ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Onerji (60 mg + 7.5 mg)/mL solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 60 mg levodopa and 7.5 mg carbidopa (as monohydrate).
Each 7.2 mL vial contains 432 mg levodopa and 54 mg carbidopa (as monohydrate).

Excipient with known effect

Each mL contains 3 mg of polysorbate 80.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion (infusion).

Clear, yellowish solution. The pH is 9.3 to 9.7 and the osmolality is approximately 900 to 1100 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Posology

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.

The maximum recommended daily dose of Onerji is 720 mg of the levodopa component and 90 mg of the carbidopa component. Onerji treatment consists of an individualised daytime dose delivered over 18 hours, which starts about 3 hours before the anticipated patient’s wake up time, and a fixed nighttime dose delivered over 6 hours.

Initiation and titration instructions

- Step 1: The daily total oral levodopa equivalent dose should be calculated by utilising the appropriate levodopa conversion factors (Table 1).

- Step 2: Onerji should be initiated with the full dose (720 mg of levodopa) along with a morning oral dose of levodopa. If patients were on more than 720 mg of daily total oral levodopa equivalent dose before initiating Onerji, adjunct oral levodopa should be added 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, the COMT-inhibitor multiplication factor should be applied to the levodopa Onerji component.

- Step 3: Adjunct oral levodopa should be adjusted, if needed. If patients need to reduce their total daily levodopa dose, adjunct oral levodopa dose should be adjusted prior to reducing Onerji dose based on Table 2.

Calculating daily total oral levodopa equivalent dose
The levodopa equivalent daily dose coming from oral levodopa formulations should be determined as well as COMT inhibitor therapy according to the conversion factors below (Table 1).

Table 1 Calculating the levodopa equivalents

Levodopa formulation	**Dose multiplication factor**
Immediate release	1
Controlled release	0.75
Prolonged release	0.5
If a COMT inhibitor is used, multiply sum of calculated levodopa equivalents by:	• 1.33 for entacapone • 1.5 for opicapone • 1.5 for tolcapone

Optimisation and maintenance
The Onerji levodopa daily dose is prescribed by the physician according to the patient's needs, choosing from 8 regimens ranging from 370 mg to 720 mg (Table 2).

Table 2 Onerji levodopa daily dose

Daytime – 18 hours		**Nighttime – 6 hours**		**Total daily**
Flow rate (mL/h)	**Levodopa dose (mg)**	**Flow rate (mL/h)**	**Levodopa dose (mg)**	**Levodopa dose (mg)**
0.64	690	0.08	30	720
0.59	640	0.08	30	670
0.55	590	0.08	30	620
0.50	540	0.08	30	570
0.45	490	0.08	30	520
0.41	440	0.08	30	470
0.36	390	0.08	30	420
0.32	340	0.08	30	370

Interruption of therapy
Sudden discontinuation or rapid dose reduction of Onerji, without administration of alternative dopaminomimetic therapy, should be generally avoided to reduce the risk of withdrawal-induced hyperpyrexia and confusion.

If the patient needs to discontinue Onerji, the dose should be reduced gradually, or the patient should be switched to oral levodopa.

Onerji can be interrupted without further actions for brief periods of time (less than 3 hours), for example when the patient is taking a shower.

If a prolonged interruption of therapy (lasting more than 3 hours) occurs or is expected, patients should be advised to take oral levodopa, as instructed by the healthcare provider, until Onerji treatment can be resumed.

Prescribing a backup oral levodopa medicinal product is recommended in the event that delivery of Onerji is interrupted.

Special populations

Elderly
Dose adjustment should be conducted with caution in patients of 85 years and older.

Renal/hepatic impairment
There are no studies on the pharmacokinetics of Onerji in patients with hepatic or renal impairment.

Dosing with Onerji is individualised by titration to optimal effect (which corresponds to individually optimised levodopa and carbidopa plasma exposures); therefore, potential effects of hepatic or renal impairment on levodopa and carbidopa exposure are indirectly accounted for in dose titration (see sections 4.4 and 5.2).

Paediatric population

There is no relevant use of Onerji in the paediatric population in the treatment of Parkinson's disease.

Method of administration

Onerji is administered as a continuous subcutaneous infusion, 24 hours per day with a medicinal product delivery pump.

Onerji should only be used with one of the following delivery systems:
- Yurway Delivery System which includes a Yurway Rechargeable Pump, sterile single-use Yurway Medication Cartridge (reservoirs) with attached vial adapters. The Yurway Delivery System is used with sterile, single-use infusion sets. For detailed instructions refer to the *Yurway Delivery System user manual*.
- Crono Twin ND pump which uses sterile single-use syringes (reservoirs), vial adapters and infusion sets. For detailed instructions refer to *Crono Twin ND Instructions for Use*.

Onerji should not be administered with any other medicinal product delivery pump. Only the Yurway Delivery System and Crono Twin ND were qualified for compatibility with Onerji. Both delivery systems can be programmed to provide daytime and night-time flow rates via two infusion sites per Onerji prescribed regimens in Parkinson's disease patients and were found to perform equivalently.

Before initiating home use, the physician must assess whether the patient can safely use the Yurway Delivery System or Crono Twin ND independently. Following training, patients who are not able to perform all critical tasks safely must use the system with the support of a trained caregiver. Only patients and/or caregivers who have received training and have been assessed as competent may operate the Yurway Delivery System or Crono Twin ND at home. Refresher training should be provided if difficulties in use are identified (see section 6.6).

The recommended infusion site locations are the abdomen, the flanks, and the outer thighs. If needed, posterolateral upper arm can also be used. The support of an appropriately trained caregiver may be required for some hard-to-reach infusion sites such as the flanks.

Patients and (if applicable) their caregiver 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. The cannulas should be placed at least 5 cm apart, and at least 5 cm away from the navel. 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 should be avoided (see section 4.4).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Narrow-angle glaucoma.

- Concomitant administration of non-selective monoamine oxidase (MAO) inhibitors (e.g. phenelzine, tranylcypromine).
- Patients with significant cognitive impairment.
- Conditions in which adrenergics are contraindicated, e.g. phaeochromocytoma, hyperthyroidism and Cushing's syndrome.

4.4 Special warnings and precautions for use

Somnolence and episodes of sudden sleep onset

Levodopa has been associated with somnolence and episodes of sudden sleep onset (see section 4.7). Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment (see section 4.7). Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore, a reduction of dose or termination of therapy may be considered.

Withdrawal-induced hyperpyrexia and confusion

A symptom complex that resembles neuroleptic malignant syndrome (characterised by elevated temperature, muscular rigidity, altered consciousness and autonomic instability) with no other obvious aetiology, has been reported in association with rapid dose reduction, withdrawal of, or change in dopaminergic therapy (see section 4.2).

Cardiovascular ischaemic events

Levodopa should be administered with caution in patients with severe cardiovascular disease. In patients with a history of myocardial infarction who have residual atrial, nodal or ventricular arrhythmias, cardiac function should be monitored with particular care during the period of initial Onerji dose adjustments.

Hallucinations, psychosis, confusion

There is an increased risk of hallucinations and psychosis in patients taking levodopa.

Hallucinations may present shortly after the initiation of levodopa therapy and be responsive to levodopa dose reduction.

Hallucinations may be accompanied by confusion, insomnia, and excessive dreaming. Abnormal thinking and behaviour may present with one or more symptoms, including paranoid ideation, delusions, hallucinations, confusion, psychotic-like behaviour, disorientation, aggressive behaviour, agitation and delirium.

Patients with a major psychotic disorder or a history of psychotic disorder must be treated cautiously with Onerji because of the risk of exacerbating psychosis.

In addition, medicinal products that antagonise the effects of dopamine used to treat psychosis may exacerbate the symptoms of Parkinson’s disease and may decrease the effectiveness of Onerji.

Impulse control, compulsive behaviours

Patients may experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge or compulsive eating, and/or other intense urges, as well as the inability to control these urges while taking one or more of the medicinal products used for the treatment of Parkinson’s disease that increase central dopaminergic tone.

In some cases, although not all, these urges were reported to have stopped when the dose was reduced, or the medicinal product was discontinued. Because patients may not recognise these behaviours as abnormal, it is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, sexual urges, uncontrolled spending, binge or compulsive eating, or other urges while being treated with Onerji.

If a patient develops such urges reducing the dose or discontinuing Onerji should be considered.

Orthostatic hypotension

Levodopa can cause orthostatic hypotension. Onerji should be administered with caution with other medicinal products that may cause orthostatic hypotension, e.g. anti-hypertensive medicinal products.

Dyskinesia

Levodopa-containing products may cause dyskinesia. A dose reduction of Onerji or other medicinal products used for the treatment of Parkinson's disease may be required.

Infusion site reactions

Onerji is associated with local infusion site reactions. 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. The cannulas should be placed at least 5 cm apart and at least 5 cm away from the navel. Infusion sites that are over skin lesions (e.g. nodules, haematoma, infection, areas with erythema or oedema), or that are over bone, blood vessels, tattoos or scar tissue should be avoided.

Patients should be instructed to carefully monitor for any skin changes at the infusion site that could indicate a potential infection, such as redness associated with warmth, swelling and pain, particularly if associated with fever. The majority of infusion site infection reactions can be resolved with topical or oral antibiotics and do not require interruption of Onerji. In more serious cases of infusion site infection (e.g. cellulitis or abscess) hospitalisation may be necessary for intravenous antibiotics, drainage of an abscess and/or removal of infected skin tissue.

Neuropathy

Patients should be monitored clinically for neuropathy after starting Onerji treatment, especially patients with pre-existing neuropathy and patients taking other medicinal products or those having medical conditions that are associated with neuropathy. For patients who develop signs and symptoms of neuropathy after starting treatment, vitamins B6, B9 and B12 should be measured (see section 4.8). Supplement in case of deficiencies, particularly if markedly low levels are observed.

Depression and suicidality

All patients should be observed carefully for the development of depression with suicidal tendencies.

Chronic wide-angle glaucoma

Patients may be treated cautiously with Onerji provided the intraocular pressure is well-controlled and the patient is monitored carefully for changes in intraocular pressure during therapy.

Peptic ulcer disease

Levodopa, treatment may increase the possibility of upper gastrointestinal haemorrhage in patients with a history of peptic ulcer.

Laboratory monitoring

Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function are recommended during extended therapy.

Interference with laboratory tests

Levodopa may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria and this reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria. Caution should be exercised when interpreting the plasma and urine measurements of catecholamines as levodopa therapy may elevate their levels.

Excipient

This medicinal product contains 3 mg of polysorbate 80 in each mL. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Onerji. The following interactions are known from the generic combination of levodopa/carbidopa.

Non-selective monoamine oxidase (MAO) inhibitors

Levodopa is contraindicated in patients treated with non-selective monoamine oxidase (MAO) inhibitors (e.g. phenelzine, tranylcypromine, see section 4.3), as coadministration of levodopa with non-selective MAO inhibitors could result in hypertensive crisis. These inhibitors must be discontinued at least 14 days prior to initiating therapy with Onerji.

Caution is needed in concomitant administration of Onerji with the following medicinal products:

Selective monoamine oxidase (MAO) inhibitors

The use of selective MAO-B inhibitors (e.g. rasagiline and selegiline) with levodopa may be associated with orthostatic hypotension. Patients who are taking these medicinal products should be monitored.

COMT inhibitors (tolcapone, entacapone, opicapone)

COMT inhibitors increase the bioavailability of levodopa. An adjustment of the dose of Onerji may be needed.

Amantadine

Amantadine has synergic effect with levodopa and may increase levodopa related renal and hepatic impairment events. An adjustment of the dose of Onerji may be needed.

Tricyclic antidepressants

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant administration of tricyclic antidepressants and levodopa.

Antihypertensives

The concurrent use of levodopa/carbidopa with antihypertensive medicinal products can cause symptomatic postural hypotension. A dose reduction of the antihypertensive medicinal products may be needed after initiating treatment or increasing the dose of Onerji.

Dopamine D2 receptor antagonists and isoniazid

Dopamine D2 receptor antagonists (e.g. phenothiazines, butyrophenones, risperidone and metoclopramide), and isoniazid, may reduce the therapeutic effect of levodopa. Monitor patients for worsening of Parkinson's disease symptoms.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of levodopa/carbidopa in pregnant women. Studies of levodopa and carbidopa in animals have shown reproduction toxicity (see section 5.3). Onerji is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

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 treatment with Onerji.

Fertility

In reproduction studies, no effects on fertility were observed in rats receiving levodopa/carbidopa.

4.7 Effects on ability to drive and use machines

Levodopa/carbidopa has major influence on the ability to drive and use machines, as it may be associated with somnolence, sudden sleep episodes, dizziness and orthostatic hypotension. Therefore, caution should be exercised when driving or using machines while on treatment with Onerji. Patients presenting with somnolence and/or sudden sleep episodes must be advised to refrain from driving or engaging in activities (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see section 4.4).

4.8 Undesirable effects

Summary of safety profile

The most frequent adverse reactions reported with Onerji were infusion site reactions including nodule (70.4%), haematoma (64.9%), pain (23.2%), infection (19.3%), erythema (18.4%), eschar (12.9%) and dyskinesia (11.5%). Refer to section 4.4 for mitigation measures.

Tabulated list of adverse reactions

In table 3 below, adverse reactions expected from Onerji are presented by System Organ Class (SOC) and frequency. Frequency categories are defined as follows: very common (≥ 1/10), common (≥ 1/100

to < 1/10), uncommon (≥ 1/1 000 to < 1/100), and not known (cannot be estimated from the available data).

Table 3 Tabulated list of adverse reactions

System Organ Class	Very common	Common	Uncommon	Not known[3]
Infections and infestations	Infusion site infection[1, 2]			Urinary tract infection
Neoplasm benign, malignant and unspecified (incl. cysts and polyps)				Malignant melanoma
Blood and lymphatic system disorders				Anaemia, Agranulocytosis, Thrombocytopenia, Leukopenia
Immune system disorders			Hypersensitivity[1]	
Metabolism and nutrition disorders	Vitamin B6 deficiency[1]	Hyperhomocysteinaemia, Folate deficiency[1], Vitamin B12 deficiency[1]	Decreased appetite	
Psychiatric disorders		Anxiety, Hallucinations[1], Insomnia	Abnormal dreams, Confusional state, Delusion, Depression[1], Impulse-control disorder[1], Rapid eye movement, Sleep behaviour disorder, Sleep disorder	Suicidal ideation, Psychotic disorder, Agitation, Disorientation, Dopamine dysregulation syndrome, Euphoric mood, Increased libido, Bruxism, Paranoia
Nervous system disorders	Dyskinesia	Dizziness, Headache, Worsening of Off periods, Peripheral neuropathy[1, 2], Tremor	Akinesia, Dysaesthesia, Dyskinesia hyperpyrexia syndrome, Dystonia, Hypokinesia, Paraesthesia, Presyncope, Somnolence, Taste disorder	Cognitive disorder, Sudden sleep onset episodes, Neuroleptic malignant syndrome, Ataxia, Horner's syndrome, Dementia
Eye disorders				Vision blurred, Diplopia, Mydriasis, Oculogyric crisis, Blepharospasm
Cardiac disorders				Palpitations, Cardiac rhythm disorders
Vascular disorders		Hypotension	Orthostatic hypotension	Hypertension, Syncope,

System Organ Class	Very common	Common	Uncommon	Not known[3]
				Thrombophlebitis, Hot flushes
Respiratory, thoracic and mediastinal disorders				Dyspnoea, Respiration abnormal, Dysphonia, Hiccups
Gastrointestinal disorders		Nausea	Dry mouth, Vomiting	Abdominal pain, Constipation, Diarrhoea, Gastrointestinal haemorrhage, Peptic ulcer, Dysphagia, Dyspepsia, Glossodynia, Flatulence, Saliva discolouration, Salivary hypersecretion
Skin and subcutaneous tissue disorders		Dermatitis contact	Panniculitis, Rash	Angioedema, Hyperhidrosis, Pruritus, Henoch-Schonlein purpura, Urticaria, Sweat discolouration, Alopecia
Musculoskeletal and connective tissue disorders			Pain in extremity	Muscle spasms, Trismus
Renal and urinary disorders				Urinary retention, Chromaturia, Urinary incontinence
Reproductive system and breast disorders				Priapism
General disorders and administration site conditions	Infusion site erythema[1, 2], Infusion site eschar[1, 2], Infusion site haematoma[1, 2], Infusion site nodule[1, 2], Infusion site pain[1, 2]	Infusion site discolouration, Infusion site haemorrhage, Infusion site induration, Infusion site pruritus, Infusion site reaction (unspecified), Infusion site swelling[1, 2], Infusion site vesicles, Therapeutic response shortened	Asthenia, Discomfort, Other infusion site reactions[1], Peripheral edema[1], Pyrexia	Fatigue, Malaise, Gait disturbance, Chest pain

System Organ Class	Very common	Common	Uncommon	Not known[3]
Investigations				Weight gain, Weight lost
Injury, poisoning and procedural complications		Fall	Skin abrasion	
Product issues			Leakage of medication on the skin that could cause local reaction	

1 Grouped terms that include closely related preferred terms.
2 See description of selected adverse reactions.
3 These adverse reactions have not been reported with Onerji, but are expected for oral levodopa.

Description of selected adverse reactions

Infusion site reactions
The most common adverse reactions associated with Onerji were infusion site reactions (88.8% of patients over a mean treatment exposure of 1.6 years) including nodules, haematoma, pain, infection, erythema, eschar and swelling. The majority of the infusion site reactions were of mild severity, non-serious and were self-manageable by patients. Infusion site infections were reported in 19.3% of patients, and in most cases resolved with topical or oral antibiotics, while some cases required intravenous antibiotics and/or incision and drainage. Refer to section 4.4 for mitigation measures.

Dyskinesia
Dyskinesia was reported as an adverse reaction in 11.5% of the Parkinson's disease patients treated with Onerji. The majority of dyskinesia events were of mild or moderate severity and resolved spontaneously or after levodopa dose reduction. Treatment was discontinued in 1% of patients due to dyskinesia.

Neuropathy
In clinical studies, 3% of the Parkinson's disease patients treated with Onerji developed peripheral neuropathy (see section 4.4). All cases were classified as subacute or chronic, and 84% of events were of mild or moderate severity. Neuropathy was most often characterised as sensory or sensorimotor. Most cases were reported in association with low vitamin B levels (78% of cases; 61%, 39% and 17% with low vitamin B6, B9 or B12 levels, respectively) and high levodopa daily dose. Treatment was discontinued in 0.7% of patients due to neuropathy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the event of an overdose with Onerji, the infusion should be stopped and the medicinal product delivery pump disconnected.

The management of an overdose is in general the same as that of an overdose of levodopa. Pyridoxine is not effective in reversing the actions of levodopa/carbidopa.

Monitor patients and provide supportive care. Electrocardiographic monitoring should be used, and the patient observed carefully for the development of cardiac arrhythmias; if necessary, an appropriate antiarrhythmic therapy should be given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Parkinson drugs, Dopa and dopa derivatives, ATC code: N04BA02.

Mechanism of action

Levodopa
Levodopa, the metabolic precursor of dopamine, crosses the blood-brain barrier and is converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa treats the symptoms of Parkinson's disease.

Carbidopa
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 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.

Clinical efficacy and safety

The efficacy of Onerji was studied in a clinical trial conducted in Parkinson’s disease patients experiencing motor fluctuations that could not be further improved by adjusting anti-parkinsonian medicinal products.

This trial consisted of the following consecutive periods:
(a) 4 to 6-week open-label adjustment period with oral immediate-release levodopa/carbidopa
(b) 4 to 6-week open-label conversion period to Onerji supplemented with oral immediate-release levodopa/carbidopa as needed
(c) 12-week, randomised, double-blind, double-dummy, parallel-group, active-controlled trial (the maintenance period).

Patients (with modified Hoehn and Yahr scale ≤ 3 in “On” stage) were eligible for participation in the trial if they were experiencing an average of at least 2.5 hours of “Off” time daily on current treatment, with at least 4 doses/day of levodopa/dopa decarboxylase inhibitor (or at least 3 doses/day of extended-release levodopa/dopa decarboxylase inhibitor) and a minimum of 400 mg/day levodopa equivalent. Concomitant treatment with dopamine agonists, selective monoamine oxidase-B inhibitors, amantadine, and anticholinergics was allowed, provided the doses were stable before enrolment.

Patients were not allowed to receive rescue levodopa or catechol-O-methyl transferase inhibitors during the trial.

The trial enrolled 381 patients. Of those, 259 patients were randomised (1:1) to receive either oral immediate-release carbidopa/levodopa (n = 131), or Onerji (n = 128), at the doses determined during the adjustment and conversion periods, with at least one dose of oral immediate-release carbidopa/levodopa in the morning. Onerji or the placebo solution were administered subcutaneously continuously over 24 hours by a medicinal product-delivery pump system.

Among the 259 randomised patients (63.7% men), at enrolment, the mean age (63.5 years, with 44.8% of patients aged 65 years or older), the mean Parkinson's disease duration (9.6 years), the mean duration of motor fluctuations (4.5 years), the daily mean "On" time without troublesome dyskinesia (9.4 hours), and the daily mean "Off" time (6.07 hours) were distributed similarly between treatment groups.

At randomisation (baseline), mean (standard deviation) levodopa total daily dose was 1237 (447) mg in patients randomised to Onerji (including the add-on immediate-release carbidopa/levodopa), and 1065 (409) mg in patients randomised to immediate-release carbidopa/levodopa.

The primary efficacy endpoint in the trial was the mean change from baseline to Week 12 in the total daily mean "On" time without troublesome dyskinesia, based on a Parkinson's disease diary normalised to a 16-hour awake period. Onerji group showed superior efficacy in the primary endpoint, compared to immediate-release levodopa/carbidopa group (1.72 hours, $p < 0.0001$). There was also a statistically significant difference between the groups in the mean change in "Off" time (key secondary endpoint), in favour of Onerji group, compared to immediate-release levodopa/carbidopa (-1.4 hours, $p < 0.0001$) (Table 4, Figure 1).

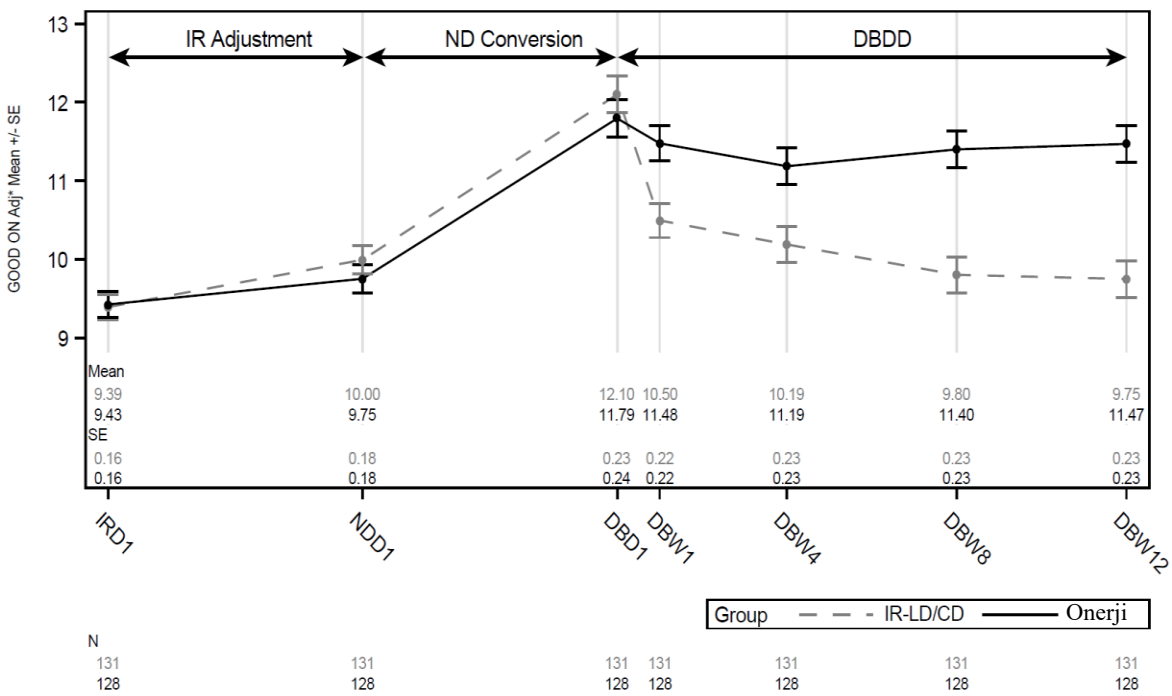
Table 4 Change from baseline to week 12 in "On" time without troublesome dyskinesia and in "Off" time

Treatment group	Baseline mean	Least square (LS) mean change from baseline to week 12	Treatment effect (difference)
"On" time without troublesome dyskinesia (hours)			
• **Onerji**	11.79	-0.48	1.72[a]
• **Immediate-release levodopa/carbidopa**	12.10	-2.20	
"Off" time (hours)			
• **Onerji**	3.72	0.50	-1.40[a]
• **Immediate-release levodopa/carbidopa**	3.38	1.90	

[a] p value < 0.0001

Least Square mean change from baseline based on Analysis of Covariance

Figure 1 Primary analysis – Least-squares means (standard error) by visit of normalised "ON" time without dyskinesia (hours) actual values (ITT Set)



Adj: Adjusted (Least-squares means); DBD1: Double-blind period Day 1; DBDD: Double-blind, double-dummy; DBW1/4/8/12: Double-blind period Week1/4/8/12; IR: Immediate-release; IRD1: Immediate-release levodopa/carbidopa (IR-LD/CD) open label Adjustment Period Day 1; ND: Onerji; NDD1: Onerji open label Conversion Period Day 1; SE: Standard error.
Analysis for actual values at each post baseline visit was performed separately and similarly as for the primary analysis using the analysis of covariance (ANCOVA) with GLM procedure in SAS® following multiple imputation under an assumption of missing at random (MAR).

Statistical significance was also achieved for other Secondary endpoints according to pre-defined hierarchy using fixed sequence approach (Table 5).

Table 5 Other secondary endpoints

Treatment group	Baseline mean	Least square (LS) mean change from baseline to week 12[a]	Treatment effect (difference)
MDS-UPDRS Part II M-EDL[b]			
• **Onerji**	15.34	-0.30	-3.05[c]
• **Immediate-release levodopa/carbidopa**	13.53	2.75	
		Least square (LS) proportions of improvement[d]	**Odds ratio**
Patient global impression of change (PGIC)			
• **Onerji**	NA	0.70	5.31[c]
• **Immediate-release levodopa/carbidopa**	NA	0.31	
Clinician global impression of improvement (CGI-I)			
• **Onerji**	NA	0.77	7.23[c]
• **Immediate-release levodopa/carbidopa**	NA	0.31	

[a] Least Square mean change from baseline based on analysis of Covariance

[b] Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II Motor Aspects of Experiences of Daily Living (M-EDL)

[c] p value < 0.0001

[d] Least Square for proportions based on General Linear Mixed model (GLIMMIX)

Cardiac electrophysiology

No relevant effects on electrocardiographic parameters were observed across Onerji clinical development program, including a thorough QT (TQT) study with carbidopa.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Onerji in all subsets of the paediatric population in treatment of Parkinson's disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

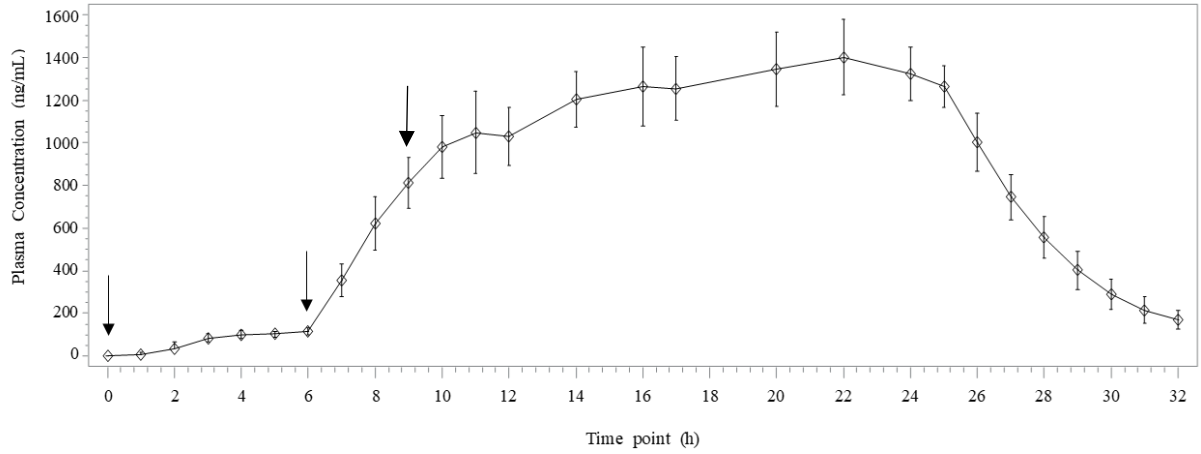
Absorption

Onerji is an 8:1 levodopa/carbidopa solution administered directly into the subcutaneous space.

Following Onerji administration in healthy volunteers, near steady state plasma levels of levodopa were achieved within approximately 2 hours after the anticipated wake-up time (see section 4.2) and maintained during the daytime infusion.

Figure 2 below shows levodopa exposure following 24-hour Onerji administration.

Figure 2 Levodopa plasma concentrations (ng/mL) following 24 h of Onerji administration



Onerji dose 720/90 mg levodopa/carbidopa infused over 24 h at 0.08 mL/h for 0 to 6 h and 0.64 mL/h for 6 to 24 h. Arrow at t = 0 indicates the start of the night-time rate infusion; arrow at t = 6 indicates the start of the daytime rate infusion which is adjustable according to anticipated wake up time; arrow at t = 9 indicates the anticipated wake up time (see section 4.2).

The estimated bioavailability of levodopa from Onerji relative to oral immediate-release levodopa/carbidopa tablets is 1.3-fold higher.

The estimated bioavailability of carbidopa from Onerji relative to oral immediate-release levodopa/carbidopa tablets is 5.7-fold higher.

Absorption of levodopa and carbidopa from Onerji is not affected by the location of the infusion site.

Distribution

Levodopa is approximately 10 to 30% bound to plasma proteins. Levodopa is transported into the brain by the carrier mechanism for large neutral amino acids.

Carbidopa is approximately 36% bound to plasma proteins. Carbidopa does not cross the blood-brain barrier.

Biotransformation

Levodopa undergoes metabolism via 4 pathways: The 2 major ones are the decarboxylation by dopa decarboxylase to dopamine, which may be further metabolised to form 3,4-dihydroxyphenyl acetic acid and homovanillic acid and, to a lesser extent, the 3-O-methylation by catechol-O-methyltransferase (COMT) to form 3-O-methyldopa. Other metabolic pathways are transamination by tyrosine aminotransferase, and oxidation by tyrosinase or other oxidants.

Carbidopa is metabolised to 3 main metabolites (2-methyl-3-methoxy-4 hydroxy-phenylpropionic acid, 2-methyl-3,4-dihydroxy-phenylpropionic acid) and 3-hydroxy-α-methyl-phenylpropionic acid. These 3 metabolites are primarily eliminated in the urine unchanged or as glucuronide conjugates. Unchanged carbidopa accounts for 30% of the total urinary excretion.

Elimination

The plasma elimination half-life of levodopa derived from Onerji is approximately 2.3 hours.
The plasma elimination half-life of carbidopa derived from Onerji is approximately 2.7 hours.

Linearity

Onerji shows dose proportional pharmacokinetics for both levodopa and carbidopa at exposures corresponding to the approved dosing range.

Special populations

Elderly
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.

Renal or hepatic impairment
The pharmacokinetics of Onerji in subjects with renal and/or hepatic impairment have not been established. Levodopa and carbidopa are primarily eliminated via non-renal routes. According to the popPK analysis, creatinine clearance may impact carbidopa elimination; however, the magnitude of the effect for creatinine clearance above 30 mL/min is not considered clinically meaningful. Dose adjustment should be conducted with caution in patients with severe renal or hepatic impairment.

Body weight
The impact of body weight on levodopa pharmacokinetics following Onerji infusion was not specifically evaluated. According to the PopPK analysis (weight range 43-136 kg), body weight may impact the volume of distribution and thus levodopa and carbidopa exposure. However, since doses are individualised per clinical response, no adjustment is required based on body weight.

Gender or race
The impact of gender on the pharmacokinetics following Onerji infusion was not specifically evaluated. Based on the PopPK analysis, clearance of levodopa in females was 13% lower than in males.

Following Onerji administration, carbidopa and levodopa exposures in Japanese subjects were comparable to those in Caucasian subjects.

No dose adjustment is required based on gender or race.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. In reproductive toxicity studies, both levodopa and the combination of levodopa/carbidopa have caused visceral and skeletal malformations in rabbits.

Effects observed in a repeated-dose toxicity study in minipigs, conducted with the formulation of Onerji administered by subcutaneous infusion, were limited to reactions at the infusion sites. In this study, at the maximum tested dose, systemic exposures to levodopa and carbidopa were nearly 6-8- and 1.5-fold higher, respectively, than exposures in humans at the maximum recommended dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Arginine
Ascorbic acid (E 300)
Acetylcysteine
Polysorbate 80 (E 433)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

3 years.

After opening

Use immediately. The medicinal product is to be used within 24 hours (infusion period).

6.4 Special precautions for storage

Store in a freezer (-25 °C to -15 °C).
Store in the original package in order to protect from light

Onerji should be thawed prior to use. Do not use Onerji for at least 5 hours after removal from the freezer.

A use-by-date, 45 days after the thawing date, is to be assigned in the space provided on the carton.

After thawing: do not store above 25 °C. Do not refrigerate or refreeze. Use within 45 days (use-by-date on the original package).

Do not use Onerji if the use-by-date and/or expiry date have passed.

Only 2 vials should be taken out from the carton package at a time for administration of the daily dose.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear Type I glass vial with a chlorobutyl rubber stopper and a royal blue flip-off plastic cap with aluminium seal.

Each vial contains 7.2 mL solution for infusion.

Pack size of 30 vials.

6.6 Special precautions for disposal and other handling

- Onerji vials are for single use only.
- The daily dose for infusion should be prepared immediately prior to administration to ensure that the period between initiation of preparation to end of daily administration will not exceed 25 hours.
- Damaged component or if its packaging is damaged should not be used; safely dispose and use a new item.
- Onerji should only be used if the solution's colour is yellowish.
- Onerji should not be used if the solution is not clear or contains particles, and/or if the solution is brown.
- If the solution contains bubbles, wait for them to disappear before proceeding to remove the blue cap from the vial.
- Do not use teeth to remove the blue cap from the Onerji vial.
- The grey rubber stopper on top of the Onerji vial should not be touched to minimise risk of contamination.
- If any Onerji is spilled, it must be cleaned up immediately to prevent accidental contact with skin and eyes.
- The reservoir (Yurway Medication Cartridge in case using Yurway Delivery System or syringe in case using the Crono Twin ND pump) should be replaced if any Onerji is spilled on it.
- Vial and vial adapter should be discarded after transfer of the medicinal product to the reservoir.
- Any remaining medicinal product in the reservoirs at the end of the daily infusion should be discarded

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

Onerji is subcutaneously administered and may only be used with one of the following delivery systems:

- **Yurway Delivery System**, which includes a Yurway Rechargeable Pump, a sterile single-use Yurway Medication Cartridge (reservoir) for the Onerji solution with attached vial adapters. It is used with sterile, single-use infusion sets. When using the Yurway Delivery System, refer to the *Yurway Delivery System user manual* for detailed instructions.
- **Crono Twin ND pump**, which uses sterile single-use syringes (reservoirs), vial adapters and infusion sets. When using Crono Twin ND, refer to *Crono Twin ND Instructions for Use* for detailed instructions.

Proper training should be provided to the patient and to the caregiver (if applicable) prior to using the Yurway Delivery System or Crono Twin ND, and thereafter if needed. Only patients and their caregivers who have been trained and deemed competent may use the infusion pumps.

An overview on how to prepare Onerji infusion for administration is provided in the package leaflet.

7. MARKETING AUTHORISATION HOLDER

Tanabe Pharma GmbH
Schiessstrasse 47
40549 Duesseldorf
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2026/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

THE QP SERVICES GmbH
Graßdorfer Straße 53
04425 Taucha
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs 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.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (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.

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 III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Onerji (60 mg + 7.5 mg)/mL solution for infusion
levodopa/carbidopa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL contains 60 mg levodopa and 7.5 mg carbidopa (as monohydrate).
Each 7.2 mL vial contains 432 mg levodopa and 54 mg carbidopa.

3. LIST OF EXCIPIENTS

Excipients: arginine, ascorbic acid (E 300), acetylcysteine, polysorbate 80 (E 433), water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
30 vials
(432 mg + 54 mg)/7.2 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
For single use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a freezer at –25 °C to –15 °C.

After thawing: Do not store above 25 °C. Do not refrigerate or refreeze.
Use-by date: …….. (Maximum 45 days. Cross out former expiry date.)

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Tanabe Pharma GmbH
Schiessstrasse 47
40549 Duesseldorf
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/26/2026/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Onerji

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Onerji (60 mg + 7.5 mg)/mL infusion
levodopa/carbidopa
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

(432 mg + 54 mg)/7.2 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Onerji (60 mg + 7.5 mg)/mL solution for infusion
levodopa/carbidopa

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Onerji is and what it is used for

Onerji contains the active substances levodopa and carbidopa, which belong to a class of medicines known as anti-Parkinson drugs.

Onerji is used to treat alternating changes in the ability to move (motor fluctuations) in adults with advanced Parkinson's disease when these cannot be adequately controlled by other medicines taken by mouth. Parkinson's disease is a progressive disease of the nervous system that causes shaking, stiffness, slow movement and problems maintaining balance.

In people with Parkinson's disease, the cells in the brain that make a chemical messenger known as dopamine begin to die causing the amount of dopamine in the brain to decrease. The active substance in Onerji, levodopa, increases dopamine in your body because the body converts levodopa into dopamine. This helps reduce the symptoms of Parkinson's disease. The other active substance in Onerji, carbidopa, helps levodopa work better by stopping it from being broken down too early in the body, so more of it reaches the brain. This also reduces side effects allowing levodopa to be used more effectively.

2. What you need to know before you use Onerji

Do not use Onerji
- if you are allergic to levodopa, carbidopa or any of the other ingredients of this medicine (listed in section 6)
- if you have narrow-angle glaucoma, damage to the nerve in the eye caused by pressure inside the eye rising rapidly because fluid cannot drain out
- if you take medicines to treat depression called non-selective monoamine oxidase (MAO) inhibitors, such as phenelzine, tranylcypromine
- if you have significant difficulty thinking clearly and remembering things (cognitive impairment)
- if you have a tumour of the adrenal gland (phaeochromocytoma)

- if you have hormone problems such as too much cortisol (Cushing's syndrome) or your thyroid hormone levels are too high (hyperthyroidism)

Do not use Onerji if any of the above apply to you. Talk to your doctor if you are unsure.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before or during use of Onerji if one or more of the following applies to you:
- had a heart attack, blocked blood vessels in your heart or any other heart problems including irregular heartbeat;
- have chronic wide-angle glaucoma, an eye disorder in which increased pressure inside the eye gradually damages the nerve in the eye. You will need to have regular checks on the pressure in your eye;
- have a stomach ulcer;
- hear, see or feel things that do not exist (hallucinations) which can cause confusion, trouble sleeping (insomnia) and vivid dreams. Or you have unusual thoughts and behaviours, such as paranoia, confusion, aggressive behaviour or restlessness;
- have depression with thoughts of suicide;
- have urges or cravings to behave in ways that are unusual for you or you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These behaviours are called impulse control disorders and can include addictive gambling, excessive eating or spending, an abnormally high sex drive or an increase in sexual thoughts or feelings;
- feel dizzy or lightheaded on standing or sitting up because of a drop in blood pressure (orthostatic hypotension);
- are very sleepy or suddenly fall asleep during daily activities;
- have involuntary and uncontrollable movements of limbs, back, neck or chin, or increased stiffness or slowness of movements (dyskinesia);
- have weakness, pain, numbness or loss of sensation in your fingers or feet (polyneuropathy). Your doctor will check for these signs and symptoms before you start Onerji and periodically thereafter. Tell your doctor if you already have any nerve disorders;
- develop skin changes at the site where you are given the infusion (drip) of Onerji. This includes redness, warmth, swelling or pain suggestive of infection, particularly if associated with fever.

Do not stop using Onerji unless your doctor tells you to. Suddenly stopping or lowering your Onerji dose quickly may cause a serious problem called withdrawal-induced hyperpyrexia and confusion. This is characterised by fever, muscle stiffness, accelerated breathing, excessive sweating and changes in consciousness.

During treatment, regular liver, kidney, heart function, blood and blood circulation checks by the doctor are recommended.

Onerji may affect certain values of tests including blood and urine measurements.

Children and adolescents
Onerji should not be used in children and adolescents under 18 years as it has not been studied in this age group.

Other medicines and Onerji
Tell your doctor or pharmacist if you are using, have recently used or might use.
- medicines to treat depression called non-selective monoamine oxidase (MAO) inhibitors such as phenelzine, tranylcypromine. Do not use Onerji when using these medicines. They must be stopped at least two weeks before you start using Onerji.

Also tell your doctor or pharmacist if you are using:
- medicines to treat depression called tricyclic antidepressants such as trimipramine, amitriptyline
- medicines to treat Parkinson's disease called:

  - selective MAO-B inhibitors such as rasagiline and selegiline
  - COMT (catechol-O-methyl transferase) inhibitors such as entacapone, opicapone, tolcapone
  - amantadine
- medicines to treat high blood pressure
- medicines to treat mental or anxiety disorders such as phenothiazines, butyrophenones, risperidone
- medicines against nausea or vomiting – particularly metoclopramide
- isoniazid, a medicine to treat tuberculosis

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using Onerji.

There are no adequate data regarding the use of medicines containing levodopa and carbidopa in pregnant women. However, studies in animals have shown that it may cause damage to the unborn baby. Onerji is not recommended during pregnancy and in women who can become pregnant who are not using effective contraception (birth control).

Breast-feeding is not recommended during treatment with Onerji.

Driving and using machines
Onerji can have a major influence on your ability to drive or use tools/machines. This is because Onerji may make you feel very sleepy, or you may sometimes find yourself suddenly falling asleep (sleep attacks). Onerji may lower your blood pressure, which can make you feel light-headed or dizzy. Do not drive or use any tools or machines until you are sure how Onerji affects you.
Do not drive, use tools or machines until you feel fully awake, or no longer feel light-headed or dizzy.

Onerji contains polysorbate 80
This medicine contains 3 mg of polysorbate 80 in each mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Onerji

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you have questions.

Stop using medicines that treat depression called non-selective monoamine oxidase (MAO) inhibitors, such as phenelzine, tranylcypromine medicines at least two weeks before you start using Onerji.

Before home use, you, and your caregiver (if applicable), will be trained on how to handle Onerji and the delivery pump. You and your caregiver may use the infusion pumps only after being trained and deemed competent. Refresher training should be provided if difficulties in use are identified.

Before using Onerji, refer to the delivery pump instructions for use provided in section 7.

When using Yurway Delivery System also refer to the Yurway Delivery System user manual for detailed instructions.

When using Crono Twin ND also refer to Crono Twin ND instructions for use for detailed instructions.

Always follow sterile techniques while using Onerji, change the infusion site and use new infusion sets daily. Avoid infusion sites over skin lesions like nodules, bruises, areas of redness or swelling, over bone, blood vessels, tattoos or scar tissue.

How much medicine to use
Always use this medicine as your doctor has instructed. Your doctor will decide how much Onerji you will use and adjust other medicines as needed. The Onerji levodopa daily dose will be prescribed by your doctor according to your needs, choosing from 8 regimens ranging from 370 mg to 720 mg. Onerji is given with a morning dose or levodopa taken by mouth (oral).

Your doctor may adjust the dose of Onerji when you take COMT inhibitors.

How Onerji is given
Onerji is given as an infusion (drip) under the skin (subcutaneously) of either the abdomen (belly), the flanks (areas on the sides of the body between the lower ribs and hips) or outer thighs. If needed, the outer back of the upper arm can also be used.
The infusion is given using a pump (Yurway Delivery System or Crono Twin ND). Onerij is given continuously through the pump over 24 hours for each cycle.

Use a different infusion site each day and do not use the same site again for at least 2 weeks. Clean the infusion area with a disinfectant as recommended by your doctor, pharmacist or nurse. Avoid infusion sites over skin lesions (e.g. bumps, redness or swelling), or over bone, blood vessels, tattoos or scar tissue (see section.
Place the thin tubes that connect to the infusion pumps and allow the medicine to flow into the body (cannulas) at least 5 cm apart and 5 cm away from the belly button (navel).).

If you forget to use Onerji
If you forget to use Onerji, start your pump with your normal dose as soon as possible.

If you stop using Onerji
Do not stop using Onerji permanently unless your doctor tells you to. Suddenly stopping Onerji dose may cause a serious problem called withdrawal-induced hyperpyrexia and confusion (see also warnings and precautions).

Onerji use can be stopped for brief periods of time, such as when taking a shower. If stopping Onerji use for more than 3 hours, take oral levodopa medicine under doctor's instruction until Onerji treatment resumes.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop using Onerji and tell your doctor immediately, if you notice any of the following serious side effects:
- swelling of the face, tongue or throat which makes it difficult to swallow or breathe, or nettle-type skin rash. These may be symptoms of a severe allergic reaction.

Frequency of these events cannot be estimated from available data. Your doctor will decide if you can keep using Onerji.

Other side effects of Onerji
Very common: may affect more than 1 in 10 people
- infection at the site of infusion
- redness (erythema) at the site of infusion
- a dry, dark scab (eschar) at the site of infusion
- a collection of blood under the skin (haematoma) at the site of infusion
- pain at the site of infusion
- a bump (nodule) at the site of infusion

- movement disorders (dyskinesia), characterised by involuntary muscle movements
- low blood levels of vitamin B6

Common: may affect up to 1 in 10 people
- a change in the colour of the skin (discolouration) at the site of infusion
- bleeding (haemorrhage) at the site of infusion
- hardening (induration) at the site of infusion
- itching (pruritus) at the site of infusion
- reactions at the site of infusion
- swelling at the site of infusion
- blisters (vesicles) at the site of infusion
- reduced control of symptoms of Parkinson's disease as effects of the medicine wears off faster (worsening of off periods)
- low blood levels of vitamin B12
- low blood levels of folate
- seeing, hearing or feeling things that do not exist (hallucinations)
- nerve problems in hands or feet, such as weakness, pain, numbness, loss of sensation (peripheral neuropathy)
- skin inflammation (dermatitis contact)
- nausea
- dizziness
- falling
- low blood pressure (hypotension)
- uncontrollable shaking (tremor)
- anxiety
- sleeplessness (insomnia)
- headache
- increased blood level of homocysteine (hyperhomocysteinaemia), a substance which helps build proteins in the body

Uncommon: may affect up to 1 in 100 people
- weakness (asthenia)
- infusion site reactions (other than above), irritation, peeling or breakdown of outer layers of the skin and others resulting from leakage of the medicine.
- feeling dizzy or lightheaded on standing or sitting up because of a drop in blood pressure (orthostatic hypotension)
- unpleasant, abnormal sense of touch (dysaesthesia)
- abnormal sensation, such as tingling, numbness, burning or prickling feeling (paraesthesia)
- swelling in lower legs or hands caused by too much fluid (peripheral oedema)
- sleepiness (somnolence)
- abnormal dreams
- difficulty to perform movements (hypokinesia)
- not being able to move muscles voluntarily (akinesia)
- decreased appetite
- muscle spasms you cannot control – affecting your eyes, head, neck and body (dystonia)
- confusion (confusional state)
- false beliefs (delusion)
- depression
- discomfort
- dry mouth
- impaired or altered sense of taste (taste disorder)
- allergic reaction
- rash
- difficulty controlling actions or reactions (impulse control disorders)

- pain in arms or legs (extremity)
- inflammation in the fatty tissue below the skin (panniculitis)
- feeling faint (presyncope)
- fever
- sleep disorder in which you physically act out vivid, often unpleasant dreams with vocal sounds and sudden movements (sleep behaviour disorder)
- poor quality sleep (sleep disorder)
- vomiting
- involuntary movements, together with fever and other symptoms such as consciousness disturbance (dyskinesia hyperpyrexia syndrome)
- rapid eye movement

Not known: these side effects have not been reported with Onerji, but are expected:
- urinary infection
- can't empty bladder fully
- coloured urine
- leaking urine
- skin cancer
- low red blood cells (causing tiredness, weakness)
- very low white blood cells (Agranulocytosis)
- low white blood cells (Leukopenia)
- low platelets
- thoughts of harming yourself
- losing touch with reality (psychotic disorder)
- agitation
- disorientation
- uncontrolled urges (dopamine dysregulation syndrome)
- extreme happiness or high energy
- heightened sex drive
- unfounded fear or suspicion
- problems with thinking, memory, or focus
- falling asleep suddenly without warning
- fever, muscle stiffness, accelerated breathing, excessive sweating and changes in consciousness (neuroleptic malignant syndrome)
- loss of coordination (unsteady walking)
- droopy eyelid, small pupil, no sweat on one face side (Horner’s syndrome)
- decline in memory and thinking skills
- vision blurred
- double vision
- dilated pupils
- eyes stuck looking up or to the side (oculogyric crisis)
- uncontrollable eyelid twitching or blinking
- palpitations
- abnormal heart rhythms
- high blood pressure
- fainting
- inflamed veins with blood clots
- sudden waves of heat
- shortness of breath
- irregular breathing
- hoarse or changed voice
- hiccups
- stomach ache
- hard to pass stool

- loose stools
- flatulence
- bleeding in the gut
- sore in stomach lining
- trouble swallowing
- indigestion
- burning tongue pain
- jaw lock (can't open mouth fully)
- teeth grinding
- saliva discolouration
- too much saliva
- swelling under the skin (face, lips)
- excessive sweating
- itchy skin
- rash with small purple spots (Henoch-Schonlein purpura)
- hives
- a change in the colour of sweat
- hair loss
- muscle spasms
- prolonged, painful erection
- extreme tiredness
- feeling unwell
- unsteady walking
- chest pain
- weight gain
- weight loss

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Onerji

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light.

This medicine is stored in a freezer before dispensed to patients or caregivers. You or your caregiver will receive Onerji only after thawing.

After opening: use immediately. The product is to be used within 24 hours (infusion period).

After thawing, do not store Onerji above 25 °C and **do not refrigerate or refreeze**. Once removed from the freezer, unopened vials may be stored for up to 45 days (use-by-date). Do not use this medicine after the use-by-date.

Only 2 vials should be taken out of the carton at a time for administration of the daily dose. Store the remaining Onerji vials in the original package.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Onerji contains

- The active substances are levodopa and carbidopa. Each millilitre contains 60 mg levodopa and 7.5 mg carbidopa (as monohydrate). Each 7.2 mL vial contains 432 mg levodopa and 54 mg carbidopa (as monohydrate).
- The other ingredients are arginine, ascorbic acid (E 300), acetylcysteine, polysorbate 80 (E 433) (see section 2 “Onerji contains polysorbate 80”), water for injections.

What Onerji looks like and contents of the pack

Onerji is a clear, yellowish solution for infusion (infusion). It is available in clear glass vials with a rubber stopper and a royal blue flip-off plastic cap with aluminium seal. Each vial contains 7.2 mL solution for infusion.
Pack size of 30 vials.

Marketing Authorisation Holder

Tanabe Pharma GmbH
Schiessstrasse 47
40549 Duesseldorf
Germany

Manufacturer

THE QP SERVICES GmbH
Graßdorfer Straße 53
04425 Taucha
Germany

This leaflet was last revised in

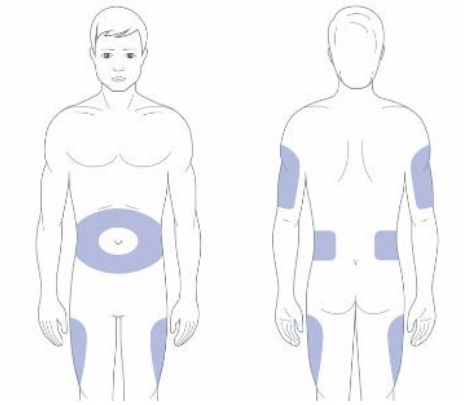
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

7. Instructions on how to prepare Onerji infusion for administration

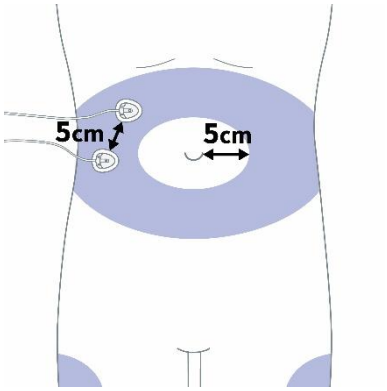
General precautions when preparing Onerji for administration

- Onerji vials are for single use only.
- Prepare the daily infusion dose just before it is given, to ensure that no more than 25 hours pass from the period between initiation of preparation to end of daily administration.
- Do not use any component if it or its packaging is damaged; safely dispose and use a new item.
- Do not use Onerji if the solution’s colour is brown.
- If the solution contains bubbles, wait for them to disappear before removing the blue cap from the vial.
- Do not use teeth to remove the blue cap from the Onerji vial.
- Do not touch the grey rubber stopper (grey septum) on top of the Onerji vial to minimise risk of contamination.
- If any Onerji is spilled, it must be cleaned up immediately to prevent accidental contact with skin and eyes.
- Any remaining medicine in the reservoir at the end of the daily infusion should be discarded.

Infusion sites selections
Onerji is administered under the skin of the:
- abdomen
- flanks
- outer thighs
- outer back of the upper arm, if needed



Place the cannulas at least 5 cm apart and at least 5 cm **away** from the navel.



Do not use the following infusion sites:
- skin lesions, such as bumps, redness, swelling, irritations, bleeding, bruise, infections
- over bone, blood vessels
- tattoos
- scar tissue

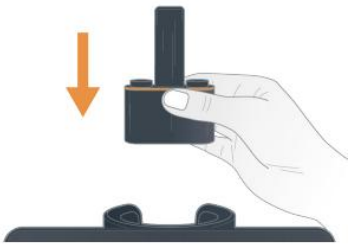
Change the infusion site locations daily (every 24-hours) and avoid reusing an infusion site for at least 2 weeks. Therefore, systematically rotate the infusion site locations.

Onerji may only be used with one of the following delivery systems:
- **Yurway Delivery System**
- **Crono Twin ND pump**

Preparation of Onerji infusion when using the Yurway Delivery System
For detailed instructions on how to deliver Onerji when using the Yurway Delivery System, refer to the Yurway Delivery System user manual.

- Wash hands thoroughly with soap and water.
- Prepare a clean working area on a flat and level surface.
- Gather the components: 1 Yurway cartridge (preassembled with 2 vial adapters), alcohol pads, 2 infusion sets, 2 Onerji vials, 2 clean gauze pads

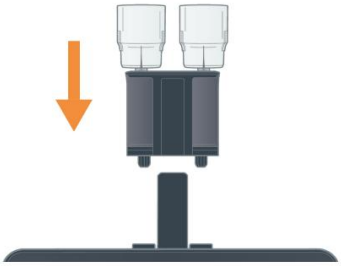
- Set up the Yurway Control Station according to the Yurway Delivery System user manual section 4.3.2.
- Insert the pump into the pump holder.



  - Insert the Yurway Rechargeable Pump into the pump holder.
  - Wait until the Yurway Control Station establishes a connection with the Yurway Rechargeable Pump (approximately 30 seconds).

  Do not use the Yurway Medication Cartridge if dropped; safely dispose and use a new cartridge.

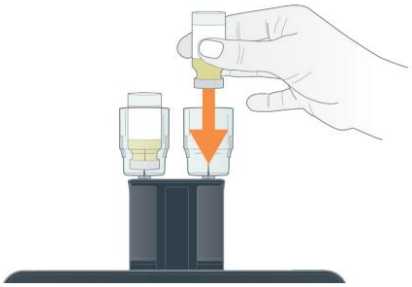
- Attach Yurway Medication Cartridge to pump.



  - Open a new Yurway Medication Cartridge and remove from packaging.
  - Slide the Yurway Medication Cartridge onto the Yurway Rechargeable Pump.
  - Tap **NEXT** on the Yurway Control Station screen to proceed.

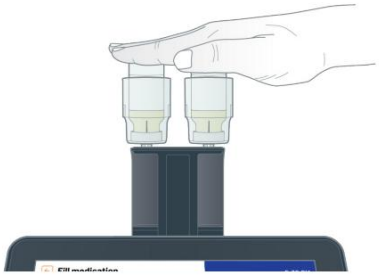
- Check Onerji solution in the vials
  - Gently invert each Onerji vial 5 times. Do not shake to avoid forming bubbles.
  - The solution should be clear, yellowish and without particles.

- Insert vial into vial adapter connected to the cartridge (reservoirs).



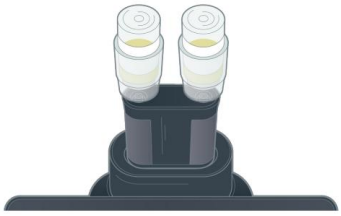
  - Remove the blue cap from the Onerji vials.
  - Dispose of the blue cap in the trash.
  - Insert the two Onerji vials, so they face down, into the vial adapters until they “click” into place.
  - Tap **NEXT** on the Yurway Control Station screen to proceed.

- Check vials are inserted correctly.



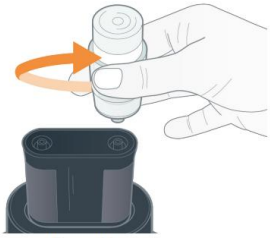
  - Press down on the Onerji vials to ensure that they are fully inserted.
  - Press the button on the Yurway Control Station according the Yurway user manual section 4.4.3.

- Wait while Yurway Medication Cartridge fills.



  - Leave the Yurway Infusion Pump (Yurway Rechargeable Pump connected to the Yurway Medication Cartridge) in the pump holder until fill is complete. This takes approximately 7 minutes.
  - The Yurway Control Station will show the progress of the filling and inform when the process is complete.

- Remove vial adapters from Yurway Medication Cartridge.



  - Unscrew the vial adapters (counter-clockwise); there may be residual solution in the Onerji vials, this is normal.
  - Dispose of used vials and connected vial adapters according to local regulations.

Refer to your Yurway Delivery System user manual for the next steps.

Preparation of Onerji infusion when using the Crono Twin ND

For detailed instructions on how to deliver Onerji when using the Crono Twin ND, refer to the Crono Twin ND instructions for use.

- Wash hands thoroughly with soap and water.
- Prepare a clean working area on a flat and level surface.
- Gather the components: 2 CRN Crono 10 mL Luer-Lock syringes, 2 vial adapters, alcohol pads, 2 infusion sets, 2 Onerji vials, 2 clean gauze pads.
- Check Onerji solution in the vials:
  - Gently invert each Onerji vial 5 times. **Do not** shake to avoid forming bubbles.
  - The solution should be clear, yellowish and without particles.

- Take 2 Onerji vials and remove the blue caps.

- Attach the vial adapters to the vials (perform for 2 vials).
  - Fully peel off the vial adapter lid.

  - Hold the vial firmly on a hard surface; push the adapter tray straight onto the vial until it 'clicks'.

  - Lift the vial adapter tray by holding the outer rim, straight off the vial.

- Connect the syringes to the vials.
  - Remove the syringe from the packaging.

  - Screw the syringe clockwise down onto the vial adapter connector.

- Draw up the solution from the vials.
  - Invert the vial. Push the plunger up until it stops.

  - Hold vertically and pull back the plunger to withdraw 6.5 mL.

  - Confirm you have at least 6.5 mL before you disconnect the vial.

- Remove the vials from the syringes
  - Invert the vial and unscrew counter-clockwise to remove the syringe.

  - Dispose of the used Onerji vials and connected vial adapters according to local regulations.

Refer to your Crono Twin ND instructions for use for the next steps.