment and if considered appropriate.

Table 8: Reason for not including an identified or potential risk in the list of safety concerns in the RMP

Reason for non-inclusion	List of risks
Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised).	- Peripheral Neuropathy - Adverse reactions reported with a common/very common frequency (incidence of ≥1%) in ND0612 clinical studies. - Other adverse drug reactions reported for oral LD/CD drugs. - Risk related to levodopa (LD) visible particles (LD precipitates) in ND0612 solution. - Wrong dose due to pump malfunction

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

The following risks have been considered important for inclusion in the list of safety concerns in the RMP of Onerji® due to their frequency and/or the potential severity of these adverse effects based on clinical available data and published literature.

Important Identified Risks:

Infusion site reactions

Risk-benefit impact: The most common adverse reactions associated with ND0612 in the clinical studies were infusion site reactions (ISRs), reported by 470 (78.6%) of all Parkinson's disease patients (N=598) who received at least one dose of ND0612, and by 372 (88.8%) of the 419 Parkinson's disease patients who received the final (to-be-marketed) formulation of ND0612 over 24 hours. ISRs led to discontinuation of 12.9% of all (598) Parkinson's disease patients and 13.8% of those who received the final formulation of ND0612 over 24 hours. The majority of ISRs were of mild severity, non-serious and self-manageable by patients. The potentially more concerning ISRs related to ND0612 such as infusion site cellulitis and abscess have been effectively treated with antibiotics and/or incision and drainage and have resolved. Refer to summary of clinical safety Section 2.7.4.2.1.8.1 for details.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: Infusion site reactions (ISRs)

Potential mechanisms:

The underlying causes for ISRs under ND0612 treatment are considered related to its subcutaneous mode of administration, as commonly seen with other drugs administered subcutaneously (Bhidayasiri R, 2016; Deeb et al., 2019; Guilhem et al., 2006; Lebrun et al., 2010). In case of ND0612 DP, Arginine, as one of the excipients has been identified as an irritant component in the formulation in a preclinical study (STUDY A4608). In this study, subcutaneous infusions of solutions containing L-arginine induced comparable infusion site reactions as the ND0612 complete formulation, while formulations without L-arginine caused minimal responses, comparable in severity and incidence to saline (refer to Part II: Module SII – Non-clinical part of the safety specification).

Evidence source(s) and strength of evidence:

The supporting data is derived from Onerji® clinical studies.

Characterisation of the risk:

In the 419 Parkinson's disease patients treated with the final formulation of ND0612 over 24 hours, ISRs reported with a very common incidence (≥10% of subjects) included infusion site nodules (70.4% of subjects), infusion site haematoma (64.9%), infusion site pain (23.2%), infusion site infection (19.3%), infusion site erythema (18.4%), and infusion site eschar (12.9%). ISRs reported with a common incidence (≥1% to <10%) were infusion site swelling (8.8%), infusion site haemorrhage (5.3%), infusion site pruritus (2.6%), infusion site discolouration (1.9%), infusion site reaction (1.7%), infusion site vesicles (1.4%), infusion site induration (1.2%) and infusion site discharge (1.0%).

Risk factors and risk groups:

- Failure to follow the recommendations provided in the Patient Information Leaflet (PL) and in the Patient Guide (Refer to Section III.1-Routine Pharmacovigilance Activities and Section V.2-Additional Risk Minimisation Measures);
- Health care provider/patient lack of experience with subcutaneous infusion-related therapies;
- Other comorbidities including diabetes, impaired immune function and thinning of the skin especially in the elderly population.
- Skin disorders reported in Parkinson´s disease patients (Niemann N, 2021)

Preventability:

Measures to minimise the risk of ISRs are described in the SmPC sections 4.2, 4.4 and 4.8, and in the PL sections 2 and 3, which state that patients should be instructed to rotate the infusion sites daily, avoiding returning to the same infusion site for at least 2 weeks, and to clean the infusion area with a disinfectant as recommended by their healthcare professional. Patients are also instructed to avoid infusion sites that are over skin lesions (e.g., nodules, haematoma, areas with erythema or oedema), or that are over bone, blood vessels, tattoos, or scar tissue.

Moreover, additional risk minimisation measures are in place, consisting of a patient guide to enhance patient awareness of the risks of infusion site reactions and to educate patients on measures they should take to help mitigate these risks (see Part V.2).

Impact on the risk-benefit balance of the product:

Infusion site reactions are one of the most common adverse reactions to ND0612 DP (88.8% of patients over a mean treatment exposure of 1.6 years), but they are generally of mild severity, reversible and led to discontinuation in a relatively small percentage of subjects over a long-term treatment (13.6% of patients over a mean treatment exposure of 1.6 years). The potentially more concerning adverse reactions related to ND0612 such as infusion site cellulitis and abscess have been effectively treated with antibiotics and/or incision and drainage and have resolved.

Public health impact:

ISRs are usually of mild severity, non-serious, and self-manageable by patients. No significant involvement of emergency services and/or hospitalisation is expected in the majority of cases. Of the 419 Parkinson's disease patients treated with the final formulation of ND0612 over 24 hours (cumulative treatment exposure of ~1.6 years), 14 (3.3%) patients were hospitalised due to an ISR (mainly for intravenous antibiotic treatment and/or abscess drainage).

Part II: Module SVIII - Summary of the safety concerns

Table 9. SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Infusion site reactions
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety concerns:

- None proposed.

Other forms of routine pharmacovigilance activities for safety concerns:

- None proposed.

III.2 Additional pharmacovigilance activities

- None proposed.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 10. Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	**Routine risk minimisation activities**
Infusion site reactions	Routine risk communication and risk minimisation activities recommending specific clinical measures to address the risk:

	- Method of administration and recommended infusion site locations are presented in SmPC section 4.2 (Posology and method of administration). - Special warnings and precautions for use are stated in SmPC section 4.4 (Special warnings and precautions for Onerji®). - Infusion site reactions (very common, common, uncommon) are listed in the Tabulated List of Adverse Reactions, in SmPC section 4.8 (Undesirable effects). A detailed description of infusion site reactions is also included in SmPC section 4.8, below the Tabulated List of Adverse Reactions. - Warnings and precautions related to infusion site reactions are included in PL section 2 (What you need to know before you use Onerji®). - Instructions for use are included in PL section 3 (How to use Onerji®) and section 7 (Instructions on how to prepare Onerji infusion for administration), including information on infusion site selection, rotation and reuse with accompanying pictures. These sections also instruct patients to always refer to YURWAY® Delivery System User manual or Crono Twin ND Instruction for Use for detailed instructions. - Infusion site reactions (very common, common, uncommon) are listed in lay language in the PL section 4 (Possible side effects). Other routine risk minimisation measures beyond the Product Information: Legal status: subject to medical prescription.

V.2. Additional Risk Minimisation Measures

Patient Guide

Objectives:

To minimise the risk of infusion site reactions.

Rationale for the additional risk minimisation activity:

To enhance patient awareness of the risks of infusion site reactions and to educate patients on measures they should take to help mitigate these risks.

Target audience and planned distribution path:

The target audience includes all Parkinson´s disease adult patients that are going to be treated with Onerji® (patients to whom the product is prescribed). The educational material shall be disseminated to healthcare professionals prescribing Onerji®, who will provide the patient guide to patients (and, if applicable, to their caregivers) at the time of the prescription.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Effectiveness will be measured by means of routine pharmacovigilance activities.

Assessment by routine pharmacovigilance activities will include signal detection, follow-up requests and review of received case reports relevant to this safety concern.

Therefore, the success of the proposed risk minimisation measures will be based on close monitoring of infusion site reaction reports and trends where distribution of the educational material has taken place.

V.3. Summary of risk minimisation measures

Table 11. Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Infusion site reactions	Routine risk minimisation measures: SmPC sections 4.2, 4.4 and 4.8. PL sections 2, 3, 4 and 7. Legal status: subject to medical prescription. Additional risk minimisation measures: Patient Guide.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none. Additional pharmacovigilance activities: none.

Part VI: Summary of the risk management plan

This is the summary of the Risk Management Plan (RMP) for Onerji®. The RMP details important risks of Onerji®, how these risks can be minimised, and how more information will be obtained about Onerji® 's risks and uncertainties (missing information).

Onerji® 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Onerji® should be used.

This summary of the RMP for Onerji® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Onerji® 's RMP.

I. The medicine and what it is used for

Onerji® is authorised for the treatment of motor fluctuations in patients with advanced Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medicinal products. It contains a solution of levodopa (60 mg/mL) and carbidopa (7.5 mg/mL) (levodopa: carbidopa ratio of 8:1) as the combination of active substances, and it is given by continuous subcutaneous infusion using the YURWAY® Delivery System or the CRONO TWIN ND infusion pump.

Further information about the evaluation of Onerji's® benefits can be found in Onerji's® EPAR, including in its plain-language summary, available on the EMA's website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/onerji

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Onerji®, together with measures to minimise such risks and the proposed studies for learning more about Onerji's risks are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionalsTable 11;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine will be supplied to the patient (with prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*. In the case of Onerji®, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Onerji® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Onerji®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Infusion site reactions
Important potential risks	None
Missing information	None

II.B Summary of important risks

Important Identified Risk: Infusion site reactions	
Evidence for linking the risk to the medicine	The supporting data is derived from Onerji® clinical studies.
Risk factors and risk groups	Failure to follow the recommendations provided in the PL and in the Patient Guide; Health care provider/patient lack of experience with subcutaneous infusion-related therapies; Other comorbidities including diabetes, impaired immune function and thinning of the skin especially in the elderly population; Skin disorders reported in Parkinson´s disease patients.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4 and 4.8. PL sections 2, 3, 4 and 7. Legal status: subject to medical prescription. Additional risk minimisation measures: Patient Guide.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Onerji®.

II.C.2 Other studies in post-authorisation development plan

There are no other studies required for Onerji®.

Part VII: Annexes

Table of contents

Annex 1 – EudraVigilance Interface

Not applicable.

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable.

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable.

Annex 4 – Specific adverse drug reaction follow-up forms

Not applicable

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Key messages of the additional risk minimisation measures:

Prior to the launch of Onerji® in each Member State, Tanabe Pharma GmbH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority. The educational programme is aimed at minimising the risk of infusion site reactions associated to Onerji® treatment, enhancing awareness and educating patients (and/or their caregivers) on measures they should take to mitigate this risk.
Tanabe Pharma GmbH will ensure that in each Member State where Onerji® is marketed, all healthcare professionals who are expected to prescribe Onerji® have access to and provide their patients with the following educational package containing:

- Patient information pack

The patient information pack consists of the patient information leaflet, the user manual provided with the drug delivery system that details the instructions for use and appropriate management of the infusion pump device (Yurway Delivery System or Crono Twin ND pump), and a patient/carer guide.

The patient guide will include the following key elements:

- Description of infusion site reactions, including symptoms, that could be signs of inflammation or infection.
- Details on how to minimise the safety concern of infusion site reactions, also ensuring that the subcutaneous infusion site location is changed daily and systematically rotated to avoid reusing an infusion site for at least 2 weeks.
- Measures to follow in case a patient experiences an infusion site reaction;
- Reference to the package leaflet and/or the user manual.

Annex 7 - Other supporting data (including referenced material)

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Annex 8 – Summary of changes to the risk management plan over time

Version	Approval Date Procedure	Change
0.1	Not Applicable	First RMP version submitted
0.2	Not Applicable	*Safety concerns*: - "Polyneuropathy" and "Effect of carbidopa on cardia repolarisation" were removed from the list of safety concerns. *Pharmacovigilance plan:* - The targeted questionnaire for serious infusion site reactions was removed from Routine Pharmacovigilance Activities - The observational post-marketing study and the TQT study were removed from Additional Pharmacovigilance Activities. *Annexes:* - Annexes 2 and 3: the observational post-marketing study and the TQT study were removed - Annex 4: the targeted questionnaire for serious infusion site reactions was removed
0.3	Not Applicable	No significant updates: wording/formatting edits per D180 List of Outstanding Issues and other minor wording corrections; update of MAA's name.
1.0	11 March 2026	No significant updates: Text of Annex 6 has been updated as per EMA request and formatting edits per D195 Joint Assessment Report