▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

VYALEV® (FOSLEVODOPA / FOSCARBIDOPA)

SOLUTION FOR SUBCUTANEOUS INFUSION

1 NAME OF THE MEDICINE

Foslevodopa and foscarbidopa.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of VYALEV contains foslevodopa 240 mg and foscarbidopa 12 mg.
Each 10 mL vial of VYALEV contains foslevodopa 2400 mg and foscarbidopa 120 mg.

Foslevodopa and foscarbidopa are prodrugs equivalent to approximately 170 mg levodopa and 9 mg carbidopa per 1 mL.

Excipient with known effect:

VYALEV contains approximately 1.84 mmol (42.4 mg) sodium per mL.

For the full list of excipients, see **Section 6.1 List of excipients**.

3 PHARMACEUTICAL FORM

Solution for infusion in a glass vial.

The solution is sterile, preservative-free and clear to slightly opalescent. It should be free from particulates. The solution may vary from colourless to yellow to brown and may have a purple or red tint. Variations in colour are expected and have no impact on product quality. The solution may become darker in colour after piercing of the vial stopper or while in the syringe.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of advanced idiopathic Parkinson's disease with severe motor fluctuations despite optimised alternative pharmacological treatment.

4.2 Dose and method of administration

VYALEV is administered as a continuous subcutaneous infusion, 24-hours per day. Administer VYALEV only with the Vyafuser pump (refer to pump instructions for use).

VYALEV is only suitable for patients who are levodopa-responsive.

Establishment of the first infusion site and dose adjustments should be carried out in association or consultation with a specialist with expertise in the management of Parkinson's disease.

The recommended starting daily dose of VYALEV is determined by converting the daily levodopa intake to levodopa equivalents (LE) and then increasing it to account for a 24-hour administration. The dose may be adjusted to reach a clinical response that maximises the functional "On" time and minimises the number and duration of "Off" episodes and "On" episodes with troublesome dyskinesia. The maximum recommended daily dose of foslevodopa is 6000 mg (or 25 ml of VYALEV per day equivalent to approximately 4260 mg levodopa per day).

VYALEV replaces levodopa containing medications and catechol-O-methyl transferase (COMT)-inhibitors. If required, other medicinal products for Parkinson's disease can be taken concurrently.

Initiation of treatment

Patients selected for treatment with VYALEV should be capable of understanding and using the delivery system themselves. In case the patient is unable to use the delivery system correctly, the delivery system should only be handled by nursing staff or an experienced caregiver.

Patients should be trained on the proper use of VYALEV and the delivery system (see method of administration) prior to initiating treatment with VYALEV and, as necessary, thereafter.

Three steps are required to initiate treatment with VYALEV.

- Step 1: Calculate the LE based on the levodopa-containing medications used during the patient's awake time.
- Step 2: Determine the hourly infusion rate of VYALEV.
- Step 3: Determine the volume of the loading dose.

Step 1: Calculate the LE based on the levodopa-containing medications used during the patient's awake time.

The levodopa amount from all levodopa-containing formulations used during the waking time of the day should be converted to LE using the appropriate dose multiplying factor from Table 1 and then summed. For this calculation, only consider levodopa and COMT-inhibitors. Do not include night-time dosing of either medication, and do not include rescue levodopa or any other anti-Parkinsonian medication or therapy in this calculation. If any COMT-inhibitors are taken within a 24-hour period, regardless of the COMT-inhibitor dose, a correction factor should be applied to the sum of LE as presented in Table 1.

Table 1. Calculating the Levodopa Equivalents (LE)

Levodopa formulation	**Dose multiplying factor**
Immediate-release, including intestinal gel	**1**
Sustained-release, controlled-release or prolonged-release[a]	**0.75**
If any COMT-inhibitor is used, multiply sum of calculated LE from above by **1.33**[a]	
[a]The levodopa contained in combined LD/CD /entacapone formulations counts as immediate-release and needs to be added to the LE from all other sources of levodopa before the sum is multiplied for the COMT-inhibitors correction factor. Do not multiply single LE before summing them up. CD = carbidopa; LD = levodopa; COMT = catechol-O-methyl transferase; LE = levodopa equivalents.	

Step 2: Determine the hourly infusion rate of VYALEV.

Refer to Table 2 for suggested VYALEV starting infusion rates based on the LE calculated in Step 1.

The hourly infusion rate for VYALEV in Table 2 is based on a patient's LE intake during a typical 16-hour awake time (LE_{16}).

If the LE determined in Step 1 were based on an awake time either longer or shorter than 16-hours, the LE should be adjusted to a 16-hour period. To adjust to a 16-hour period, take the LE calculated in Step 1, divide by the number of hours the patient is typically awake and then multiply by 16. Then refer to Table 2 for VYALEV suggested starting infusion rates.

The hourly infusion rate determined in this step should be entered as the Base infusion rate when programming the pump (refer to the pump instructions for use for details).

Table 2. Suggested VYALEV starting hourly infusion rate

LE_{16} (LE from all oral LD-containing medications taken over 16-hour awake time (mg))	**Suggested VYALEV starting hourly infusion rate (mL/hr)[a]**
< 400	0.15
400-499	0.15-0.17
500-599	0.17-0.20
600-699	0.20-0.24
700-799	0.24-0.27
800-899	0.27-0.30
900-999	0.30-0.34
1000-1099	0.34-0.37
1100-1199	0.37-0.40
1200-1299	0.40-0.44
1300-1399	0.44-0.47
1400-1499	0.47-0.51
1500-1599	0.51-0.54
1600-1699	0.54-0.57
1700-1799	0.57-0.61
1800-1899	0.61-0.64
1900-1999	0.64-0.68
2000-2099	0.68-0.71
2100-2199	0.71-0.74
2200-2299	0.74-0.78
2300-2399	0.78-0.81
2400-2499	0.81-0.84
2500-2599	0.84-0.88
2600-2699	0.88-0.91
2700-2799	0.91-0.94
2800-2899	0.94-0.98
2900-2999	0.98-1.01
3000-3099	1.01-1.04
>3100	1.04

Assumptions used to generate the "Suggested VYALEV starting hourly infusion rate":

- Total daily LE over 16 hours are increased by 50% to account for 24-hour dosing
- Subcutaneous foslevodopa is 8% more bioavailable than enterally absorbed levodopa
- The molecular weight ratio of foslevodopa:levodopa is 1.41:1
- One millilitre of VYALEV contains 240 mg of foslevodopa and 12 mg of foscarbidopa
- Most Parkinson's disease (PD) patients are treated with oral PD medications during their waking time (typically 16-hour/day treatment period); once the amount of foslevodopa needed over the 16-hour period has been calculated, it is divided by 240 mg to determine the number of millilitres needed over the 16-hour period, and then divided over 16 hours to establish the hourly infusion rate

[a]The hourly infusion rate is calculated using the following formula,
Hourly infusion rate (mL/hr) = $[(LE_X \cdot 0.92 \cdot 1.41) / 240] / X$
where X is the number of patient's awake hours used to determine the LE (e.g., X=16, in the table above).
LE = levodopa equivalents; LD = levodopa.

Step 3: Determine the volume of the loading dose.

A loading dose can be administered immediately prior to commencing the hourly infusion to quickly achieve symptomatic control when starting VYALEV therapy in an "Off" state (or if the pump has been off for more than 3 hours).

Table 3 provides the recommended loading dose volume (mL) of VYALEV to be programmed into the pump (refer to the pump instructions for use for details) and the corresponding amount, in milligrams, of immediate-release levodopa, regardless of the peripheral inhibitor of the DOPA decarboxylase (e.g., carbidopa, benserazide) co-administered.

Table 3. Determination of VYALEV volume recommended for the loading dose

Recommended loading dose volume (mL) to be programmed into the pump	**Approximate corresponding levodopa amount (mg)**
0.6	100
0.9-1.2	150-200
1.5-1.8	250-300
2.0	350
0.1 mL of VYALEV contains 24 mg foslevodopa (equivalent to approximately 17 mg of levodopa). The pump is capable of delivering a loading dose ranging from 0.1 mL to a maximum of 3.0 mL, in increments of 0.1 mL.	

Treatment with VYALEV may be initiated while patients are either in the “Off” state or in the “On” state. Patients initiating VYALEV therapy in the “On” state may start the infusion without the need for a VYALEV loading dose. Loading doses can be administered both via the pump or using oral levodopa tablets.

Optimisation and maintenance

The healthcare professional may adjust the starting hourly infusion rate to achieve the optimal clinical response for the patient. The hourly infusion rate should be delivered continuously, over the 24-hour daily infusion period. If desired, the healthcare professional can program and enable 2 alternative infusion rates (Low/High). All infusion rates may be adjusted in increments of 0.01 mL/hr (which is equivalent to approximately 1.7 mg of levodopa/hr) and should not exceed 1.04 mL/hr (or approximately 4260 mg levodopa/day [6000 mg of foslevodopa/day]).

VYALEV can be taken alone or, if necessary, with other concurrent medicinal products for Parkinson’s disease, based on the judgement of the healthcare professional. A reduction in other concomitant medications for Parkinson’s disease, followed by an adjustment in VYALEV dosage, may be considered during VYALEV infusion. The concomitant use of VYALEV with other levodopa-containing medications or with medicinal products that significantly regulate synaptic dopamine levels (such as COMT-inhibitors) has not been studied.

Alternative flow rate

The pump also allows for 2 alternative infusion rate options to be programmed for patient use. The alternative infusion rates must be enabled and pre-programmed by the healthcare professional and may be selected by patients to account for changes in functional demand, e.g., lowering the dosage at night-time or increasing the dose for prolonged intense activity (refer to the pump instructions for use for details). The pump includes a lockout feature to prevent the patient from making changes to the pre-programmed flow rates or Extra Dose functionality.

Extra doses

If enabled by their healthcare professional, patients may self-administer an Extra Dose to manage acute “Off” symptoms experienced during continuous infusion. The Extra Dose volume can be chosen from 5 options (see Table 4). The Extra Dose feature is limited to no more than 1 extra dose per hour. If 5 or more extra doses are used by the patient during the 24-hour/day treatment period, a revision of the Base Continuous Infusion Rate should be considered. The ability to enable this function, as well as the minimum time required between extra doses, is determined by the healthcare professional and cannot be modified by the patient (refer to the pump instructions for use for details on programming the Extra Dose feature).

Table 4. Extra dose option for VYALEV

VYALEV volume (mL)	**Levodopa equivalents (mg)**
0.10	17
0.15	25.5
0.20	34
0.25	42.5
0.30	51

Method of administration

VYALEV is administered subcutaneously, preferably in the abdomen, avoiding a 5 cm radius area from the navel. Use aseptic technique when preparing and administering this product. The infusion set (cannula) can remain in place for up to 3 days when the medication is infused continuously. Rotate the infusion site and use a new infusion set at least every 3 days. It is recommended that new infusion sites be at least 2.5 cm from sites used within the previous 12 days. VYALEV should not be infused into areas where the site is tender, bruised, red or hard to touch. For administration, only the Vyafuser pump should be used (refer to the pump instructions for use for details) using sterile, single-use infusion components (syringe, infusion set, and vial adapter) qualified for use. Patients should be trained on the proper use of VYALEV and the delivery system (pump, solution vial, vial adapter, syringe, infusion set,

carrying accessory, rechargeable battery, and charger) prior to initiating treatment with VYALEV and, as necessary, thereafter.

In a Pharmacokinetic crossover study, administration of VYALEV via the arm and thigh resulted in nearly equivalent exposure to the abdomen (see **Section 5.2 Pharmacokinetic properties - Absorption**). Long-term safety and efficacy of administration to the arm and thigh have not been evaluated.

The medication should be stored and handled as described in **Section 6.4 Special Precautions for Storage**. The medication vials are for single use only. Once the content of a vial is transferred into the syringe, the contents of the syringe should be administered within 24 hours. Used medication vials and syringes should be discarded according to local regulations. Syringes must be discarded, even if residual product remains (see **Section 6.6 Special precautions for disposal**).

Interruption of therapy

Sudden discontinuation or rapid dose reduction of VYALEV, without administration of alternative dopaminergic therapy, should be generally avoided (see **Section 4.4 Special Warnings and Precautions for use**).

VYALEV can be interrupted without further actions for brief periods of time, such as when the patient is taking a shower. For interruptions longer than 1 hour, a new infusion set (tubing and cannula) should be used and rotated to a different infusion site. If the infusion has been interrupted for longer than 3 hours, the patient may also self-administer a loading dose to quickly re-establish symptom control.

If treatment with VYALEV is interrupted for a prolonged time (>24 hours) or permanently discontinued, the healthcare professional should determine appropriate alternative dopaminergic treatment (e.g., oral levodopa/carbidopa). Treatment with VYALEV may be resumed at any time following instructions as for initiation of VYALEV (see **Section 4.2 Dose and Method of Administration - Initiation of treatment**).

Special populations

Paediatric population

The pharmacokinetics of VYALEV in paediatric subjects has not been established.

Elderly

The impact of age on the levodopa pharmacokinetics following VYALEV infusion was not specifically evaluated. The effect of age on the pharmacokinetics of levodopa has been evaluated and studies suggested modest reduction of levodopa clearance with increase in age. Any difference in exposure based on age is not clinically significant because VYALEV is intended for use in Parkinson's disease patients who are already on a stable dose of oral levodopa and VYALEV is optimised once patients begin therapy. Therefore, covariate effects are not expected to impact clinical efficacy or safety.

Renal or hepatic impairment

The pharmacokinetics of VYALEV in subjects with renal and/or hepatic impairment has not been established.

The anticipated daily phosphorus load from the highest proposed clinical dose of foslevodopa/foscarbidopa (6000/300 mg/day of foslevodopa/foscarbidopa) is approximately 700 mg, which is considerably less than the United States National Academy of Sciences dietary reference intake upper limit of 3000 mg/day; however, there are no pharmacokinetic or safety data with VYALEV in patients with End Stage Renal Disease requiring dialysis. Therefore, caution should be exercised in patients with End Stage Renal Disease on dialysis requiring treatment with VYALEV because of diminished ability of the kidneys to eliminate phosphate.

Body weight

The impact of body weight on the levodopa pharmacokinetics following VYALEV infusion was not specifically evaluated. Previous studies of levodopa have shown that weight increases volume of distribution and can lower levodopa exposure. Any difference in exposure based on body weight is not clinically significant because VYALEV is intended for use in Parkinson's disease patients who are already on a stable dose of oral levodopa and VYALEV is optimised once patients begin therapy. Therefore, covariate effects are not expected to impact clinical efficacy or safety.

Gender or race

Following VYALEV administration, carbidopa and levodopa exposures in both Japanese subjects and Han Chinese subjects were comparable to those in Caucasian subjects.

The impact of gender on the pharmacokinetics following VYALEV infusion was not specifically evaluated. The effect of gender on the pharmacokinetics of levodopa has been evaluated and studies suggested there is no clinically meaningful gender-related difference in levodopa exposure. Following VYALEV dosing, levodopa exposure was higher in females once weight

was considered by approximately 18% based on AUC. This difference in exposure is not clinically significant because VYALEV is intended for use in Parkinson's disease patients who are already on a stable dose of oral levodopa and VYALEV is optimised once patients begin therapy. Therefore, covariate effects are not expected to impact clinical efficacy or safety.

4.3 Contraindications

VYALEV is contraindicated in patients with:

- hypersensitivity to foslevodopa and/or foscarbidopa, its active metabolites levodopa and/or carbidopa or to any of the excipients listed in **Section 6.1 List of Excipients**
- narrow-angle glaucoma
- severe heart failure
- acute stroke
- severe cardiac arrhythmia
- non-selective monoamine oxidase (MAO) inhibitors and selective MAO type A inhibitors are contraindicated for use with VYALEV. These inhibitors must be discontinued at least two weeks prior to initiating therapy with VYALEV. VYALEV may be administered concomitantly with the manufacturer's recommended dose of a MAO inhibitor with selectivity for MAO type B (e.g., selegiline hydrochloride (HCl)) (see **Section 4.5 Interactions with other medicines and other forms of interactions**).
- conditions in which medication with adrenergic activity are contraindicated, e.g. pheochromocytoma, hyperthyroidism and Cushing's syndrome

Because levodopa may activate malignant melanoma, VYALEV should not be used in patients with suspicious undiagnosed skin lesions or a history of melanoma.

4.4 Special warnings and precautions for use

- VYALEV is not recommended for the treatment of drug-induced extrapyramidal reactions.
- VYALEV therapy should be administered with caution to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease or of convulsions.

- 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 dosage adjustments.
- All patients treated with VYALEV should be monitored carefully for the development of mental changes, depression with suicidal tendencies, and other serious mental changes. Patients with past or current psychosis should be treated with caution. Higher frequency of hallucinations can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa including VYALEV. Higher frequency of hallucinations can also occur in patients with Japanese heritage. Review of treatment is recommended if such symptoms develop.
- Concomitant administration of antipsychotics with dopamine receptor blocking properties, particularly D2 receptor antagonists, should be carried out with caution, and the patient should be carefully observed for loss of anti-Parkinson's effect or worsening of Parkinsonian symptoms, see **Section 4.5 Interactions with other medicines and other forms of interactions**.
- Patients with chronic wide-angle glaucoma may be treated with VYALEV with caution, provided the intra-ocular pressure is well controlled and the patient is monitored carefully for changes in intra-ocular pressure during therapy.
- VYALEV may induce orthostatic hypotension. Therefore, VYALEV should be given cautiously to patients who are taking other medicinal products which may cause orthostatic hypotension (see **Section 4.5 Interactions with other medicines and other forms of interactions**).
- Levodopa has been associated with somnolence and episodes of sudden sleep onset in patients with Parkinson's disease and caution should, therefore, be exercised when driving and operating machines (see **Section 4.7 Effects on Ability to Drive and Use Machines**).
- A symptom complex resembling Neuroleptic Malignant Syndrome (NMS), including muscular rigidity, increased body temperature, mental changes (e.g. agitation, confusion, coma) and increased serum creatine phosphokinase, has been reported when anti-Parkinsonian medicinal products were withdrawn abruptly. Rhabdomyolysis secondary to NMS or severe dyskinesias have been observed rarely in patients with Parkinson's disease. Therefore, patients should be carefully observed when the dose of levodopa/carbidopa combinations are abruptly reduced or discontinued, especially if the patient is receiving antipsychotics. Neither NMS nor rhabdomyolysis has been reported in association with VYALEV.
- Epidemiological studies have shown that patients with Parkinson's disease have a higher risk of developing melanoma than the general population. It is unclear whether the increased risk observed was due to Parkinson's disease or other factors, such as

medicines used to treat Parkinson's disease. Therefore, patients and providers are advised to monitor for melanomas on a regular basis when using VYALEV for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

- Dopamine Dysregulation Syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with levodopa/carbidopa. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS.
- The dose of VYALEV may need to be adjusted downwards in order to avoid levodopa induced dyskinesias.
- Periodic evaluation of hepatic, haematopoietic, cardiovascular and renal function is recommended during extended therapy with VYALEV.
- Reduced ability to handle the system (pump, tube connections) can lead to complications. In such patients a caregiver (e.g., nurse or close relative) should assist the patient.
- A sudden or gradual worsening of bradykinesia may indicate an obstruction in the device for whatever reason and needs to be explored.
- Polyneuropathy has been reported in patients treated with levodopa/carbidopa-containing products. Before starting therapy evaluate patients for history or signs of polyneuropathy and known risk factors, and periodically thereafter.
- VYALEV contains 42.4 mg (approximately 1.84 mmol) of sodium per mL equivalent to 2.1% of the WHO recommended maximum daily dietary intake of sodium. The maximum daily dose of this medicine contains 54% of the WHO recommended maximum daily intake of sodium. VYALEV is high in sodium. This should be considered especially in patients on a low salt diet.
- Infusion site events (see Section 4.8 Adverse effects (Undesirable effects)) have been reported in patients receiving VYALEV. Following aseptic techniques while using this medication and frequent rotation of the infusion site are recommended to reduce the risk. In clinical studies, a few patients who reported infusion site reactions also experienced infusion site infections. Therefore, careful monitoring of serious infusion site reactions and infusion site infections is recommended.

Compulsive behaviour

Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathologic gambling, increased libido and hypersexuality, compulsive spending or buying, binge-eating, and compulsive-eating can occur in patients treated with

dopamine agonists and/or other dopaminergic treatments containing levodopa including VYALEV. Review of treatment is recommended if such symptoms develop.

Hydrazine

VYALEV contains hydrazine, a degradation product of foscarbidopa, that can be genotoxic and potentially carcinogenic. The median daily dose of VYALEV is approximately 2541 mg/day of foslevodopa and 127 mg/day of foscarbidopa. The maximum recommended daily dose is 6000 mg foslevodopa and 300 mg foscarbidopa. This includes hydrazine at up to a median exposure of 0.2 mg/day, with a maximum of 0.5 mg/day. The clinical significance of this hydrazine exposure is not known.

Use in hepatic impairment

There are no studies on the pharmacokinetics of levodopa and carbidopa in patients with hepatic impairment. Dosing with foslevodopa/foscarbidopa is individualised by titration to optimal effect (which corresponds to individually optimised levodopa and carbidopa plasma exposures); therefore, potential effects of hepatic impairment on levodopa and carbidopa exposure are indirectly accounted for in dose titration.

Use in renal impairment

There are no studies on the pharmacokinetics of levodopa and carbidopa in patients with renal impairment. Dosing with foslevodopa/foscarbidopa is individualised by titration to optimal effect (which corresponds to individually optimised levodopa and carbidopa plasma exposures); therefore, potential effects of renal impairment on levodopa and carbidopa exposure are indirectly accounted for in dose titration.

Use in the elderly

There is considerable experience in the use of levodopa/carbidopa in elderly patients. The dosage recommendations set out in **Section 4.2 Dose and Method of Administration** reflect the clinical data derived from this experience.

Paediatric use

The safety and efficacy of foslevodopa/foscarbidopa in paediatric patients less than 18 years of age have not been established. Use in patients below the age of 18 is not recommended.

Effects on laboratory tests

The following laboratory abnormalities have been reported with levodopa/carbidopa: Elevated serum urea, alkaline phosphatases, AST (GOT), ALT (GPT), LDH, bilirubin, creatinine, and uric acid; elevated blood sugar; positive Coombs test; reduced haemoglobin and haematocrit.

Leucocytes, bacteria and blood in the urine have been reported. Levodopa/carbidopa, and thus VYALEV, may cause a false positive result when a dipstick is used to test for urinary ketone; this reaction is not altered by boiling the urine sample. The use of glucose oxidase methods may give false negative results for glucosuria.

4.5 Interactions with other medicines and other forms of interactions

No *in vivo* interaction studies have been performed with VYALEV. *In vitro*, neither foslevodopa nor foscarbidopa demonstrated clinically-relevant inhibition or induction of CYP450 enzymes, nor inhibition of transporters. The following interactions are known from the generic combination of levodopa/carbidopa:

Antihypertensives
Symptomatic postural hypotension has occurred when combinations of levodopa and a decarboxylase inhibitor are added to the treatment of patients already receiving anti-hypertensives. Dosage adjustment of the antihypertensive agent may be required.

Antidepressants
There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant administration of tricyclic antidepressants and levodopa/carbidopa preparations (see **Section 4.3 Contraindications - MAO inhibitors**).

COMT inhibitors (tolcapone, entacapone, opicapone)
Concomitant use of COMT inhibitors and VYALEV can increase the bioavailability of levodopa. The dose of VYALEV may need to be adjusted.

Other medicinal products
Dopamine receptor antagonists (some antipsychotics, e.g. phenothiazines, butyrophenones and risperidone and antiemetics, e.g. metoclopramide), benzodiazepines, isoniazid, phenytoin and papaverine can reduce the therapeutic effect of levodopa. Patients taking these medicinal products together with VYALEV, should be observed carefully for loss of therapeutic response.

MAO inhibitors are contraindicated in patients taking VYALEV, with the exception of MAO-B selective inhibitors (for instance selegiline hydrochloride). The dose of VYALEV may need to be reduced when a MAO inhibitor selective for type B is added.

Concomitant use of selegiline and levodopa/carbidopa has been associated with serious orthostatic hypotension.

Amantadine has a synergistic effect with levodopa; levodopa-related adverse events as well as amantadine-related adverse events may increase when both medications are co-administered. An adjustment of the posology of either medication may be needed.

The mechanism of action of amantadine in Parkinson's disease is thought to be due to direct and indirect effects on dopamine neurons. Amantadine has also been shown to be a weak, non-competitive NMDA-receptor antagonist. Therefore, amantadine does not directly interact with or affect the bioavailability of levodopa.

Anticholinergics may further reduce tremor when used in combination with medicines containing levodopa.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No reproduction studies have been conducted with the combination of foslevodopa/foscarbidopa. Oral administration of combinations of levodopa and carbidopa to male and female rats prior to mating and during gestation had no adverse effects on fertility, reproductive performance, or pup survival

Use in pregnancy (Category B3)

There are no adequate or well controlled studies in pregnant women. No studies on the effect on embryofetal development have been conducted with the foslevodopa/foscarbidopa combination. Levodopa and combinations of carbidopa and levodopa, but not carbidopa alone, have caused visceral and skeletal malformations in rabbits. Carbidopa and combinations of levodopa and carbidopa were not teratogenic in mice. An oral combination of levodopa, carbidopa and entacapone was not teratogenic in rats and rabbits.

The effects of VYALEV on human pregnancy are unknown. VYALEV is not recommended during pregnancy and in women of childbearing potential not using contraception unless the benefits for the mother outweigh the possible risks to the fetus.

Use in lactation

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 milk.

There is insufficient information on the effects of VYALEV or their metabolites in newborns/infants. VYALEV should not be used by breast-feeding mothers.

4.7 Effects on ability to drive and use machines

Levodopa and carbidopa may cause dizziness and orthostatic hypotension. Therefore, caution should be exercised when driving or using machines. Patients being treated with VYALEV and presenting with somnolence and/or sudden sleep episodes must be advised to refrain from driving or engaging in activities where impaired alertness may put them, or others, at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also **Section 4.4 Special Warnings and Precautions for use**).

4.8 Adverse effects (Undesirable effects)

Summary of the safety profile

The most frequent adverse reactions (≥10%) were infusion site events (infusion site erythema, infusion site cellulitis, infusion site nodule, infusion site pain, infusion site oedema, infusion site reaction and infusion site infection), hallucination, fall and anxiety.

Tabulated list of adverse reactions

Adverse reactions reported in all Phase 3 studies in patients exposed to VYALEV (379 patients) based on treatment emergent frequencies, regardless of causality assigned are presented in Table 5 listed by MedDRA system organ class. Adverse reaction frequencies are based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); and very rare (<1/ 10 000).

Table 5. List of adverse reactions

System organ class	Frequency	Adverse reactions	Subjects with Adverse Drug Reactions (N = 379) n (%)
Infections and infestations	Very common	Infusion site cellulitis Infusion site infection	105 (27.7) 39 (10.3)
	Common[a]	Infusion site abscess	37 (9.8)
Metabolism and nutrition disorders	Common	Decreased appetite	9 (2.4)

Psychiatric disorders	Very common	Anxiety	45 (11.9)
		Hallucination[b]	93 (24.5)
	Common	Confusional state	17 (4.5)
		Delusion	17 (4.5)
		Depression	9 (2.4)
		Impulse control disorder	6 (1.6)
		Insomnia	28 (7.4)
		Paranoia	5 (1.3)
		Psychotic disorder	14 (3.7)
		Suicidal ideation	6 (1.6)
	Uncommon	Dopamine dysregulation syndrome	1 (0.3)
Nervous system disorders	Common	Cognitive disorder	14 (3.7)
		Dizziness	33 (8.7)
		Dizziness postural	8 (2.1)
		Dyskinesia	33 (8.7)
		Dystonia	12 (3.2)
		Headache	23 (6.1)
		Hypoaesthesia	9 (2.4)
		On and off phenomenon	27 (7.1)
		Paraesthesia	11 (2.9)
		Polyneuropathy[c]	11 (2.9)
		Somnolence	15 (4.0)
		Syncope	6 (1.6)
Cardiac disorders	Uncommon	Palpitations	3 (0.8)

Vascular disorders	Common	Hypertension Hypotension Orthostatic hypotension	13 (3.4) 10 (2.6) 21 (5.5)
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea	12 (3.2)
Gastrointestinal disorders	Common	Abdominal pain Constipation Diarrhoea Dry mouth Nausea Vomiting	6 (1.6) 32 (8.4) 15 (4.0) 11 (2.9) 28 (7.4) 7 (1.8)
Skin and subcutaneous tissue disorders	Common	Pruritus Rash	4 (1.1) 10 (2.6)
Musculoskeletal and connective tissue disorders	Common	Muscle spasms	8 (2.1)
Renal and urinary disorders	Common	Urinary incontinence Urinary retention	9 (2.4) 4 (1.1)
General disorders and administration site conditions	Very common	Infusion site erythema Infusion site reaction Infusion site nodule Infusion site oedema Infusion site pain	177 (46.7) 42 (11.1) 93 (24.5) 67 (17.7) 80 (21.1)

	Common[a]	Asthenia	7 (1.8)
		Fatigue	20 (5.3)
		Infusion site bruising	33 (8.7)
		Infusion site exfoliation	5 (1.3)
		Infusion site extravasation	27 (7.1)
		Infusion site haematoma	21 (5.5)
		Infusion site haemorrhage	17 (4.5)
		Infusion site induration	16 (4.2)
		Infusion site inflammation	14 (3.7)
		Infusion site irritation	11 (2.9)
		Infusion site mass	12 (3.2)
		Infusion site papule	23 (6.1)
		Infusion site pruritus	11 (2.9)
		Infusion site rash	12 (3.2)
		Infusion site swelling	14 (3.7)
		Malaise	4 (1.1)
		Oedema peripheral	12 (3.2)
Investigations	Common	Vitamin B6 decreased	19 (5.0)
		Weight decreased	32 (8.4)
Injury, poisoning and procedural complications	Very common	Fall	76 (20.1)
[a] Common adverse reactions pertaining to infusion site events included if ≥2%. [b] Hallucination includes hallucination, hallucination visual, hallucination auditory, hallucination olfactory, hallucinations tactile, and hallucinations mixed. [c] Polyneuropathy includes neuropathy peripheral, polyneuropathy, decreased vibratory sense, peripheral sensory neuropathy, sensory disturbance and sensory loss.			

Description of selected adverse reactions

Infusion site infection

Infusion site skin events including infusion site reactions and infections, commonly seen with subcutaneous infusions were observed with VYALEV in the clinical studies. The majority of the infusion site skin events were non-serious, mild or moderate in severity, and resolved spontaneously or with treatment with antibiotics and/or incision and drainage. Three subjects with infusion site infections had a complication of sepsis resulting in hospitalisation. Monitor for any skin changes at the infusion site that could indicate a potential infection, such as redness associated with warmth, swelling, pain, and discolouration when pressure is applied to it. Aseptic techniques should be followed while using this medication and consider rotating the infusion site more frequently than every 3rd day, using a new infusion set if these skin changes show. It is recommended that new infusion sites be at least 2.5 cm from sites used within the previous 12 days.

Adverse reactions observed for Duodopa (levodopa and carbidopa intestinal gel) in Duodopa clinical studies

Additional common adverse reactions observed in Duodopa clinical trials are presented below.

- Gastrointestinal disorders: abdominal distension, dyspepsia, flatulence
- General disorders and administration site conditions: pain
- Investigations: blood homocysteine increased, amino acid level increased, Vitamin B12 decreased
- Metabolism and nutrition disorders: Vitamin B6 deficiency, Vitamin B12 deficiency, hyperhomocysteinaemia
- Musculoskeletal disorders: neck pain
- Nervous system disorders: Parkinson’s disease, syncope, tremor
- Psychiatric disorders: sleep attacks, abnormal dreams, sleep disorder, agitation, impulsive behaviour
- Respiratory, thoracic, and mediastinal disorders: oropharyngeal pain
- Skin and subcutaneous tissue disorders: hyperhidrosis, dermatitis contact

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

In the event of an overdosage with VYALEV, the infusion should be stopped immediately. Most prominent clinical symptoms of an overdose with foslevodopa/foscarbidopa are dystonia and dyskinesia. Blepharospasm can be an early sign of overdose. The treatment of an acute overdose of VYALEV is the same as that of an acute overdose of levodopa; however, pyridoxine has no effect on the reversal of the action of VYALEV. 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. Patients must also be monitored for hypotension. The possibility that the patient took other medicinal products together with VYALEV should be taken into consideration. To date experiences with dialysis have not been reported, therefore its value in the treatment of VYALEV overdose is unknown.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Parkinson drugs, foslevodopa and decarboxylase inhibitor
ATC code: <Not yet assigned>.

Mechanism of action

VYALEV (foslevodopa/foscarbidopa) 240 mg/12 mg per mL solution for infusion is a prodrug combination of levodopa monophosphate and carbidopa monophosphate (ratio 20:1) in a solution for 24 hour/day continuous subcutaneous infusion in Parkinson's disease patients who are not adequately controlled with current medical therapy. Foslevodopa and foscarbidopa are converted *in-vivo* to levodopa and carbidopa. Levodopa relieves symptoms of Parkinson's disease following decarboxylation to dopamine in the brain. Carbidopa, which does not cross the blood-brain barrier, inhibits the extracerebral decarboxylation of levodopa to dopamine, which means that a larger amount of levodopa becomes available for transportation to the brain and transformation into dopamine.

Pharmacodynamic effects

VYALEV subcutaneous administration and Duodopa intestinal administration were shown to have comparable levodopa $C_{max,}$ AUC, and degree of fluctuation, which supports a comparable efficacy profile. By achieving the same plasma concentrations of levodopa as Duodopa, VYALEV reduces the motor fluctuations and increases the "On"-time in levodopa-responsive patients with advanced Parkinson's disease. The motor fluctuations and hyperkinesia or dyskinesia are reduced because the plasma concentrations of levodopa are

being kept at a steady level within the individual therapeutic window. Therapeutic effect on motor symptoms (“On” state) is achieved on the first treatment day.

Clinical trials

Studies with Duodopa intestinal gel formulation

The efficacy of Duodopa intestinal gel was confirmed in two identically-designed Phase 3, 12-week, randomised, double-blind, double-dummy, active-controlled, parallel group, multicentre studies to evaluate the efficacy, safety, and tolerability of the Duodopa intestinal gel system against levodopa/carbidopa 100/25 mg tablets. The studies were conducted with patients with advanced Parkinson's disease who were levodopa-responsive and had persistent motor fluctuations, despite optimised treatment with oral levodopa/carbidopa and other available anti-Parkinson's disease medications, enrolling a total of 71 patients. The results of the two studies were combined and a single analysis was conducted.

Patients were eligible for participation in the studies if their response to anti-Parkinson's disease drug treatment was inadequate (i.e., they were experiencing ≥3 hours of “Off” time) and they demonstrated a clear responsiveness to treatment with levodopa. Seventy-one (71) patients enrolled in the study and 66 patients completed the treatment (3 patients discontinued treatment because of adverse events, 1 patient for lack of effect, and 1 patient for non-compliance).

Patients in this study had a mean age of 64.4 years and disease duration of 10.9 years.

Patients were randomised to 1 of 2 treatment arms:

1) Levodopa/carbidopa intestinal gel + placebo capsules, or

2) Placebo gel + levodopa/carbidopa capsules.

Duodopa or placebo gel was infused over 16 hours daily through a PEG-J tube using an ambulatory infusion pump. Patients in both treatment arms had a PEG-J device placement. Therefore, the primary difference between the treatment groups was the method of administration of levodopa/carbidopa (intestinal infusion versus oral capsule).

The primary efficacy endpoint, change in normalised "Off" time (baseline to endpoint) based on Parkinson's Disease Diary (PD Diary) data using last observation carried forward demonstrated a statistically significant least square (LS) mean difference in favour of the Duodopa treatment group (Table 6).

The primary end point results were supported by a Mixed Model Repeated Measures (MMRM) analysis which examined the change from baseline to each post-baseline study visit. This analysis of “Off” time demonstrated a statistically significant greater improvement of the Duodopa group over the Active control group at Week 4, and that improvement was shown to be statistically significant at Weeks 8, 10, and 12.

This change in “Off” time was associated with a statistically significant LS mean difference from baseline in the average daily normalised "On" time without troublesome dyskinesia between the Duodopa intestinal gel treatment group and the active control group based on PD Diary data. The baseline values were collected three days prior to randomisation and after 28 days of oral therapy standardisation.

Table 6. Change from baseline to endpoint in "off" time and in "on" time without troublesome dyskinesia

Treatment Group	N	Baseline mean (SD) (hours)	Endpoint Mean (SD) (hours)	LS mean (SE) of change (hours)	LS mean (SE) of difference (hours)	*P* value
Primary measure						
"Off" time Active control[a]	31	6.90 (2.06)	4.95 (2.04)	-2.14 (0.66)		
Duodopa intestinal gel	35	6.32 (1.72)	3.05 (2.52)	-4.04 (0.65)	-1.91 (0.57)	0.0015
Secondary measure						
"On" time without troublesome dyskinesia Active control	31	8.04 (2.09)	9.92 (2.62)	2.24 (0.76)		
Duodopa intestinal gel	35	8.70 (2.01)	11.95 (2.67)	4.11 (0.75)	1.86 (0.65)	0.0059
SD = standard deviation; SE = standard error [a.] Active control, oral levodopa/carbidopa 100/25 mg tablets (Sinemet® tablets over-encapsulated)						

Analyses of other secondary efficacy endpoints, in order of the hierarchical testing procedure, demonstrated statistically significant results for Duodopa intestinal gel compared to oral levodopa/carbidopa for the Parkinson's Disease Questionnaire (PDQ-39) Summary Index (*an index for Parkinson’s disease-related quality of life*), Clinical Global Impression-Improvement (CGI-I) score, and Unified Parkinson's Disease Rating Scale (UPDRS) Part II score (Activities of Daily Living). The PDQ-39 Summary Index showed a decrease from baseline of 10.9 points at week 12 for Duodopa intestinal gel group. Other secondary endpoints UPDRS Part III score, EuroQol 5-dimensions Questionnaire (EQ-5D) Summary Index, and Zarit Burden Interview (ZBI) total score, did not meet statistical significance based on the hierarchical testing procedure.

A Phase 3, open-label, single-arm, multicentre study was conducted to assess the long-term safety and tolerability of Duodopa over 12 months in 354 patients. The target population was levodopa-responsive patients with advanced Parkinson's disease and motor fluctuations despite optimised treatment with available Parkinson's disease medications. The average daily normalised "Off" time changed by – 4.44 hours from Baseline to Endpoint (6.77 hours at Baseline and 2.32 hours at Endpoint) with a corresponding 4.8 hour increase in “On” time without troublesome dyskinesia.

A Phase 3b, open-label, randomised, multicentre study was conducted to assess the effect of Duodopa on dyskinesia compared with optimised medical treatment (OMT) over 12 weeks in patients with advanced Parkinson's disease who were levodopa-responsive and had persistent motor fluctuations that have not been controlled with OMT. Patients were eligible for participation in the study if they had a baseline Unified Dyskinesia Rating Scale (UDysRS) total score ≥30. Sixty-one (61) patients (28 on Duodopa intestinal gel and 33 on OMT) were treated in the study. The change from baseline to Week 12 in UDysRS total score demonstrated a statistically significant LS mean difference in favour of the Duodopa treatment group (Table 7). Analysis of all secondary efficacy endpoints, except UPDRS Part III (motor examination), demonstrated statistically significant results for Duodopa compared to the OMT group (Table 7).

Table 7. Primary and Key Secondary Efficacy Measures at Week 12

Treatment Group	Baseline		Week 12				
	N	Mean (SD)	N	Change (SD)	LS Mean (SE) of Change	LS Mean (SE) of Difference	*P* value
Primary Measure							
UDysRS total score							
OMT	32	51.2 (11.56)	26	-1.5 (11.19)	-2.33 (2.56)	-15.05 (3.20)	<0.0001
Duodopa	27	53.2 (12.24)	24	-18.7 (14.39)	-17.37 (2.79)		
Key Secondary Measures							
“ON” time without troublesome dyskinesia (hours)							
OMT	32	9.7 (3.57)	28	-0.2 (2.60)	-0.12 (0.63)	3.27 (0.78)	0.0001
Duodopa	27	8.8 (2.88)	25	3.3 (3.37)	3.15 (0.69)		
PDQ-8 summary index							
OMT	32	43.4 (15.81)	29	-0.7 (15.00)	-4.95 (3.11)		

Duodopa	27	45.1 (20.46)	25	-16.8 (19.28)	-21.62 (3.47)	-16.66 (3.89)	<0.0001
CGI-C score OMT	32	5.0 (1.05)[a]	29	4.6 (1.12)[b]	4.58 (0.25)[b]	-2.11 (0.33)	<0.0001
Duodopa	27	5.2 (1.03)[a]	25	2.5 (1.36)[b]	2.48 (0.28)[b]		
UPDRS Part II (ADL) score OMT	33	18.4 (6.44)	29	-0.0 (3.40)	0.21 (1.16)	-5.54 (1.52)	0.0006
Duodopa	27	18.3 (6.35)	24	-5.7 (8.28)	-5.33 (1.28)		
"OFF" time (hours) OMT	32	4.0 (2.99)	28	0.5 (2.39)	0.18 (0.49)	-2.35 (0.58)	0.0002
Duodopa	27	4.8 (2.41)	25	-2.1 (2.19)	-2.17 (0.53)		
UPDRS Part III[c] (Motor Examination) OMT	33	25.4 (10.91)	29	-0.4 (7.23)	-0.87 (1.89)	-4.05 (2.24)	0.0762
Duodopa	27	26.3 (6.66)	25	-4.2 (10.06)	-4.93 (2.08)		

SD = standard deviation; SE = standard error
[a] Baseline CGI-S score
[b] Week 12 CGI-C score rather than change from baseline score
[c] Performed during "On" time

Studies with VYALEV

VYALEV is a prodrug combination of levodopa monophosphate and carbidopa monophosphate (ratio 20:1) in a solution intended for 24-hour/day continuous subcutaneous infusion. Subcutaneous VYALEV administration and Duodopa intestinal administration were shown to have comparable levodopa C_{max} and AUC parameters, which supports a comparable efficacy profile. The study showed stable levodopa exposure with fluctuation values of 0.262 and 0.404 for VYALEV and Duodopa, respectively (see **Section 5.2 Pharmacokinetic properties**).

A Phase 3, double-blind, double-dummy, randomised, active-controlled, multicentre study was conducted to assess the effect of VYALEV in patients with advanced PD over 12 weeks. A total of 141 patients were randomised in 1:1 ratio to receive either 24-hour/day continuous subcutaneous administration of VYALEV plus oral placebo capsules (N=74) or 24-hour/day continuous subcutaneous administration of placebo solution plus oral encapsulated carbidopa-levodopa IR tablets (N=67).

The study population was patients with levodopa-responsive PD whose motor fluctuations were inadequately controlled by their current medications and who experienced a minimum of 2.5 hours of “Off” time/day as assessed by PD diaries. Patients had a mean age of 66.4 years and a mean disease duration of 8.58 years. At baseline, 66.7% (N=44) of patients in the oral IR carbidopa-levodopa group and 74.3% (N=55) in the VYALEV group were taking at least 1 or more classes of PD medications besides carbidopa-levodopa. During the double-blind treatment period 25.7% (N=19) of patients in the VYALEV group were not receiving any concomitant PD medication.

VYALEV demonstrated statistically significant and clinically meaningful improvements from baseline to Week 12 for "On" time without troublesome dyskinesia compared with the oral IR carbidopa-levodopa group (p=0.0083; Table 8) and “Off” time compared with the oral IR carbidopa-levodopa group (p=0.0054; Table 8). VYALEV demonstrated improvements from baseline to Week 12 in motor experiences of daily living, morning akinesia, sleep, and quality of life indicators, although results did not achieve statistical significance.

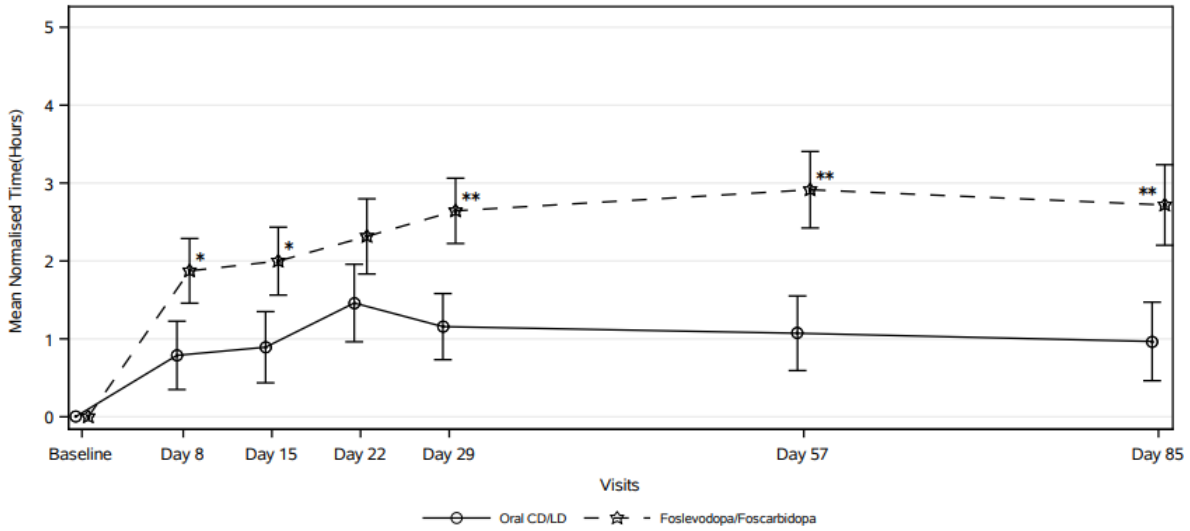
Table 8. Change from Baseline to Endpoint in Primary and Key Secondary Measures

Treatment Group	N	Baseline Mean (SD)	Change from Baseline to Endpoint Mean (SD)	LS Mean (SE) of Change	LS Mean (SE) of Difference	*P* value
Primary Measure						
“On” time without troublesome dyskinesia (hours)[a]						
Oral IR carbidopa-levodopa[b]	67	9.49 (2.62)	0.85 (3.46)	0.97 (0.50)		
VYALEV	73	9.20 (2.42)	3.36 (3.62)	2.72 (0.52)	1.75 (0.65)	0.0083
Secondary Measure						
“Off” time (hours)[a]						
Oral IR carbidopa-levodopa[b]	67	5.91 (1.88)	-0.93 (3.31)	-0.96 (0.49)		
VYALEV	73	6.34 (2.27)	-3.41 (3.76)	-2.75 (0.50)	-1.79 (0.63)	0.0054

SD = standard deviation; SE = standard error.
[a] Derived from Parkinson’s Disease (PD) diary.
[b] Oral immediate release carbidopa-levodopa tablets.

Figure 1 shows results over time according to treatment for the efficacy variable (mean change from baseline to week 12 in the total daily mean “On” time without troublesome dyskinesia based on PD diary).

Figure 1. LS Mean Change from Baseline in "On" Time Without Troublesome Dyskinesia over 12 Weeks



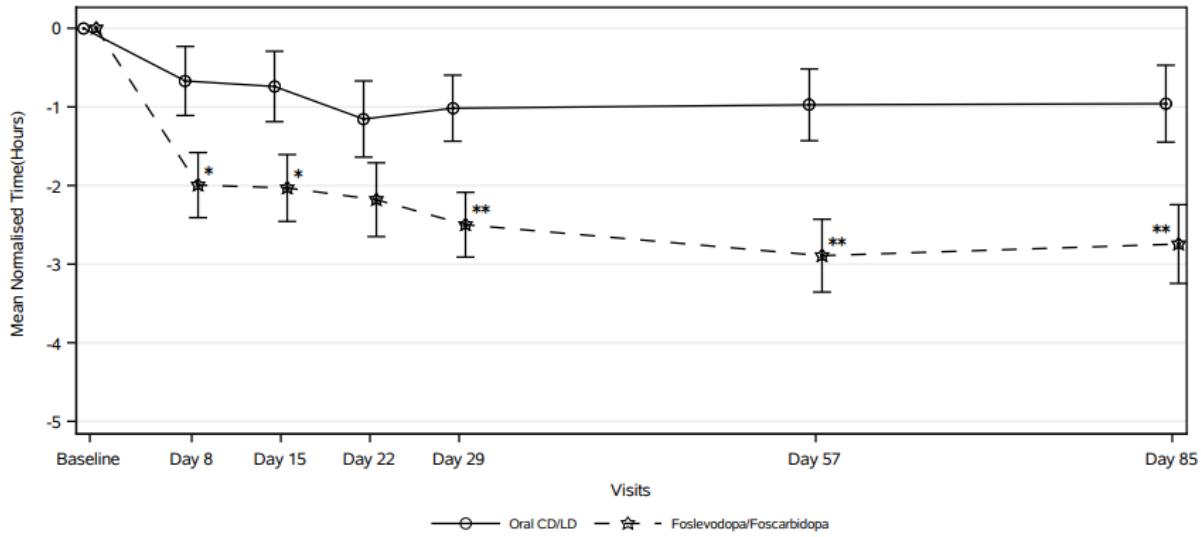
Sample Size

Oral CD/LD	67	65	63	39	62	62	62
Foslevodopa/Foscarbidopa	73	70	66	39	54	47	47

* p ≤ 0.05, ** p ≤ 0.01. P value reflects comparison between treatment groups
CD = carbidopa; LD = levodopa
Note - Day 22 was an optional visit.

Figure 2 shows results over time according to treatment for the efficacy variable (mean change from baseline to week 12 in the total daily mean "Off" time based on PD diary).

Figure 2. LS Mean Change from Baseline in "Off" Time over 12 Weeks



Sample Size

Oral CD/LD	67	65	63	39	62	62	62
Foslevodopa/Foscarbidopa	73	70	66	39	54	47	47

* p ≤ 0.05, ** p ≤ 0.01. P value reflects comparison between treatment groups
CD = carbidopa; LD = levodopa
Note - Day 22 was an optional visit.

A Phase 3, open-label, single-arm study was conducted to evaluate the safety and tolerability of 24-hour daily exposure of continuous subcutaneous infusion of VYALEV over 52 weeks in 244 patients. The target population was levodopa-responsive patients with Parkinson's disease whose motor symptoms were inadequately controlled with current treatment who experienced a minimum of 2.5 hours of "Off" time per day as assessed by PD diaries. The dose conversion from oral medications to VYALEV was achieved with one outpatient office visit.

The summary of the safety profile of VYALEV from this study are provided in **Section 4.8 Adverse effects (Undesirable effects)**. The mean daily normalised "Off" time (PD Diary) decreased from 5.79 hours at baseline to 2.85 hours at Week 26, for a mean improvement of 2.94 hours. This change in "Off" time was associated with a mean increase of 3.24 hours from baseline in "On" time without troublesome dyskinesia. The mean increase from baseline in "On" time without dyskinesia was 4.00 hours. The percentage of patients with morning akinesia, defined as reporting "Off" state as the first symptom upon awakening as derived from the PD Diary, decreased from 77.8% at baseline to 20.8% at Week 26. There was meaningful improvement in other secondary endpoints: motor aspects of experiences of daily living (MDS-

UPDRS Part II score), sleep symptoms (Parkinson's Disease Sleep Scale-2 (PDSS-2) total score)), quality of life (PDQ-39 and EQ-5D-5L summary indices). (Table 9).

Table 9. Change from baseline to week 26 in efficacy endpoints

Measure	N	Baseline mean (SD)	Week 26 Mean (SD)	Mean change (SD)
"Off" time (hours)[a]	97	5.79 (2.35)	2.85 (3.02)	-2.94 (3.16)
"On" time without troublesome dyskinesia (hours)[a]	97	9.62 (2.42)	12.87 (3.08)	3.24 (3.16)
"On" time without dyskinesia (hours)[a]	97	7.01 (3.39)	11.02 (4.23)	4.00 (4.42)
Motor aspects of experiences of daily living[b]	104	15.9 (7.17)	12.7 (7.65)	-3.2 (6.82)
Sleep symptoms[c]	104	20.6 (9.93)	15.0 (9.64)	-5.7 (11.20)
Quality of life[d]	104	34.5 (14.93)	27.3 (15.05)	-7.2 (11.36)
Health-related quality of life[e]	86	0.662 (0.184)	0.744 (0.1375)	0.082 (0.1712)
Measure		**Baseline (%)**	**Endpoint (%)**	**Difference (%)**
Morning akinesia (%)[f]	77	77.8%	20.8%	-57.0%

SD = standard deviation.
[a] Parkinson's disease (PD) Diary.
[b] Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II score.
[c] Parkinson's Disease Sleep Scale-2 (PDSS-2) total score.
[d] Parkinson's Disease Questionnaire-39 items (PDQ-39) summary index.
[e] EuroQol 5-dimensions Questionnaire (EQ-5D-5L) summary index.
[f] % of subjects with early morning "Off" status based on the first morning symptom upon awakening derived from PD Diary.

At Week 52, the mean daily normalised "Off" time (PD Diary) decreased from 5.98 hours at baseline to 2.47 hours (a mean improvement of 3.51 hours) as demonstrated by a reduction

in the number of patients reporting morning OFF (morning akinesia) in their PD Diaries from baseline to study end. The reduction in “Off” was associated with a corresponding mean increase of 3.77 hours from baseline in “On” time without troublesome dyskinesia, as shown in the increase in “On“ time without any dyskinesia (3.94 hours) rather than “On” time with non-troublesome dyskinesia (decrease of 0.17 hours).

Paediatric population

The safety of VYALEV in patients under 18 years of age has not been established and its use in patients below the age of 18 is not recommended.

5.2 Pharmacokinetic properties

Absorption

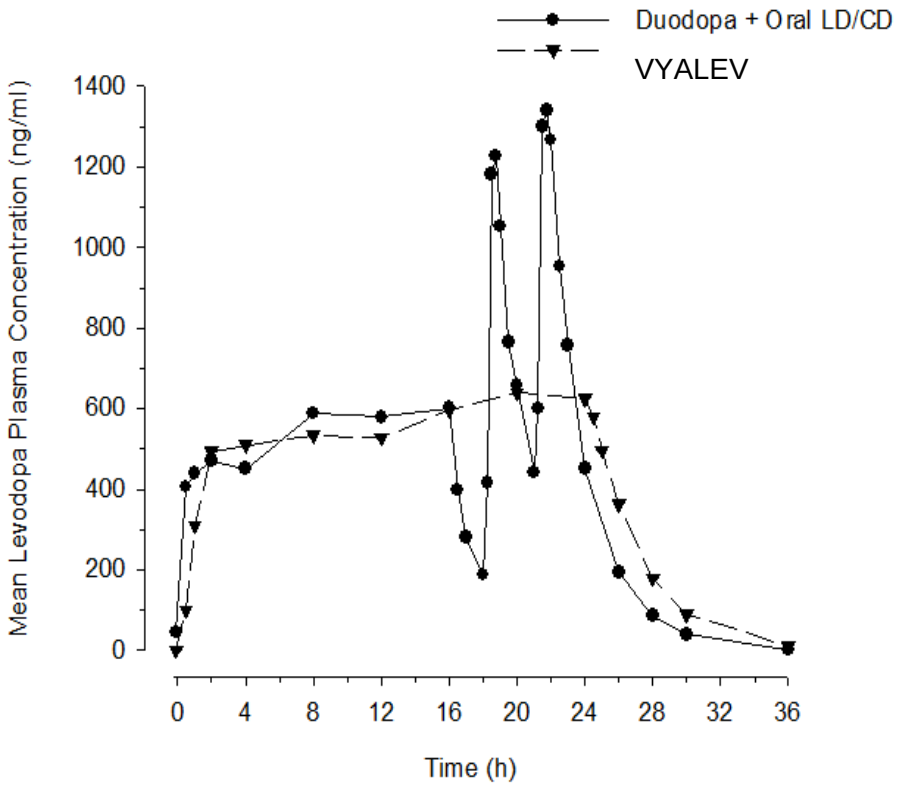
VYALEV is administered directly into the subcutaneous space and is quickly absorbed and converted to levodopa and carbidopa. In a phase 1 study in healthy volunteers, levodopa and carbidopa were detectable in plasma within 30 minutes at the first pharmacokinetic (PK) collection point. In most subjects the steady state was achieved within 2 hours when VYALEV dosing was delivered as loading dose followed by continuous infusion.

In order to determine absorption of VYALEV at different subcutaneous sites, healthy volunteers were administered VYALEV to the abdomen, arm and thigh using a 3-way crossover design. Pharmacokinetic analysis from this study showed that the 3 sites have nearly identical levodopa and carbidopa exposure suggesting VYALEV absorption is similar at the different subcutaneous sites.

VYALEV bypasses the gut, so food does not change absorption or exposure of levodopa/carbidopa.

Following VYALEV administration in healthy volunteers, levodopa steady state is achieved rapidly and maintained during the infusion period. Figure 1 below shows levodopa exposure following both 24-hour VYALEV administration and 16-hour Duodopa administration followed by night-time oral levodopa/carbidopa dosing.

Figure 3. Levodopa exposure (mean ± standard deviation) following 24-hour VYALEV infusion and 16-hour Duodopa infusion followed by night-time oral doses



Results from an additional PK comparability study demonstrated that levodopa exposure was comparable between VYALEV and Duodopa when both were delivered over a 24-hour period.

Distribution

The volume of distribution of levodopa is moderately small. Levodopa has low binding to plasma proteins (about 10%-30%).

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

Both foslevodopa and foscarbidopa have low protein binding (approximately 30%).

Metabolism

Foslevodopa and foscarbidopa prodrugs are rapidly converted by alkaline phosphatases into levodopa and carbidopa and thus the prodrugs are removed quickly from circulation. Levodopa is mainly metabolised by the aromatic amino acid decarboxylase (AAAD) and the COMT enzymes. Other routes of metabolism are transamination and oxidation. The decarboxylation of levodopa to dopamine by AAAD is the major enzymatic pathway when no enzyme inhibitor is co-administered. When levodopa is co-administered with carbidopa the

decarboxylase enzyme is inhibited so that metabolism via COMT becomes the dominant metabolic pathway. O-methylation of levodopa by COMT forms 3-O-methyldopa. When administered with carbidopa, the elimination half-life of levodopa is approximately 1-2 hours.

Carbidopa is metabolised to two main metabolites (α-methyl-3-methoxy-4-hydroxyphenylpropionic acid and α-methyl-3,4-dihydroxyphenylpropionic acid). These 2 metabolites are primarily eliminated in the urine unchanged or as glucuronide conjugates. The elimination half-life of carbidopa is approximately 2 hours.

Excretion

Unchanged carbidopa accounts for 30% of the total urinary excretion of radioactive labelled oral carbidopa.

5.3 Preclinical safety data

Genotoxicity

Foslevodopa was negative and foscarbidopa was positive in a bacterial mutagenicity assay. Both foslevodopa and foscarbidopa were negative in a chromosome aberration assay *in vitro* and a clastogenicity assay *in vivo*. These data are broadly consistent with those reported for levodopa and carbidopa. (See **Section 4.4 Special Warnings and Precautions for use – Hydrazine**).

Carcinogenicity

Foslevodopa and foscarbidopa are metabolised to levodopa and carbidopa *in vivo*. There was no evidence of carcinogenicity following daily oral administration of a combination of levodopa and carbidopa to rats for 106 weeks or following daily oral administration of carbidopa alone to rats for 96 weeks (See **Section 4.4 Special Warnings and Precautions for use – Hydrazine**).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each vial contains sodium hydroxide, hydrochloric acid, water for injections.

Excipient with known effect:

VYALEV contains approximately 1.84 mmol (42.4 mg) sodium per mL.

6.2 Incompatibilities

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

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store at 2°C-8°C. Refrigerate. Do not freeze.

Keep the vials in the outer carton to protect the vials from breaking.

May be stored at room temperature up to a maximum of 30°C for a single period of up to 28 days. Once a vial has been stored at room temperature, do not return the product to the refrigerator. Record the date when VYALEV is first removed from the refrigerator in the space provided on the carton.

Discard any unused product in the vial or the syringe within 24 hours see **Section 6.6 Special precautions for disposal** for further information.

6.5 Nature and contents of container

VYALEV is supplied as a sterile solution for infusion in a glass vial.

Each vial contains foslevodopa 2400 mg and foscarbidopa 120 mg in 10mL in the following packaging configuration:

Each carton contains 7 vials.

Sterile, single-use infusion components (syringe, infusion set, and vial adapter) qualified for use are provided separately.

6.6 Special precautions for disposal

Vials are for single use in one patient only. The entire contents of a vial should be transferred into a syringe for administration. Discard any residue in the vial after transfer of the medicinal product to the syringe.

After transferring the medicinal product from the vial into a syringe, the prepared syringe should be used immediately in the Vyafuser pump. Do not store the prepared syringe prior to inserting it into the pump. After the syringe has been in the pump for a maximum of 24 hours, discard the syringe and any unused product in the syringe. Do not use the product from the same vial or same syringe for more than 24 hours.

Discard the vial if not used within the 28-day room temperature period.

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

CAS number

Foslevodopa: 97321-87-4

Foscarbidopa: 2407648-70-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription only medicine.

8 SPONSOR

AbbVie Pty Ltd
241 O'Riordan Street
Mascot NSW 2020
AUSTRALIA
Tel: 1800 043 460
www.abbvie.com.au

9 DATE OF FIRST APPROVAL

27 March 2024

10 DATE OF REVISION

N/A

Summary table of changes

Section Changed	Summary of new information
All	New product information