## 1. NAME OF THE MEDICINAL PRODUCT

Ongentys® 50 mg

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 50 mg of opicapone.

Excipient(s) with known effect

Each hard capsule contains 148.2 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Hard capsule

Dark blue capsules, size 1, approximately 19 mm, imprinted “OPC 50” on the cap and “Bial” on the body.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Ongentys 50 mg is indicated as adjunctive therapy to preparations of levodopa/ DOPA decarboxylase inhibitors (DDCI) in adult patients with Parkinson’s disease and end-of-dose motor fluctuations who cannot be stabilised on those combinations.

### 4.2 Posology and method of administration

Posology

The recommended dose is 50 mg of opicapone.
Ongentys 50 mg should be taken once-daily at bedtime at least one hour before or after levodopa combinations.

*Dose adjustments of antiparkinsonian therapy*
Ongentys 50 mg is to be administered as an adjunct to levodopa treatment and enhances the effects of levodopa. Hence, it is often necessary to adjust levodopa dose by extending the dosing intervals and/or reducing the amount of levodopa per dose within the first days to first weeks after initiating the treatment with opicapone according to the clinical condition of the patient (see section 4.4).

*Missed dose*
If one dose is missed, the next dose should be taken as scheduled. The patient should not take an extra dose to make up for the missed dose.

Special populations

*Elderly*
No dose adjustment is needed for elderly patients (see section 5.2).
Caution must be exercised in patients ≥ 85 years of age as there is limited experience in this age group.

*Renal impairment*
No dose adjustment is necessary in patients with renal impairment, as opicapone is not excreted by the kidney (see section 5.2).

*Hepatic impairment*
No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh Class A). There is limited clinical experience in patients with moderate hepatic impairment (Child-Pugh Class B). Caution must be exercised in these patients and dose adjustment may be necessary (see section 5.2).
There is no clinical experience in patients with severe hepatic impairment (Child-Pugh Class C), therefore, opicapone is not recommended in these patients (see section 5.2).

*Paediatric population*
There is no relevant use of Ongentys 50 mg in the paediatric population with Parkinson's disease and motor fluctuations.

Method of administration

Oral use.

The capsules should be swallowed whole with water.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Phaeochromocytoma, paraganglioma, or other catecholamine secreting neoplasms.

History of neuroleptic malignant syndrome and/or non-traumatic rhabdomyolysis.

Concomitant use with monoamine oxidase (MAO-A and MAO-B) inhibitors (e.g. phenelzine, tranylcypromine and moclobemide) other than those for the treatment of Parkinson's disease (see section 4.5).

## 4.4 Special warnings and precautions for use

Dose adjustments of antiparkinsonian therapy

Ongentys 50 mg is to be administered as an adjunct to levodopa treatment. Hence, the precautions valid for levodopa treatment should also be taken into account for Ongentys 50 mg. Opicapone enhances the effects of levodopa. To reduce levodopa-related dopaminergic adverse reactions (e.g. dyskinesia, hallucinations, nausea, vomiting and orthostatic hypotension), it is often necessary to adjust the daily dose of levodopa by extending the dosing intervals and/or reducing the amount of levodopa per dose within the first days to first weeks after initiating treatment with Ongentys 50 mg, according to the clinical condition of the patient (see section 4.2).

If Ongentys 50 mg is discontinued it is necessary to adjust the dosing of the other antiparkinsonian treatments, especially levodopa, to achieve a sufficient level of control of the symptoms.

Psychiatric disorders

Patients and care-givers should be made aware that impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic

treatments. Patients should be monitored regularly for the development of impulse control disorders and review of treatment is recommended if such symptoms develop.

Others

Increases in liver enzymes were reported in studies with nitrocatechol inhibitors of catechol-*O*-methyltransferase (COMT). For patients who experience progressive anorexia, asthenia and weight decrease within a relatively short period of time, a general medical evaluation including liver function should be considered.

Excipients

Ongentys 50 mg contains lactose. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Ongentys 50 mg contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

## 4.5 Interaction with other medicinal products and other forms of interaction

Monoamino oxidase (MAO) inhibitors

Combination of opicapone and MAO inhibitors could result in inhibition of the majority of the pathways responsible for the metabolism of catecholamines. Because of this, concomitant use of opicapone with MAO inhibitors (e.g. phenelzine, tranylcypromine and moclobemide) other than those for the treatment of Parkinson's disease is contraindicated (see section 4.3).
Concomitant use of opicapone and MAO inhibitors for the treatment of Parkinson's disease, e.g. rasagiline (up to 1 mg/day) and selegiline (up to 10 mg/day in oral formulation or 1.25 mg/day in buccal absorption formulation), is permissible.

There is no experience with opicapone when used concomitantly with the MAO-B inhibitor safinamide. Therefore, their concomitant use should be considered with appropriate caution.

Medicinal products metabolised by COMT

Opicapone may interfere with the metabolism of medicinal products containing a catechol group that are metabolised by COMT, e.g. rimiterole, isoprenaline, adrenaline, noradrenaline, dopamine, dopexamine or dobutamine, leading to potentiated effects of these medicinal products. Careful monitoring of patients being treated with these medicinal products is advised when opicapone is used.

Tricyclic antidepressants and noradrenaline re-uptake inhibitors

There is limited experience with opicapone when used concomitantly with tricyclic antidepressants and noradrenaline re-uptake inhibitors (e.g. venlafaxine, maprotiline and desipramine). Thus, their concomitant use should be considered with appropriate caution.

Quinidine

A study conducted in healthy volunteers showed that when a single dose of 50 mg opicapone was co-administered (within 1 hour) with a single dose of quinidine (600 mg), systemic exposure of opicapone decreased by 37% ($AUC_{0\text{-}tlast}$). Thus, particular consideration should be given to cases where quinidine needs to be administered together with opicapone as their co-administration should be avoided.

CYP2C8 and OATP1B1 substrates

Opicapone is a weak *in vitro* inhibitor of CYP2C8 and OATP1B1, whereas repaglinide is a sensitive CYP2C8 and OATP1B1 substrate. A study conducted in healthy subjects showed that there were no changes in repaglinide's exposure when repaglinide was administered following multiple once-daily administration of opicapone 50 mg.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of opicapone in pregnant women. Opicapone crossed the placenta in rats. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Ongentys 50 mg is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

Opicapone levels in the milk of lactating rats were equivalent to those in plasma. It is unknown whether opicapone or its metabolites are excreted into human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Ongentys 50 mg.

Fertility

The effects of opicapone on fertility in humans have not been studied. Animal studies with opicapone do not indicate harmful effects with respect to fertility (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Opicapone in association with levodopa may have major influence on the ability to drive and use machines. Opicapone may, together with levodopa, cause dizziness, symptomatic orthostatism and somnolence. Therefore, caution should be exercised when driving or using machines.

## 4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions reported were nervous system disorders. Dyskinesia was the most frequently reported treatment-emergent adverse reaction (17.7%).

Tabulated list of adverse reactions

In the table below (Table 1) all adverse reactions are presented by System Organ Class 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), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

**Table 1 – Frequency of adverse reactions (MedDRA) in placebo-controlled Phase 3 studies**

| System Organ Class | Very common | Common | Uncommon |
|---|---|---|---|
| **Metabolism and nutrition disorders** | | | Decreased appetite, Hypertriglyceridaemia |
| **Psychiatric disorders** | | Abnormal dreams, Hallucination, Hallucination visual, Insomnia | Anxiety, Depression, Hallucination auditory, Nightmare, Sleep disorder |

| | | | |
|---|---|---|---|
| **Nervous system disorders** | Dyskinesia | Dizziness,<br>Headache,<br>Somnolence | Dysgeusia,<br>Hyperkinesia,<br>Syncope |
| **Eye disorders** | | | Dry eye |
| **Ear and labyrinth disorders** | | | Ear congestion |
| **Cardiac disorders** | | | Palpitations |
| **Vascular disorders** | | Orthostatic Hypotension | Hypertension,<br>Hypotension |
| **Respiratory, thoracic and mediastinal disorders** | | | Dyspnoea |
| **Gastrointestinal disorders** | | Constipation,<br>Dry mouth,<br>Nausea,<br>Vomiting | Abdominal distention,<br>Abdominal pain,<br>Abdominal pain upper,<br>Dyspepsia |
| **Musculoskeletal and connective tissue disorders** | | Muscle spasms | Muscle twitching,<br>Musculoskeletal stiffness,<br>Myalgia,<br>Pain in extremity |
| **Renal and urinary disorders** | | | Chromaturia,<br>Nocturia |
| **Investigations** | | Blood creatine phosphokinase increased | Weight decreased |
| **Injury, poisoning and procedural complications** | | | Fall |
| **General disorders and administration site conditions** | | | Fatigue |

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

### 4.9 Overdose

There is no known specific antidote. Symptomatic and supportive treatment should be administered as appropriate. Removal of opicapone by gastric lavage and/or inactivation by administering activated charcoal should be considered.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-parkinson drugs, other dopaminergic agents, ATC code: N04BX04

Mechanism of action

Opicapone is a peripheral, selective and reversible catechol-*O*-methyltransferase (COMT) inhibitor endowed with a high binding affinity (sub-picomolar) that translates into a slow complex dissociation rate constant and a long duration of action (>24 hours) *in vivo*.

In the presence of a DOPA decarboxylase inhibitor (DDCI), COMT becomes the major metabolising enzyme for levodopa, catalysing its conversion to 3-*O*-methyldopa (3-OMD) in the brain and periphery. In patients taking levodopa and a peripheral DDCI, such as carbidopa or benserazide, opicapone increases levodopa plasma levels thereby improving the clinical response to levodopa.

Pharmacodynamic effects

Opicapone showed a marked (>90%) and long-lasting (>24 hours) COMT inhibition in healthy subjects after administration of 50 mg opicapone.

At steady state, 50 mg opicapone significantly increased the extent of levodopa systemic exposure approximately 2 fold compared to placebo following a single oral administration of either 100/25 mg levodopa/carbidopa or 100/25 mg levodopa/benserazide administered 12 h after the opicapone dose.

Clinical efficacy and safety

The efficacy and safety of opicapone has been demonstrated in two Phase 3 double-blind, placebo and active (Study 1 only) controlled studies in 1,027 randomized adult patients with Parkinson's disease treated with levodopa/DDCI (alone or in combination with other antiparkinsonian medicinal products) and end-of-dose motor fluctuations for up to 15 weeks. At screening, the mean age was similar in all treatment groups in both studies, ranging between 61.5 and 65.3 years. Patients had disease severity stages 1 to 3 (modified Hoehn and Yahr) at ON, were treated with 3 to 8 daily doses of levodopa/DDCI and had a daily average OFF-time of at least 1.5 hours. In both studies, 783 patients were treated with 25 mg or 50 mg of opicapone or placebo. In Study 1, 122 patients were treated with 5 mg of opicapone and 122 patients were treated with 200 mg of entacapone (active comparator). The majority of patients treated in both pivotal studies were treated with immediate-release levodopa/DDCI. There were 60 patients in the combined Phase 3 studies who were predominantly using controlled-release levodopa (i.e. >50% of their levodopa/DDCI formulations), 48 of whom were treated solely with controlled-release formulations of levodopa. Although there is no evidence that either the efficacy or safety of opicapone would be affected by use of controlled-release levodopa preparations, the experience with such preparations is limited.

Opicapone demonstrated clinical efficacy superior to placebo during the double-blind treatment, both for the primary efficacy variable used in both pivotal studies, i.e. reduction in OFF-time (Table 2), the proportion of OFF-time responders (i.e. a subject who had a reduction in OFF-time of at least 1 hour from baseline to endpoint) (Table 3) and for most diary-derived secondary endpoints.

The LS mean reduction in absolute OFF-time from baseline to endpoint in the entacapone group was -78.7 minutes. The difference in LS mean change in OFF-time of entacapone to placebo in Study 1 was -30.5 minutes. The difference in LS mean change in OFF-time of opicapone 50 mg to entacapone was -24.8 minutes and non-inferiority of opicapone 50 mg to entacapone was demonstrated (95% confidence interval: -61.4, 11.8).

**Table 2 – Change in absolute OFF-time and ON-time (minutes) from baseline to endpoint**

| Treatment | N | LS mean | 95% CI | p-value |
|---|---|---|---|---|
| **Study 1** | | | | |
| **Change in OFF-time** | | | | |
| Placebo | 121 | -48.3 | -- | -- |
| OPC 5 mg | 122 | -77.6 | -- | -- |
| OPC 25 mg | 119 | -73.2 | -- | -- |
| OPC 50 mg | 115 | -103.6 | -- | -- |
| OPC 5 mg – Placebo | -- | -29.3 | -65.5, 6.8 | 0.0558 |

| Treatment | N | LS mean | 95% CI | p-value |
|---|---|---|---|---|
| OPC 25 mg – Placebo | -- | -25.0 | -61.5, 11.6 | 0.0902 |
| OPC 50 mg – Placebo | -- | -55.3 | -92.0, -18.6 | 0.0016 |
| **Change in total ON-time without troublesome dyskinesias[a]** | | | | |
| Placebo | 121 | 40.0 | -- | -- |
| OPC 5 mg | 122 | 75.6 | -- | -- |
| OPC 25 mg | 119 | 78.6 | -- | -- |
| OPC 50 mg | 115 | 100.8 | -- | -- |
| OPC 5 mg – Placebo | -- | 35.6 | -2.5, 73.7 | 0.0670 |
| OPC 25 mg – Placebo | -- | 38.6 | 0.2, 77.0 | 0.0489 |
| OPC 50 mg – Placebo | -- | 60.8 | 22.1, 99.6 | 0.0021 |
| **Study 2** | | | | |
| **Change in OFF-time** | | | | |
| Placebo | 136 | -54.6 | -- | -- |
| OPC 25 mg | 125 | -93.2 | -- | -- |
| OPC 50 mg | 150 | -107.0 | -- | -- |
| OPC 25 mg – placebo | -- | -38.5 | -77.0, -0.1 | 0.0900 |
| OPC 50 mg – placebo | -- | -52.4 | -89.1, -15.7 | 0.0101 |
| **Change in total ON-time without troublesome dyskinesias[a]** | | | | |
| Placebo | 136 | 37.9 | -- | -- |
| OPC 25 mg | 125 | 79.7 | -- | -- |
| OPC 50 mg | 150 | 77.6 | -- | -- |
| OPC 25 mg – placebo | -- | 41.8 | 0.7, 82.9 | 0.0839 |
| OPC 50 mg – placebo | -- | 39.7 | 0.5, 78.8 | 0.0852 |

CI = confidence interval; LS mean = least square mean; N = number of non-missing values; OPC = opicapone.

a. ON-time without troublesome dyskinesias=ON-time with non-troublesome dyskinesias + ON-time without dyskinesias

**Table 3 – OFF-time responder rates at endpoint**

| Response type | Placebo (N=121) | Entacapone (N=122) | OPC 5 mg (N=122) | OPC 25 mg (N=119) | OPC 50 mg (N=115) |
|---|---|---|---|---|---|
| **Study 1** | | | | | |
| **OFF-time reduction** | | | | | |
| Responders, n (%) | 55 (45.5) | 66 (54.1) | 64 (52.5) | 66 (55.5) | 75 (65.2) |
| **Difference to placebo** | | | | | |
| p-value | -- | 0.1845 | 0.2851 | 0.1176 | 0.0036 |
| (95% CI) | | (-0.039; 0.209) | (-0.056; 0.193) | (-0.025; 0.229) | (0.065; 0.316) |
| **Study 2** | | | | | |
| **OFF-time reduction** | | | | | |
| Responders, n (%) | 65 (47.8) | NA | NA | 74 (59.2) | 89 (59.3) |
| **Difference to placebo** | | | | | |
| p-value | -- | -- | -- | 0.0506 | 0.0470 |
| (95% CI) | | | | (0.001; 0.242) | (0.003; 0.232) |

CI = confidence interval; N = total number of patients; n = number of patients with available information; NA = not applicable; OPC = opicapone

*Note: A responder was a patient who had a reduction of at least 1 hour in absolute OFF-time (OFF-time responder)*

The results of the open-label (OL) extension studies of 1 year duration in 862 patients who continued treatment from the double-blind studies (Study 1-OL and Study 2-OL) indicated maintenance of the effect achieved during DB study periods. In the OL studies, all patients began at a dose of 25 mg opicapone for the first week (7 days), regardless of their prior treatment in the double-blind period. If end-of-dose motor fluctuations were not sufficiently controlled and tolerability allowed, the opicapone

dose could be increased to 50 mg. If unacceptable dopaminergic adverse events were seen, the levodopa dose was to be adjusted. If not sufficient to manage the adverse events, the opicapone dose could then be down titrated. For other adverse events, the levodopa and/or opicapone dose could be adjusted.

## 5.2 Pharmacokinetic properties

Absorption

Opicapone presents a low absorption (~20%). Pharmacokinetic results showed that opicapone is rapidly absorbed, with a $t_{max}$ of 1.0 h to 2.5 h following once-daily multiple-dose administration up to 50 mg opicapone.

Distribution

*In vitro* studies over the opicapone concentration range 0.3 to 30 mcg/mL showed that binding of $^{14}$C-opicapone to human plasma proteins is high (99.9%) and concentration-independent. The binding of $^{14}$C-opicapone to plasma proteins was unaffected by the presence of warfarin, diazepam, digoxin and tolbutamide, and the binding of $^{14}$C-warfarin, 2-$^{14}$C-diazepam, $^{3}$H-digoxin and $^{14}$C-tolbutamide was unaffected by the presence of opicapone and opicapone sulphate, the major human metabolite.

After oral administration, the apparent volume of distribution of opicapone at a dose of 50 mg was 29 L with an inter-subject variability of 36%.

Biotransformation

Sulphation of opicapone appears to be the major metabolic pathway in humans, yielding the inactive opicapone sulphate metabolite. Other metabolic pathways include glucuronidation, methylation and reduction.

The most abundant peaks in plasma after a single-dose of 100 mg $^{14}$C-opicapone are metabolites BIA 9-1103 (sulphate) and BIA 9-1104 (methylated), 67.1 and 20.5% of radioactive AUC respectively. Other metabolites were not found in quantifiable concentrations in the majority of plasma samples collected during a clinical mass balance study.

The reduced metabolite of opicapone (found to be active in non-clinical studies) is a minor metabolite in human plasma and represented less than 10% of total systemic exposure to opicapone.

In *in vitro* studies in human hepatic microsomes, minor inhibition of CYP1A2 and CYP2B6 was observed. All reductions in activity essentially occurred at the highest concentration of opicapone (10 mcg/mL).

An *in vitro* study showed opicapone inhibited CYP2C8 activity. A single dose study with opicapone 25 mg showed an average increase of 30 % in the rate, but not the extent, of exposure to repaglinide (a CYP2C8 substrate), when the two drugs were co-administered. A second study conducted showed that, at steady state, opicapone 50 mg had no effect on repaglinide systemic exposure.

Opicapone reduced CYP2C9 activity through competitive / mixed type mode of inhibition. However, clinical interaction studies conducted with warfarin showed no effect of opicapone on the pharmacodynamics of warfarin, a substrate of CYP2C9.

Elimination

In healthy subjects, the opicapone elimination half-life ($t_{1/2}$) was 0.7 h to 3.2 h following once-daily multiple-dose administration up to 50 mg opicapone.

Following once-daily multiple oral doses of opicapone in the dose range of 5 to 50 mg, opicapone sulphate presented a long terminal phase with elimination half-life values ranging from 94 h to 122 h and, as a consequence of this long terminal elimination half-life, opicapone sulphate presented a high accumulation ratio in plasma, with values close of up to 6.6.

After oral administration, the apparent total body clearance of opicapone at a dose of 50 mg was 22 L/h, with an inter-subject variability of 45%.

Following administration of a single oral dose of $^{14}$C-opicapone, the main excretion route of opicapone and its metabolites was faeces, accounting for 58.5% to 76.8% of the administered radioactivity (mean 67.2%). The remainder of the radioactivity was excreted in urine (mean 12.8%) and via expired air (mean 15.9%). In urine, the primary metabolite was the glucuronide metabolite of opicapone, while parent drug and other metabolites were generally below the limit of quantification. Overall, it can be concluded that the kidney is not the primary route of excretion. Therefore, it can be presumed that opicapone and its metabolites are mainly excreted in the faeces.

Linearity/non-linearity

Opicapone exposure increased in a dose proportional manner following once-daily multiple dose administration up to 50 mg opicapone.

Transporters

*Effect of transporters on opicapone*
*In vitro* studies have shown that opicapone is not transported by OATP1B1, but is transported by OATP1B3, and efflux transported by P-gp and BCRP. BIA 9-1103, its major metabolite, was transported by OATP1B1 and OATP1B3, and efflux transported by BCRP, but is not a substrate for the P-gp/MDR1 efflux transporter.

*Effect of opicapone on transporters*
At clinically relevant concentrations, opicapone is not expected to inhibit OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, BCRP, P-gp/MDR1, BSEP, MATE1 and MATE2-K transporters as suggested by *in vitro* and *in vivo* studies.

Elderly (≥ 65 years old)

The pharmacokinetics of opicapone was evaluated in elderly subjects (aged 65-78 years old) after 7-day multiple-dose administration of 30 mg. An increase in both the rate and extent of systemic exposure was observed for the elderly population when compared to the young population. The S-COMT activity inhibition was significantly increased in elderly subjects. The magnitude of this effect is not considered to be of clinical relevance.

Weight

There is no relationship between exposure of opicapone and body weight over the range of 40-100 kg.

Hepatic impairment

There is limited clinical experience in patients with moderate hepatic impairment (Child-Pugh Class B). The pharmacokinetics of opicapone was evaluated in healthy subjects and moderate chronic hepatic impaired patients after administration of a single-dose of 50 mg. The bioavailability of opicapone was significantly higher in patients with moderate chronic hepatic impairment and no safety concerns were observed. However, as opicapone is to be used as adjunctive levodopa-therapy, dose adjustments may be considered based on a potentially enhanced levodopa dopaminergic response and associated tolerability. There is no clinical experience in patients with severe hepatic impairment (Child-Pugh Class C) (see section 4.2).

Renal impairment

The pharmacokinetics of opicapone was not directly evaluated in subjects with chronic renal impairment. However, an evaluation with 50 mg opicapone was performed in subjects included in both phase 3 studies with GFR/1.73 $m^2$ <60 mL/min (i.e. moderately decreased renal elimination capacity), and using pooled BIA 9-1103 data (major metabolite of opicapone). BIA 9-1103 plasma levels were not affected in patients with chronic renal impairment, and as such, no dose adjustment needs to be considered.

### 5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In rats, opicapone did not affect male and female fertility or prenatal development at exposure levels 22 times the therapeutic exposure in humans. In pregnant rabbits, opicapone was less well tolerated resulting in maximum systemic exposure levels around or below the therapeutic range. Although embryo-foetal development was not negatively influenced in rabbits, the study is not considered predictive for human risk assessment.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Capsule content
Lactose monohydrate
Sodium starch glycolate, Type A
Maize starch, pregelatinized
Magnesium stearate

Capsule shell
Gelatin
Indigo carmine aluminium lake (E 132)
Erythrosine (E 127)
Titanium dioxide (E 171)

Printing ink
Shellac
Titanium dioxide (E 171)
Propylene glycol
Ammonia solution, concentrated
Simeticone

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

### 6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Store in the original blister in order to protect from moisture.

### 6.5 Nature and contents of container

OPA/Al/PVC//Al blisters containing 10, 30 or 90 capsules

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

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

## 7. MANUFACTURER

Bial - Portela & Cª, S.A.
À Av. da Siderurgia Nacional
4745-457 S. Mamede do Coronado
Portugal

## 8. REGISTRATION HOLDER

Truemed Ltd.,
10 Beni Gaon St., Poleg Industrial Park,
P.O.B 8105, Netanya 4250499

## 9. REGISTRATION NUMBER

170-17-37801

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