# 歐健體斯膠囊50毫克

## Ongentys 50 mg Hard Capsules

衛部藥輸字第027952號
本藥須由醫師處方使用

【成分】
主成分： 每粒膠囊含opicapone 50 mg。
賦形劑： Lactose monohydrate、Sodium starch glycolate, Type A、Maize starch, pregelatinized、Magnesium stearate。
膠囊成分： Gelatin、Indigo carmine aluminium lake (E132)、Erythrosine (E127)、Titanium dioxide (E171)。
印刷油墨： Shellac、Titanium dioxide (E171)、Propylene glycol、Ammonia、Simethicone。

【劑型】
硬膠囊劑(膠囊劑)。
大小約19 mm的深藍色1號膠囊，膠囊帽上印有「OPC 50」、膠囊體上印有「Bial」標誌。

【適應症】
表現藥效終期運動功能波動現象(end-of-dose motor fluctuations)，以左多巴/多巴脫羧基酶抑制劑(levodopa/DOPA decarboxylase inhibitors)無法達到穩定治療效果之巴金森氏症成人病人的輔助治療。

【用法用量】
用法用量
Opicapone的建議劑量為50 mg。
本品一天一次，睡前服用。與服用levodopa類製劑前、後至少須相隔1小時。
在使用本品前、後一小時內，病人不可使用食物。
*抗巴金森氏症藥物劑量的調整*
Opicapone會加強levodopa的作用。因此，在開始使用opicapone治療的最初幾天至幾週，需要調整levodopa的用量。(參閱【警語與注意事項】欄)
*錯過劑量*
如果錯過了一次劑量，下一個劑量按時服用即可。病人請勿為了補服錯過劑量而服用多倍劑量。
特殊族群
老年人：
老年患者無需調整本品劑量。(參閱【藥物動力學】欄)
85歲以上的病人須小心使用，因這個年齡層的使用經驗有限。
腎功能不全患者：
在opicapone的體內清除上，腎排除為次要的排除途徑，ESRD患者(CLcr < 15 mL/min)應避免使用本品。輕度、中度與重度腎功能不全患者可無需調整本品劑量；然而，因仍有暴露量增加的可能，故需要隨時監測重度腎功能不全者副作用發生的狀況。若患者發生耐受性不佳的狀況，應停止繼續使用本品。(參閱【藥物動力學】欄)
肝功能不全患者：
輕度肝功能不全(Child-Pugh Class A)病人無需調整本品劑量。
中度肝功能不全(Child-Pugh Class B)病人不建議使用本品。(參閱【藥物動力學】欄)
沒有重度肝功能不全(Child-Pugh Class C)病人的臨床使用經驗；因此，本品不建議用於此類病人。(參閱【藥物動力學】欄)
在樞紐試驗中AST或ALT大於正常值上限2倍之受試者被排除，因此這些群組使用本品之安全性未知。
兒童：
在患有巴金森氏症和運動功能波動的兒童族群，本品沒有相關使用經驗。
投與方式
口服使用，必須整顆與水吞服。

**【禁忌】**

- **對本品主成分或任一賦形劑過敏者。**
- **患有嗜鉻細胞瘤(pheochromocytoma)、副神經節瘤(paraganglioma)或其他兒茶酚胺分泌腫瘤(catecholamine secreting neoplasms)。**
- **曾有抗精神藥物惡性症候群(neuroleptic malignant syndrome)和/或非外傷性橫紋肌溶解(non-traumatic rhabdomyolysis)病史者。**
- **與非用於治療巴金森氏症的單胺氧化酶(MAO-A和MAO-B)抑制劑併用(如：phenelzine、tranylcypromine和moclobemide)。(參閱【藥物交互作用】欄)**

**【警語與注意事項】**

**抗巴金森氏症藥物劑量的調整**

**本品是levodopa治療的輔助劑，因此，使用本品時也須考慮到levodopa治療的注意事項。Opicapone會加強levodopa的作用。為降低與levodopa相關的多巴胺性不良反應(例如：異動症**

(dyskinesia)、幻覺、噁心、嘔吐和姿勢性低血壓)，常需要調整levodopa每日劑量。根據病人臨床狀況，可在開始使用本品的最初幾天到最初幾週內延長levodopa的給藥間隔時間和/或降低levodopa每次的用量。(參閱【用法用量】欄)

當停止使用本品時，需調整其他抗巴金森氏症藥品之治療劑量，特別是levodopa，以便達到足以控制症狀的治療濃度。

精神疾病

病人與其照護者都應該了解接受多巴胺作用劑(dopamine agonists)和/或其他多巴胺類藥品治療(dopaminergic treatments)的病人可能會出現衝動控制障礙，包括病態性賭博、性欲增強、性欲亢進、強迫性消費或購物、暴食及強迫性進食。須定期監測病人是否出現衝動控制障礙，若出現該等症狀，建議檢視治療方法。

其他

曾有使用兒茶酚-氧-甲基轉移酶(COMT)抑制劑造成肝臟酵素增加的案例。病人若在很短時間內發生漸進性厭食、無力和體重減輕，應考慮接受包括肝功能在內的一般醫學檢查。

對賦形劑不耐受症

本品含乳糖。半乳糖不耐症、Lapp乳糖酵素缺乏症或葡萄糖-半乳糖吸收不良等罕見遺傳性疾病的病人不可服用本品。

【藥物交互作用】

單胺氧化酶抑制劑 (MAOI)

Opicapone與MAOI併用可能導致兒茶酚胺的大部分代謝途徑被抑制。因此，禁止與非用於治療巴金森氏症的MAOI(如：phenelzine、tranylcypromine和moclobemide)併用。

Opicapone可與用於治療巴金森氏症的MAOI併用，如：rasagiline (每日劑量最多1 mg)、selegline (口服劑型每日劑量最多10 mg或口腔黏膜吸收劑型每日劑量最多1.25 mg)。(參閱【禁忌】欄)

Opicapone未有與MAO-B抑制劑(safinamide)併用的經驗。

經由COMT代謝的藥物

Opicapone會干擾須經COMT代謝之含兒茶酚基結構藥物(如：rimiterole、isoprenaline、adrenaline、noradrenaline、dopamine、dopexamine或dobutamine)的代謝並加強這些藥物的作用。Opicapone與這些藥物併用時應嚴密監測病人狀況。

三環抗憂鬱劑與正腎上腺素再吸收抑制劑

Opicapone未有與三環抗憂鬱劑和正腎上腺素再吸收抑制劑(如：venlafazine、maprotiline和desipramine)併用的經驗。

CYP2C8和OATP1B1受質

體外試驗顯示，opicapone是弱效的CYP2C8和OATP1B1抑制劑。在一項以健康受試者進行的藥物交互作用試驗顯示，多劑量給予opicapone 50 mg後，並不會對repaglinide 0.5 mg的暴露量造成影響。

【生育力、懷孕與授乳】

懷孕

無孕婦使用opicapone的數據，或其資料有限。未有足夠的動物生殖毒性研究(參閱【臨床前安全性資料】欄)。故本品不建議在懷孕期間以及未採取避孕措施之育齡婦女使用。

授乳

尚不清楚opicapone或其代謝物是否會分泌至母乳中，無法排除對新生兒/嬰兒的影響。故服用本品治療期間應停止授乳。

生育力

尚未有opicapone對人類生育能力影響的研究。在動物研究並未發現opicapone對生育能力的有害影響(參閱【臨床前安全性資料】欄)。

【對駕駛與操作機器能力的影響】

Opicapone加上levodopa可能會嚴重影響駕駛與操作機器的能力。Opicapone與levodopa併用時可能引起暈眩、姿勢性低血壓、嗜睡，或日常活動時忽然睡著。因此，駕駛或操作機器時應特別小心。

【不良反應】

安全性資料摘要

**最常被通報的不良反應是神經系統疾病。最常被通報因治療引起的不良反應為異動症(17.7%)。**

**不良反應列表**

**下表1列出依器官系統分類之所有不良反應與其發生頻率。**

**發生頻率之定義：**

**非常常見（≥ 1/10）；常見（≥ 1/100 ~ < 1/10）；不常見（≥ 1/1,000 ~ < 1/100）；罕見（≥ 1/10,000 ~ < 1/1,000）；非常罕見（< 1/10,000）；以及發生頻率未知(無法從現有資料估算)。**

**表 1 – 安慰劑對照之第三期臨床試驗通報的不良反應頻率(MedDRA)**

| 器官系統分類 | 非常常見 | 常見 | 不常見 |
|---|---|---|---|
| 代謝和營養異常 | | | 食慾降低、高三酸甘油酯血症 |
| 精神異常 | | 異常夢境、幻覺、視幻覺、失眠 | 焦慮、憂鬱、聽幻覺、夢魘、睡眠障礙 |
| 神經系統異常 | 異動症(dyskinesia) | 頭暈、頭痛、嗜睡 | 味覺障礙(dysgeusia)、運動機能亢進(hyperkinesia)、昏厥 |
| 眼睛異常 | | | 乾眼 |
| 耳朵及迷路異常 | | | 耳塞(ear congestion) |
| 心臟異常 | | | 心悸 |
| 血管異常 | | 姿勢性低血壓 | 高血壓、低血壓 |
| 呼吸、胸腔及縱膈異常 | | | 呼吸困難 |
| 腸胃異常 | | 便祕、口乾、嘔吐 | 腹脹、腹痛、上腹痛、消化不良 |
| 肌肉骨骼及結締組織異常 | | 肌肉痙攣 | 肌肉抽搐、肌肉骨骼僵硬、肌肉疼痛、四肢疼痛 |
| 腎臟及泌尿系統異常 | | | 尿液變色、夜尿 |
| 各類檢查 | | 血中肌酐磷酸酶(blood creatine phosphokinase)濃度升高 | 體重下降 |

**疑似不良反應的通報**

**藥品核可上市後通報疑似不良反應非常重要，如此可以持續對藥品進行風險效益的監測。醫療專業人員須向全國藥物不良反應通報中心通報任何疑似不良反應。**

**【藥物過量】**

**目前無特定的解毒藥。應適當地給予症狀和支持性治療。可考慮藉由洗胃和/或給予活性炭去除opicapone。**

【藥效學】

藥理治療分類：抗巴金森氏症藥、其它多巴胺類藥。

ATC code：N04BX04。

作用機轉

Opicapone是一種作用於周邊且具有選擇性和可逆性的兒茶酚-氧-甲基轉移酶(COMT)抑制劑，在活體內親和力高(達亞-皮莫耳濃度)，有緩慢且複雜的解離速率常數和長作用時間(>24小時)。

若併用DOPA decarboxylase inhibitor (DDCI)，COMT會成為levodopa的主要代謝酵素，會催化腦內和周邊的levodopa代謝成3-O-methyldopa (3-OMD)。對服用levodopa與周邊DDCI(如:carbidopa或benserazide)的患者，opicapone會增加levodopa血中濃度，進而改善levodopa的臨床使用效果。

藥效動力學

健康受試者在服用opicapone 50 mg後有明顯(>90%)且長效(>24小時)的COMT抑制作用。

在穩定狀態下，和安慰劑相比，服用opicapone 50 mg 12小時後，單次口服levodopa/carbidopa 100/25 mg或levodopa/benserazide 100/25 mg，opicapone會顯著增加levodopa的全身暴露量(約2倍)。

臨床效用與安全性

在兩項第3期、隨機分配、雙盲、安慰劑和活性對照藥物(僅試驗1)試驗中，針對1027位以levodopa/DDCI(單獨或併用其他抗巴金森氏症藥物)治療具有藥效終期運動功能波動現象(end-of-dose moto fluctuations)的巴金森氏症成人病人長達15週，證實了opicapone作為輔助治療的有效性和安全性。此兩項試驗所篩選的治療組平均年齡相似，均在61.5~65.3歲之間。患者在ON時期的疾病嚴重度達modified Hoehn and Yahr第1~3級，每日服用3~8次levodopa/DDCI治療劑量且每日平均OFF時間至少1.5小時。此兩項試驗中，共783位患者分別服用opicapone 25 mg、opicapone 50 mg或是安慰劑。在試驗1中，122位患者服用opicapone 5 mg而122位患者服用entacapone 200 mg (活性對照藥物)。此兩項樞紐試驗的大多數患者都是服用速放劑型的levodopa/DDCI。在第3期試驗

的合併分析發現有共60位患者主要服用控釋劑型的levodopa(即levodopa/DDCI處方>50%)，其中48位僅單一接受控釋製劑levodopa的治療。雖然沒有證據顯示使用控釋劑型的levodopa會影響opicapone的效用或安全性，但這類製劑的使用經驗是有限的。
在雙盲治療期間，opicapone表現出優於安慰劑的臨床療效，結果可見於兩項樞紐試驗的主要療效指標(即「表2:減少的OFF時間」、「表3:OFF時間治療有反應者的比例(患者從基準點到結束點的OFF時間至少減少1小時)」)和根據巴金森患者日記數據所衍生的大部分次要療效指標。

在entacapone組中，從基準點到結束點的平均絕對OFF時間減少96.3分鐘。在試驗1中，entacapone相對於安慰劑，OFF時間平均減少40.3分鐘；在依計畫書群體中，opicapone 50 mg相對於entacapone，OFF時間平均減少26.2分鐘，且證實opicapone 50 mg效用不劣於entacapone (95%信賴區間：-63.8, 11.4)。

**表 2 – 從基準點到結束點的絕對 OFF 時間與 ON 時間的變化 (分鐘) (全分析群體)**

| | Placebo | Entacapone | OPC 5 mg | OPC 25 mg | OPC 50 mg |
|---|---|---|---|---|---|
| **試驗 1** | | | | | |
| **OFF 時間的變化** | | | | | |
| N | 120 | 120 | 119 | 116 | 115 |
| LS mean | -56.0 | -96.3 | -91.3 | -85.9 | -116.8 |
| 與安慰劑的差異 | -- | -40.3 | -35.2 | -29.9 | -60.8 |
| 95% CI | -- | -76.2, -4.3 | -71.4, 0.9 | -66.3, 6.5 | -97.2, -24.4 |
| p-value | -- | -- | 0.0558 | 0.0796 | 0.0015 |
| **無惱人異動症之整個 ON 時間的變化 [a]** | | | | | |
| N | 120 | 120 | 119 | 116 | 115 |
| LS mean | 46.5 | 94.1 | 85.9 | 84.7 | 109.1 |
| 與安慰劑的差異 | -- | 47.6 | 39.4 | 38.2 | 62.6 |
| 95% CI | -- | 9.3, 86.0 | 1.0, 77.8 | -0.6, 77.0 | 23.8, 101.4 |
| p-value | -- | 0.0150 | 0.0442 | 0.0535 | 0.0016 |
| **惱人異動症之整個 ON 時間的變化** | | | | | |
| N | 120 | 120 | 119 | 116 | 115 |
| LS mean | 0.6 | 5.6 | 4.4 | 1.4 | 9.9 |
| 與安慰劑的差異 | -- | 5.0 | 3.8 | 0.8 | 9.3 |
| 95% CI | -- | -11.2, 21.2 | -12.4, 20.0 | -15.5, 17.2 | -7.0, 25.7 |
| p-value | -- | 0.5436 | 0.6436 | 0.9219 | 0.2635 |
| **試驗 2** | | | | | |
| **OFF 時間的變化** | | | | | |
| N | 135 | NA | NA | 125 | 147 |
| LS mean | -64.5 | -- | -- | -101.7 | -118.8 |
| 與安慰劑的差異 | -- | -- | -- | -37.2 | -54.3 |
| 95% CI | -- | -- | -- | -80.8, 6.4 | -96.2, -12.4 |
| P-value | -- | -- | -- | 0.1061 | 0.0081 |
| **無惱人異動症之整個 ON 時間的變化 [a]** | | | | | |
| N | 135 | NA | NA | 125 | 147 |
| LS mean | 48.2 | -- | -- | 84.1 | 85.6 |
| 與安慰劑的差異 | -- | -- | -- | 36.0 | 37.4 |
| 95% CI | -- | -- | -- | -5.6, 77.5 | -2.4, 77.2 |
| P-value | -- | -- | -- | 0.0897 | 0.0651 |
| **惱人異動症之整個 ON 時間的變化** | | | | | |
| N | 135 | NA | NA | 125 | 147 |
| LS mean | 11.2 | -- | -- | 19.4 | 25.6 |
| 與安慰劑的差異 | -- | -- | -- | 8.2 | 14.4 |
| 95% CI | -- | -- | -- | -15.1, 31.5 | -8.0, 36.8 |
| P-value | -- | -- | -- | 0.4898 | 0.2060 |

CI = 信賴區間；LS mean = 最小平方平均；
NA = 不適用；OPC = opicapone
a. 無惱人異動症之整個 ON 時間 = 非惱人異動症之 ON 時間 + 無異動症之 ON 時間

**表 3 – 結束點的 OFF 時間治療有反應者的比例 (全分析群體)**

| | Placebo | Entacapone | OPC 5 mg | OPC 25 mg | OPC 50 mg |
|---|---|---|---|---|---|
| **試驗 1** | | | | | |
| **減少的 OFF 時間** | | | | | |
| N | 120 | 120 | 119 | 116 | 115 |
| 治療有反應者，n (%) | 57 (47.5%) | 70 (58.3%) | 71 (59.7%) | 70 (60.3%) | 80 (69.6%) |
| 與安慰劑的差異 | | | | | |
| P-value | -- | 0.0938 | 0.0650 | 0.0464 | 0.0011 |
| **試驗 2** | | | | | |
| **減少的 OFF 時間** | | | | | |
| N | 135 | NA | NA | 125 | 147 |
| 治療有反應者，n (%) | 68 (50.4%) | -- | -- | 76 (62.4%) | 97 (66.0%) |
| 與安慰劑的差異 | | | | | |
| P-value | -- | -- | -- | 0.0405 | 0.0088 |

CI = 信賴區間；N = 患者人數；n = 有可分析數據之患者人數；
NA = 不適用；OPC = opicapone
注意: 治療有反應者(OFF-time responder)是指患者 OFF 時間至少減少 1 小時

自雙盲試驗後繼續接受治療的 862 位患者之持續 1 年的開放式延伸研究(試驗 1-OL 和試驗 2-OL)顯示 opicapone 維持了在雙盲試驗期間所達到的療效。在開放式研究中，所有患者無論其在雙盲試驗期間所接受的治療為何，在第一週(前 7 天)的起始劑量均為 opicapone 25 mg。若無法有效控制藥效終期運動功能波動現象且在耐受情況下，則可以將 opicapone 的劑量增加至 50 mg。若出現不可接受的多巴胺類不良事件，則調整 levodopa 的劑量。若此不良事件無法獲得有效處理，才可降低 opicapone 的劑量。對於其他不良事件，則可以調整 levodopa 和/或 opicapone 劑量。

兒童族群

在患有巴金森氏症及運動功能波動的兒童族群，本品沒有相關使用經驗。

【藥物動力學】

吸收

給與單劑 opicapone 50 mg 後，opicapone 達到最高血中濃度的時間($T_{max}$)為 2.0 (1.0~4.0) 小時。

食物效應

在使用中脂/中度卡路里後，opicapone 的最高血中濃度降低了 62%，AUC 降低了 31%，$T_{max}$ 則延後了 4 小時。在試驗 1，本品為與食物或不與食物併用。在試驗 2，本品則是與食物間隔一小時使用。

分佈

體外研究顯示，在濃度範圍 0.3~30 mcg/mL 下，$^{14}$C-opicapone 與人類血漿蛋白結合率很高(99.9%)且與濃度無關。$^{14}$C-opicapone 與血漿蛋白的結合不會受到 warfarin、diazepam、digoxin 和 tolbutamide 存在的影響，且 $^{14}$C-warfarin、2-$^{14}$C-diazepam、$^{3}$H-digoxin 和 $^{14}$C-tolbutamide 的結合也不受 opicapone 及其人體主要代謝物(opicapone sulphate)存在的影響。

口服 opicapone 50 mg 後擬似分佈體積為 29L 且不同個體間變異為 36%。

生物轉化作用

硫酸化(sulphation) opicapone 似乎是人體內主要的代謝途徑，且會產生無活性的 opicapone sulphate 代謝物。其他代謝途徑包括葡萄醣醛酸化(glucuronidation)、甲基化(methylation)和還原反應。

投與單劑量 $^{14}$C-opicapone 100 mg 後，代謝物 BIA 9-1103(硫酸鹽)和 BIA 9-1104(甲基化)有最高血漿濃度，其放射活性 AUC 值分別為 67.1 和 20.5%。在質量平衡試驗期間，採集的大多數血漿樣品中未發現其他可量化濃度的代謝物。

在人類血漿中，opicapone 的還原代謝物(非臨床試驗中顯示其具有活性)為次要的代謝物，占 opicapone 全身暴露量不到 10%。

在人類肝臟微粒體的體外試驗中，觀察到代謝酵素 CYP1A2 和 CYP2B6 受到輕微抑制。所有代謝酵素活性的降低是發生在 opicapone 最高濃度時(10 mcg/mL)。

體外試驗顯示 opicapone 會抑制 CYP2C8 活性。在一單劑量 opicapone 25 mg 併用 rapaglinide 的研究顯示，rapaglinide (CYP2C8 受質)的吸收速率平均增加 30%，但不影響其暴露量。另一研究顯示，在穩定狀態下，opicapone 50 mg 對 rapaglinide 的全身暴露量並無影響。Opicapone 藉由競爭性/混合型抑制模式降低 CYP2C9 活性。然而，和 warfarin 的臨床交互作用研究顯示，opicapone 不影響 warfarin (CYP2C9 受質)的藥效學。

排除

Opicapone 的平均排除半衰期($t_{1/2}$)約 1-2 小時。

單劑量給與健康受試者放射性標定之 opicapone 100 mg (2 倍建議劑量)後，約 70%的投與劑量自糞便回收(其中 22%為原型藥)，20%由呼出氣體回收且 5%自尿液回收(原型藥<1%)。

線性/非線性

在 25 mg ~ 50 mg 的劑量範圍內，opicapone 具線性藥物動力學特性。

轉運蛋白

*轉運蛋白對 opicapone 的作用*

體外研究顯示 opicapone 非經有機陰離子轉運蛋白 OATP1B1 運輸，而是經 OATP1B3 運輸，藉由 p-醣蛋白(P-gp)和乳癌抗藥蛋白(BCRP)排出體外。其主要代謝物(BIA 9-1103)則是經由 OATP1B1 與 OATP1B3 運輸，且藉由 BCRP 排出體外，但並非 p-醣蛋白(P-gp)/多重抗藥基因(MDR1)轉運蛋白的受質。

*Opicapone 對轉運蛋白的作用*

根據體外和體內的研究顯示，在臨床相關濃度下，opicapone 不預期會抑制 OAT1、OAT3、OATP1B1、OATP1B3、OCT1、OCT2、BCRP、P-gp/MDR1、BSEP、MATE1 和 MATE2-K 轉運蛋白。

老年人 (≥ 65 歲)

老年受試者(年齡 65~78 歲)在 7 天多劑量給與 opicapone 30 mg 後的藥動學研究顯示，相較於年輕族群，老年受試者的全身暴露量之吸收速率和吸收程度都會增加。老年受試者的 S-COMT 活性抑制有顯著增加，但此影響程度不被認為具有臨床意義。

肝功能不全

中度肝功能不全患者(Child-Pugh Class B)的臨床使用經驗有限。

健康受試者和中度肝功能不全患者在服用單一劑量 opicapone 50 mg 後的藥動學研究顯示，opicapone 的暴露量在中度肝功能不全患者中明顯增加($C_{max}$ 增加 89%，AUC 增加 84%)。尚未在重度肝功能不全患者(Child-Pugh Class C)中進行過研究。(參閱【用法用量】欄)

腎功能不全

沒有直接在慢性腎功能不全患者進行過 opicapone 的藥動學研究。針對以兩個第三期臨床試驗中服用 opicapone 50 mg 之中度腎功能不全受試者(GFR/1.73m$^2$ < 60 mL/min)的合併分析研究，結果

顯示中度腎功能不全患者的 BIA 9-1103 (opicapone 的主要代謝物)的血中濃度未受影響。尚未在重度腎功能不全患者或 ESRD (CLcr < 30 mL/min)患者中進行過研究。

【臨床前安全性資料】
根據安全性、藥理、重複劑量毒性、基因毒性和致癌潛在性等常規非臨床研究顯示，opicapone對人類並無特定的危害性。
在人類治療劑量22倍的暴露量下，opicapone並不影響雄性和雌性大鼠的生育能力或胚胎發育。懷孕的兔子，因耐受性較差，故其最大全身暴露量是在治療範圍之內或之下。雖然對兔子的胚胎-胎兒發育沒有負面影響，但該研究不認為可用於預測人類風險評估。

【儲存條件】
低於30ºC儲存。需存放於原鋁箔包裝內以避免潮解。

【包裝】
鋁箔盒裝。

【廢棄物處理】
任何未使用之藥品或醫療廢棄物應依醫療廢棄物處理之規定處理。

國外許可證持有者/製造廠：Bial - Portela & Companhia, S.A.
地址：Av. da Siderurgia Nacional Apartado 19 S. Mamede do Coronado 4745-457 Portugal
藥商：台灣美強股份有限公司
地址：台北市南京東路二段66號4樓

IFU-Ongentys-2010-V01
TFDA labeling approved

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Ongentys 50 mg hard capsules

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

*Dose adjustments of antiparkinsonian therapy*
Opicapone enhances the effects of levodopa. Hence, it is often necessary to adjust levodopa dosage within the first days to first weeks after initiating the treatment with opicapone (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, Ongentys is not recommended in these patients (see section 5.2).

*Paediatric population*
There is no relevant use of Ongentys 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 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. 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, according to the clinical condition of the patient (see section 4.2).

If Ongentys 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.

Intolerance to excipients

Ongentys contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Ongentys.

## 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.
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 (see section 4.3).

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.

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.

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.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

It is unknown whether opicapone or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Ongentys.

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, Headache, Somnolence | Dysgeusia, Hyperkinesia, Syncope |
| **Eye disorders** | | | Dry eye |
| **Ear and labyrinth disorders** | | | Ear congestion |

| | | | |
|---|---|---|---|
| **Cardiac disorders** | | | Palpitations |
| **Vascular disorders** | | Orthostatic Hypotension | Hypertension, Hypotension |
| **Respiratory, thoracic and mediastinal disorders** | | | Dyspnoea |
| **Gastrointestinal disorders** | | Constipation, Dry mouth, Vomiting | Abdominal distention, Abdominal pain, Abdominal pain upper, Dyspepsia |
| **Musculoskeletal and connective tissue disorders** | | Muscle spasms | Muscle twitching, Musculoskeletal stiffness, Myalgia, Pain in extremity |
| **Renal and urinary disorders** | | | Chromaturia, Nocturia |
| **Investigations** | | Blood creatine phosphokinase increased | Weight decreased |

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

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: [not yet assigned]

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, opicapone 50 mg 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 drugs) 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 opicapone 5 mg and 122 patients were treated with entacapone 200 mg (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 |
| 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** | | | | |

| Treatment | N | LS mean | 95% CI | p-value |
|---|---|---|---|---|
| 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.

Paediatric population

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

## 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 (E132)
Erythrosine (E127)
Titanium dioxide (E171)

Printing ink

Shellac, titanium dioxide (E171), propylene glycol, ammonia, simethicone

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

HDPE bottles: 3 years
Blisters: 5 years

### 6.4 Special precautions for storage

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

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

HDPE bottles: Keep the bottle tightly closed in order to protect from moisture.

### 6.5 Nature and contents of container

White high density polyethylene (HDPE) bottles with polypropylene (PP) child resistant closures containing 10, 30 or 90 capsules.

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. MARKETING AUTHORISATION HOLDER

Bial - Portela & Cª, S.A.
À Av. da Siderurgia Nacional
4745-457 S. Mamede do Coronado
Portugal
Tel:+351 22 986 61 00
Fax: +351 22 986 61 90
e-mail: info@bial.com

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1066/002-007

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 June 2016

## 10. DATE OF REVISION OF THE TEXT

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