1.5 毫克 衛署藥輸字第 025260 號 完整處方資訊 5.7 橫紋肌溶解症(Rhabdomyolysis 1. 適應症與用途 在速放劑型 pramipexole 的臨床開發計畫中,有一名 49 歲的末期帕金森氏症男性病。 治療巴金森氏症的徵候及症狀。 發生橫紋肌溶解症。該病人住院時肌酸磷酸激酶(CPK)升高(10,631 IU/L),其症狀 請告知病人,若出現任何不明原因的肌肉疼痛、觸痛或無力感覺,就必須就醫,因為這 2.1 一般用藥考量 MIRAPEX PR 錠劑為一天口服一次,空腹用藥或與食物併用均可。 些都可能是橫紋肌溶解症的症狀。 MIRAPEX PR 錠劑必須整顆吞服,不可嚼碎、壓碎或切割。 5.8 白化大鼠的視網膜變化 若 MIRAPEX PR 錠劑的治療中斷過久,就可能必須重新調整治療劑量。 2.2 在帕金森氏症病人的用藥方法 在一項為期兩年的致癌性研究中,觀察到白化大鼠(albino rats)的視網膜出現病理性 初始劑量為 0.375 mg,一天一次。可根據療效與耐受性,逐漸調高劑量,但調整變化(感光細胞的退化與喪失)。雖然在接受 2 年治療的有色大鼠並未發現視網膜退化頻率不可多於每 5 至 7 天一次 (not more frequently than every 5 to 7 days),首但相較於對照組,這些藥物治療組大鼠視網膜外核層變薄的幅度稍大。 先調至一天 0.75 mg,然後每次增加 0.75 mg,最多增至一天 4.5 mg(最大建議 對白化小鼠、猴子與迷你豬的視網膜進行評估時,並未發現類似的變化。雖然此作用對 人體的可能重要性尚未確立,但不能忽視,因為這可能為一種普遍存在脊椎動物的機制 在臨床試驗中,劑量從一天 0.375 mg 開始,再依個別病人的治療反應與耐受性 逐漸調升劑量。從未在臨床試驗中研究過高於一天 4.5 mg 的劑量。每次調升劑 量後,均應至少隔 5 天或更久評估一次病人的治療反應與耐受性。 精神疾病病人僅應於潛在利益大於風險的情況下,接受多巴胺致效劑治療。不建議將抗 你中斷 MIRAPEX PR 治療時,應於一週期間逐漸降低劑量 [*請參閱警語與注意事* 項 *(5*)]。但在某些速放劑型 pramipexole 錠劑的研究中,突然停藥並未引發不良 結果。 5.10 以多巴胺療法進行治療時所報告的事件 雖然以下所列舉的事件在 pramipexole 的研發計畫中可能未曾報告,但使用其他 多巴胺藥物可能與這些事件的發生有關。不過,這些事件的預期發生率極低,即使 pramipexole 引發這些事件的頻率與其他多巴胺療法相近,以目前為止在研究中暴露於 <u>に再列ルビス 現柄人的州栗刀ය</u> Pramipexole 的清除須仰賴腎功能[*請参閱臨床藥理學 (12.3)*]。輕度腎功能受損 (肌酸酐清除率高於 50mL /分鐘)的病人無須降低毎日劑量。 (肌酸酐清除率高於 50mL / 分鐘) 的病人無須降低每日劑量。 在中度腎功能受損(肌酸酐清除率在 30 至 50 mL / 分鐘)的病人,開始時必須每隔一天服用一次 MIRAPEX PR。須謹慎用藥,並仔細評估治療反應及耐受性,才可於一週後調高每日劑量,並進一步以每次 0.375 mg 的增幅將劑量調至最高一天 2.25 mg。劑量調整頻率不可多於一週一次。 麥角鹼衍生物之多巴胺致效劑是否亦可導致其發生。 ,在速放劑型 pramipexole 錠劑的上市後經驗中,曾有纖維化併發症(包括腹膜纖維化, 肋膜纖維化與肺臟纖維化)的可能病例報告。雖然無足夠的證據可供確認 pramipexol 樂伯克 持續性藥效錠 0.375 毫克為白色 圓形 具斜邊之錠劑。錠劑正面刻有"P1", 反面刻有 百靈佳殷格翰公司標誌。 與這些纖維化併發症之間的因果關係,但無法完全排除 pramipexole 可能具有的影響 樂伯克 持續性藥效錠 0.75 毫克為白色、圓形、具斜邊之錠劑。錠劑正面刻有"P2" '黑色素瘤(Melanoma 反面刻有 百靈佳殷格翰公司標誌。 流行病學研究顯示,帕金森氏症病人罹患黑色素瘤的風險高於一般大眾(高2至6倍左右), 樂伯克 持續性藥效錠 1.5 毫克為白色、橢圓形之錠劑。錠劑正面刻有"P3", 不清楚所增加的風險是否為帕金森氏症或其他因素(例如用於治療帕金森氏症的藥物)所導致 反面刻有 百靈佳殷格翰公司標誌。 基於上述原因,應告知病人與照護者,在使用 MIRAPEX PR 錠劑治療任何適應症時, 均須經常或定期監測是否發生黑色素瘤,最好由有能力的適當人士(例如皮膚科醫師) 對 pramipexole 或製劑中任一成分過敏者禁用。 進行定期皮膚檢查。 5. 警語與注意事項 肌張力障礙 (Dystonia 巴金森氏症病人可能出現軸索性肌張力障礙 (axial dystonia),如頸項前屈 (antecollis) 曾有報告指出,接受 pramipexole 的病人於日常活動(包括駕駛)中睡 #輕幹前傾 (camptocormia) 或側弓反張 (pleurothotonus) (比薩症候群 Pisa syndrom 著而發生意外。雖然許多病人表示於使用 pramipexole 錠劑期間出現困 倦嗜睡情形,但有些病人並未察覺自己出現過於困倦的警訊,而且相信自 尚未被確立。藥物治療開始或調整後數月也可能發生肌張力障礙。如果發生肌張力障礙。 |己是在即將發生事件之前仍為清醒。這些事件有些遲至開始治療一年後才||應該重新審視並考慮調整多巴胺藥物治療方案。 發生。在以安慰劑對照的帕金森氏症臨床試驗中,服用 MIRAPFX PR 錠 □ 原發性腮部躁動症之惡化 劑的 387 名病人中有 8 人(2%)出現突然睡著或猝睡症,281 名服用安 曾有文獻指出以多巴胺激性藥物治療原發性腿部躁動症有可能發生惡化 惡化的情況為症狀提早在傍晚前出現(或甚至下午),症狀增加,且症狀延伸至 在早期帕金森氏症病人,接受 MIRAPEX PR(劑量中位數:3.0 mg /天)的 223 名病人中有 36% 出現困倦嗜睡現象,103 名安慰劑組病人中則有 15% 出 Pramipexole 組有 11.8% 惡化,安慰劑組有 9.4% 惡化。經 Kaplan-Meier 分析,很 現此情形。在末期帕金森氏症病人,接受 MIRAPEX PR(劑量中位數:3 mg /天) 用藥組(pramipexole,人數為 152) 與安慰劑組(人數為 149)間,其症狀至惡化 重新評估病人是否出現困倦嗜睡,尤其因為有些事件是在開始治療相當久之後才 藝生。醫師亦應瞭解,病人可能並不認為自己有困倦嗜睡現象,除非被直接問到 5.12 藥物戒斷症候群 可た心型別間定省出現困惨皆理。 開始以 MIRAPEX PR 錠劑治療之前,須告知病人可能發生困倦嗜睡現象,尤其 須詢問病人是否存在可能增加此風險的因素,例如,併用鎮靜劑或喝酒、有睡眠 失調問題,以及併用可增加血中 pramipexole 濃度的藥物(例如 cimetidine)。 若病人出現日間嚴重瞌睡或於須主動參與的活動(例如對話、飲食等)中睡著, 通常即須停用 MIRAPEX PR 錠劑。若決定繼續使用 MIRAPEX PR 錠劑,則應告 知病人勿開車,並避免從事其他可能具有危險性的活動。雖然降低劑量可述小因 6. 不良反應 知病人勿開車,並避免從事其他可能具有危險性的活動。雖然降低劑量可減少困 6. 不良反應 倦嗜睡的程度,但並無充分資訊可證明降低劑量能夠完全避免於日常活動期間睡 **國染與侵染** 在臨床試驗與臨床經驗中,多巴胺拮抗劑可能造成全身性血壓調節作用受損,而 導致起立型低血壓症(orthostatic hypotension),尤其在劑量調升期。此外, 帕金森氏症病人對於起立的反應能力亦較低。基於這些原因,對於接受多巴胺 性欲禍高及症能賭博行為 性慾過高及病態賭博行為 致效劑(dopaminergic agonists)(包括 MIRAPEX PR)治療的帕金森氏症病 升期,亦應告知病人有此風險存在。在以安慰劑對照的帕金森氏症臨床試驗中, 接受 MIRAPEX PR 錠劑治療的 387 名病人中有 10 人(3%)出現有症狀的起 立型低血壓症,281 名安慰劑組病人中則有 3 人(1%)出現此現象。387 名 推食過度 MIRAPEX PR 組病人中有一人因低血壓症而中斷治療。 5.3 衝動控制/強迫行為 | 性慾失調 病例報告與橫斷面研究 (cross-sectional studies) 結果顯示,在使用一種或多種 偏執 可增加中樞多巴胺活性(central dopaminergic tone)的藥物與帕金森氏症的常 出一次 用治療藥物(包括 MIRAPEX PR)時,病人可能出現賭博衝動、性慾增加、花錢 神經系統異常 您望強烈、暴飲暴食與/或其他強烈慾望,而且無法控制這些衝動。在某些病例 **健**忘 (但非全部),這些衝動可在降低劑量或停藥之後消失。因為病人可能並未察 頭項前屈 (antecollis) 覺這些行為不正常,請醫生務必特別詢問病人或其照護者,病人是否於服用 MIRAPEX PR 期間出現賭博衝動、性衝動、無法自制地花錢或其他衝動,或原有 運動困難 的衝動加重的情形。若病人於服用 MIRAPEX PR 時出現這類衝動,醫生應考慮 頭痛 總計有 1056 名帕金森氏症病人參與兩項最長為期 33 週、以安慰劑對照的 MIRAPEX PR 試驗。在這些受試者每次就診時,均特別詢問其是否發生這些症狀。 突然入睡 總計接受 MIRAPEX PR 治療的 387 名受試者中有 14 人(4%)、接受速放劑型 量嚴 pramipexole 錠劑治療的 388 名受試者中有 12 人(3 %)、以及接受安慰劑治 眼睛異常 療的 281 名受試者中有 4 人(1%)出現強迫行為,包括病態性賭博、性慾過高 視力損傷 (含複視、視覺模糊及視覺敏銳度降低) 與/或強迫性購買行為。 5.4 幻覺 在以安慰劑對照的帕金森氏症臨床試驗中,接受 MIRAPEX PR 錠劑治療的 387 血管異常 名受試者中有 25 人(6%)出現幻覺(視覺或聽覺或兩者混合出現),接受安,低血壓 慰劑治療的 281 名受試者則有 5 人(2%)出現此現象。使用 MIRAPEX 呼吸、胸腔及橫隔膜異常

皮膚及皮下組織異常

一般異常及使用部位症狀

藥物戒斷症候群(多巴胺促進劑戒斷症候群)(參見警語與注意事項)

樂伯克[®]持續性藥效錠 Prolonged-Release Tablets

衛署藥輸字第 025258 號

衛署藥輸字第 025253 號

PR 錠劑的 387 名病人中有 5 人(1%)因出現幻覺而中斷治療。

5.5 運動困難 (Dyskinesia)

原有運動困難現象加劇。

病人進行研究。

中有 15 人(9%)出現幻覺,225 名 <65 歲者則有 10 人(4%)出現幻覺。

Pramipexole 所導致的幻覺發生風險可能隨年齡增長而增高。在以安慰劑對照的 打嗝 帕金森氏症臨床試驗中,在服用 MIRAPEX PR 錠劑的受試者,162 名≧ 65 歲者 腸胃道異常

MIRAPEX PR 錠劑可能強化左多巴的多巴胺副作用,並可能引發運動困難或導致

Pramipexole 的清除須仰賴腎功能 [*請參閱臨床藥理學 (12.3)*]。輕度腎功能受損

(肌酸酐清除率高於 50 mL /分鐘)的病人無須降低每日劑量。MIRAPEX PR 錠

劑尚未在中度至重度腎功能受損(肌酸酐清除率低於 50 mL / 分鐘)或洗腎的

率,無法與另一藥物於臨床	f. トが出1 / ハル	比某藥物於臨床試驗中戶	h 觀察到的小艮事件發生	便秘	5		6	ri'i Z
				重液分泌過多	0	7 2	0	E
率直接進行比較,亦可能無			T AND A DEV DD (A)				-	7
在 MIRAPEX PR 錠劑上市前				腹瀉	1	2	1	p
安慰劑或速放劑型 pramipex 與 Yahr 第 I-III 期)病人進行	KOIE 椞削冶療 5—TB陸繼公約	.° 此外,办住 156 右干: 8、帷章、亚行织则的封	期附並株氏征(HOENN · 脸,以过仕处油协利	精神病症				ll¦
型 pramipexole 錠劑隔日即				幻覺,包括視覺、聽	2	9	7	1117
可同時接受穩定劑量之左多巴				覺與混合出現				ll'r
amantadine 等藥物的單方療				失眠	2	4	4	117
受 MIRAPEX PR 錠劑、安慰	劑或速放劑型	pramipexole 錠劑治療	,作為左多巴的輔助療法。	代謝與營養異常	_			1112
早期帕金森氏症				10初兴名食共市	_	_		ß
在早期帕金森氏症病人的試	驗中,以 MI	RAPEX PR 錠劑治療 3.	3 週之後,最常見的不一	- 食慾不振	2	5	1	7
良事件(發生率≥ 5% 且較		型括困倦、噁心、便秘、	、暈眩、疲勞、幻覺、口	肌肉骨骼與結締組織異				F
乾、肌肉痙攣與周邊水腫。				常				8
接受 MIRAPEX PR 錠劑治療				背痛	1	2	3	8
事件而中斷治療,接受安慰				* 第 18 週時的最後分析				1
pramipexole 錠劑的 213 名 MIRAPEX PR 錠劑治療中斷			.此从兀°取吊等坎		田東女的記事	田此無法証件劑	量對不良事件發生率的影響。	Ì
表1所列為在早期帕金森氏			,IV MIRΔPEX PR 治療				EIIT R 等件發生學可影響。 MIRAPEX PR 治療者的某些不	1
33週期間發生率至少2%1							(亦即,MIRAPEX PR 組 % -	Į
多巴,但允許以左多巴作為				安慰劑組 % = 治療差異≥				F
表 1:在為期 33 週、雙盲、				實驗室檢測	2 707 - C7E			12
良事件發生率(在以 MIRAP	PEX PR 治療之	2受試者的發生率 > 2%	且高於安慰劑的事件)。	在 MIRAPEX PR 錠劑研發	期間,在例	行性實驗室檢測中	並未發現任何全身性異常結果。	1
					並無具體的指	i引供遵循,須由P	醫生自行決定病人需要接受哪些	1
身體系統/不良事件	安慰劑	MIRAPEX PR	速放劑型	監測。				-
			pramipexole	速放劑型 pramipexole 錠				並
	(n=103)	(n=223)	(n=213)				療的臨床試驗中,至少出現兩	
	%	%	%				件,如下所示。無論其與速放	В
 : 神經系統異常				劑型 pramipexole 錠劑的			-冯予以納人。 5、白血球減少症、淋巴結發炎、	
				<u> </u>			:、日皿球减少症、淋巴結發炎、	1
困倦	15	36	33				吸房室傳導阻滯、第二級房室傳	١١٤
暈眩	7	12	12				8、充血性心臟衰竭、心臟肥大、	
 顫抖	1	3	3				塞、結性心律不整、實性心律不	
	1	2	0				心室上心搏過速、心搏過速、心	
	1			室顫動、心室性期外收縮	、心室肥大。)		
腸胃異常				先天性、家族性與遺傳性				
噁心	9	22	24		聾、耳朵疼痛	痛、聽力受損、聽力	力減退、動量症、前庭性共濟失	5
	2	14	12	調(vestibular ataxia)。		LVA		ì
				<i>内分泌病症</i> :甲狀腺腫、「				8
	1	5	4				x)、眼瞼炎、眼瞼痙攣、白內障、 Kira,眼睛疼疼,眼瞼水腫,眼	F
嘔吐	0	4	4				下適、眼睛疼痛、眼瞼水腫、眼 見網膜剝離、視網膜血管異常、	Ļ
上腹痛	1	3	4	:			元,阿庆初唯、元,阿庆皿 旨共市、	1
	2	3	3				· 	Ē
							、糞便失禁、胃潰瘍、出血性胃	
腹部不適	0	2	1				更血、痔瘡、食管裂孔疝、胃酸	
全身性異常與用藥部位							・食道狹窄、食道炎、胰臓炎、	4
狀況 				牙周炎、直腸出血、逆流				ď
疲勞	4	6	6				k腫、感覺冷、感覺熱、緊張不	
	4	5	8		力受損、類似	以流感症狀、焦躁	易怒、局部水腫、水腫、身體不	F
無力		3	1	適、壓凹性水腫、口渴。		ミン ゆてた		ç
				<i>肝膽病症</i> :膽絞痛、膽囊 免疫系統異常:藥物過敏		《 父 〉 膽 仁 征 。		F
肌肉骨骼與結締組織異				201203 1110 211 1131C 31		火,言胆火,细去 。	氣管炎、支氣管炎、支氣管肺炎、	
常							R 目 及 、 又 来 目 及 、 又 来 目 所 及 、 情感染 、 毛囊炎 、 真菌 感染 、 癤 、]]1
肌肉痙攣	3	5	3				(針眼)、流行性感冒、椎間盤炎、	, 7
							、睪丸炎、骨髓炎、外耳炎、中	ŗ
	1	5	6				扁桃腺炎、牙膿腫、牙齒感染、	
與混合出現	1	3	O	上呼吸道感染、尿道炎、	陰道念珠菌症	主、陰道感染、病	毒感染、傷口感染。	ll r
失眠	3	4	4				:髁炎、車禍、曬傷、肌腱破裂。	ュ 車
		-					下降、脫水、糖尿病、液體滯留、	ţ
突然睡著	1	3	6				定、低鈣血症、低血糖症、低鉀 	[]
睡眠障礙	1	2	3	血症、低鈉血症、維生素質			t鯫毐症。 、腹側疼痛、脊椎盤異常、脊椎	1
憂鬱症	0	2	0				、废则终州、对作盗共吊、对作 炎、小肌肉僵硬、肌肉骨骼僵直、-	C
 受傷、中毒與療法所引							®死、骨質疏鬆症、四肢疼痛、	įt
發之併發症				多發性肌痛症、類風濕性				ا ¦ د د
3X Z_1/1 3X /III								- In 1
	1	,	,		窗:腹部腫瘤	、腺癌、良性腺瘤	、基底細胞癌、膀胱癌、乳癌、	1
摔倒	1	4	4		血病、結腸經	癌、結腸直腸癌、-	ā、基底細胞癌、膀胱癌、乳癌、 子宮內膜癌、膽囊癌、胃癌、腸	
摔倒 血管性異常	1	4	4	胃腫瘤、血管瘤、肝臟腫	血病、結腸經 窗、惡性肝腑	ā、結腸直腸癌、 繊腫瘤、唇部與/或	7、基底細胞癌、膀胱癌、乳癌、 子宮内膜癌、膽囊癌、胃癌、腸 或口腔癌、惡性肺部腫瘤、轉移	
	1	3	0	胃腫瘤、血管瘤、肝臟腫 性肺癌、淋巴瘤、惡性黑	血病、結陽經 廇、惡性肝腑 色素瘤、黑素	高、結腸直腸癌、 繊腫瘤、唇部與/或 素細胞痣、肺部之	7、基底細胞癌、膀胱癌、乳癌、 子宮內膜癌、膽囊癌、胃癌、腸 或口腔癌、惡性肺部腫瘤、轉移 轉移癌症、多發性骨髓瘤、良性	
血管性異常 起立型低血壓症				胃腫瘤、血管瘤、肝臟腫 性肺癌、淋巴瘤、惡性黑 口腔腫瘤、腫瘤、惡性腫	血病、結腸經 廇、惡性肝腑 色素瘤、黑素 瘤、攝護腺腫	語、結腸直腸癌、 繊腫瘤、唇部與/或 素細胞痣、肺部之 種瘤、皮膚腫瘤、れ	7、基底細胞癌、膀胱癌、乳癌、 子宮內膜癌、膽囊癌、胃癌、腸 或口腔癌、惡性肺部腫瘤、轉移 轉移癌症、多發性骨髓瘤、良性 申經瘤、卵巢癌、攝護腺癌、攝	
血管性異常				胃腫瘤、血管瘤、肝臟腫; 性肺癌、淋巴瘤、惡性黑; 口腔腫瘤、腫瘤、惡性腫; 護腺腺瘤、假性淋巴瘤、	血病、結腸經 廇、惡性肝腑 色素瘤、黑素 瘤、攝護腺腫	語、結腸直腸癌、 繊腫瘤、唇部與/或 素細胞痣、肺部之 種瘤、皮膚腫瘤、れ	7、基底細胞癌、膀胱癌、乳癌、 子宮內膜癌、膽囊癌、胃癌、腸 或口腔癌、惡性肺部腫瘤、轉移 轉移癌症、多發性骨髓瘤、良性	
血管性異常 起立型低血壓症 耳朵與內耳迷路 (labyrinth) 異常	1	3	0	胃腫瘤、血管瘤、肝臟腫 性肺癌、淋巴瘤、惡性黑 口腔腫瘤、腫瘤、惡性腫 護腺腺瘤、假性淋巴瘤、 子宮肌瘤。	血病、結陽經 瘤、惡性肝腑 色素瘤、無護 瘤、攝護瘤、 腎臟腫瘤、 皮	語、結腸直腸癌、 蔵腫瘤、唇部與/豆 繊腫瘤、唇部與/豆 素細胞痣、肺部之 種瘤、皮膚腫瘤、 皮膚乳頭 に に に に に に に に に に に に に	京、基底細胞癌、膀胱癌、乳癌、 子宮內膜癌、膽囊癌、胃癌、腸 或口腔癌、惡性肺部腫瘤、轉移 轉移癌症、多發性骨髓瘤、良性 轉經瘤、卵巢癌、攝護腺癌、攝 代瘤、鱗狀細胞癌、甲狀腺腫瘤、	
血管性異常 起立型低血壓症 耳朵與內耳迷路 (labyrinth) 異常 眩暈				胃腫瘤、血管瘤、肝臟腫 性肺癌、淋巴瘤、惡性黑 口腔腫瘤、腫瘤、惡性腫 護腺腺瘤、假性淋巴瘤、 子宮肌瘤。 神經系統異常:味覺喪失、	血病、結陽經 瘤、惡性肝 色素瘤、黑 會、攝護原 層 以 層 類 屬 種 動 不 能 、 便 、 題 、 題 、 題 、 題 、 題 、 題 、 題 、 題 、 題	語、結腸直腸癌、 遠腫瘤、唇部與/ 素細胞痣、肺部之 腫瘤、皮膚腫瘤、 腫瘍、皮膚乳頭 患症、靜坐不能、 建忘症、靜坐不能、	京、基底細胞癌、膀胱癌、乳癌、 子宫內膜癌、膽囊癌、胃癌、腸 成口腔癌、惡性肺部腫瘤、轉移 轉移癌症、多發性骨髓瘤、良性 申經瘤、卵巢癌、攝護腺癌、攝 代瘤、鱗狀細胞癌、甲狀腺腫瘤、 抗膽鹼症候群、失語症、腦水腫、	, ,
血管性異常 起立型低血壓症 耳朵與內耳迷路 (labyrinth) 異常 眩暈 代謝與營養異常	1	3	2	胃腫瘤、血管瘤、肝臟腫 性肺癌、淋巴瘤、惡性黑 口腔腫瘤、腫瘤、惡性腫 護腺腺瘤、假性淋巴瘤、 子宮肌瘤。 神經系統異常:味覺喪失、 頸動脈阻塞、腕隧道症候	血病、結腸照解、 結腸照解 医鱼畜素 人名英格兰 医克克克 医克克克克克 医克克克克克克克克克克克克克克克克克克克克克克克克	區、結腸直腸癌、- 繊腫瘤、唇部與/I 素細胞痣、肺部之I 腫瘤、皮膚腫瘤、i E膚癌、皮膚乳頭狀 は定症、靜坐不能、 全塞、腦出血、腦	京、基底細胞癌、膀胱癌、乳癌、 子宫內膜癌、膽囊癌、胃癌、腸 或口腔癌、惡性肺部腫瘤、轉移 轉移癌症、多發性骨髓瘤、良性 申經瘤、卵巢癌、攝護腺癌、攝 洗瘤、鱗狀細胞癌、甲狀腺腫瘤、 抗膽鹼症候群、失語症、腦水腫、 更塞、腦缺血、舞蹈症、認知異	
血管性異常 起立型低血壓症 耳朵與內耳迷路 (labyrinth) 異常 眩暈	1	3	0	胃腫瘤、血管瘤、肝臟腫 性肺癌、淋巴瘤、惡性黑 口腔腫瘤、腫瘤、惡性腫 護腺腺瘤、假性淋巴瘤、 子宫肌瘤。 子宫肌癌。 野動脈阻塞、腕隧道症候, 常、昏迷、抽搐、協調異	血瘤 医霉肾 运车 医角质 医角角 医角角 医角角 医角角 医角角 医角角 医角角 医角角 医角角	區、結腸直腸癌、- 結腸直腸癌 > 減腫瘤、皮膚腫瘤、計 軽細胞痣、肺部之。 腫瘤、皮膚腫瘤、引 健腐癌、皮膚乳頭狀 能忘症、靜坐不能、 全塞、腦出血、注意 意識下降、意意	京、基底細胞癌、膀胱癌、乳癌、 子宮內膜癌、膽囊癌、胃癌、腸 或口腔癌、惡性肺部腫瘤、轉移 轉移癌症、多發性骨髓瘤、良性 申經瘤、卵巢癌、攝護腺癌、攝 抗瘤、鱗狀細胞癌、甲狀腺腫瘤、 抗膽鹼症候群、失語症、腦水腫 更塞、腦缺血、舞蹈症、認知異 力不集中、姿勢性暈眩、發音困	
血管性異常 起立型低血壓症 耳朵與內耳迷路 (labyrinth) 異常 眩暈 代謝與營養異常	1	3	2	胃腫瘤、血管瘤、肝臟腫 性肺癌、淋巴瘤、惡性黑 與腺瘤、腫瘤、惡性腫 護腺腺瘤、假性淋巴瘤、 子宮肌瘤 神經系統異常:味覺喪失、 神輕脈症 常、昏迷、抽搐、協調異 難、書寫障礙、肌張力不至	血病、結腸肝胃炎症病、惡性、無性、無性、無性、無性、無性、無性、無性、無性、無性、無性、不動、性、不動、	高、結腸直腸癌、 。 。 。 。 。 。 。 。 。 。 。 。 。	京、基底細胞癌、膀胱癌、乳癌、 子宮內膜癌、膽囊癌、胃癌、腸 或口腔癌、惡性肺部腫瘤、轉移 轉移癌症、多發性骨髓瘤、良性 申經瘤、卵巢癌、攝護腺癌、攝 抗瘤、鱗狀細胞癌、甲狀腺腫瘤、 抗膽鹼症候群、失語症、腦水腫、 更塞、腦缺血、舞蹈症、認知異 力不集中、姿勢性暈眩、發音困 amidal syndrome)、臉部麻痺、	
血管性異常 起立型低血壓症 耳朵與內耳迷路 (labyrinth) 異常 眩暈 代謝與營養異常 食慾增加	1	3	2	胃腫瘤、血管瘤、肝臟腫性肺癌、淋巴瘤、惡性黑口腔腫瘤、腫瘤、惡性腫態腺腺瘤、假性淋巴瘤、野子宮肌瘤。神經系統異寒、院隧道症患等下昏迷、抽搐、隐避症患異策、善寒障礙、肌張力不全大發作抽搐(grand malo	血病、結陽 病、惡性 、 、 、 、 、 、 、 、 、 、 、 、 、 、 、 、 、 、	語、結腸直腸癌、三 遠腫瘤、結腸直腸癌、三 遠腫瘤、原語與之 腫瘤、皮膚腫乳 腫瘤、皮膚乳頭 に膚癌、皮膚乳頭 に定な、静坐不、注 に変し、静性 に変し、 に酸群(とはすりが、 に変し、 に酸け、 に変し、 に	京、基底細胞癌、膀胱癌、乳癌、 子宫內膜癌、膽囊癌、胃癌、腸 或口腔癌、惡性肺部腫瘤。 良性 申經瘤、卵巢癌、攝護腺癌、殖 性瘤、瓣狀細胞癌、甲狀腺腫瘤、 抗膽鹼症候群、失語症、腦水腫、 更塞、腦缺血、舞蹈皆症、 認知異 力。不明付。 如可怕al syndrome)、臉部麻痺 以過敏、運動機能亢進、反射亢	
血管性異常 起立型低血壓症 耳朵與內耳迷路 (labyrinth) 異常 眩暈 代謝與營養異常 食慾增加 呼吸、胸部與縱隔膜異 常	1 1	3 4 3	2	胃腫瘤、血管瘤、肝臟腫性肺癌、淋巴瘤、惡性黑口腔腫瘤、腫瘤、惡性黑態腺腺瘤、假性淋巴瘤、野子宮肌瘤。神經系統異寒、院隧道症實等下昏迷、抽搐、短調異、難、書寫障礙、肌張力不至大發作抽搐(grand mald進、反射機能不足、肌張力	血瘤 系統 語解 語為	語、結腸直腸癌、 遠腫腫瘤、結腸唇部與之 連瘤的患、肺部瘤 腫腫瘤、皮膚腫乳頭 止膚癌、皮膚乳頭 定毒症、腦出血、注 意候群(ext 意候性(ext 意候性(ext 意候者、感過 意候者、感過 意候者、感過 意候者、感過 過過	京、基底細胞癌、膀胱癌、乳癌、 子宮內膜癌、膽囊癌、胃癌、腸 或口腔癌、惡性肺部腫瘤、轉移 轉移癌症、多發性骨髓瘤、良性 申經瘤、卵巢癌、攝護腺癌、攝 抗瘤、鱗狀細胞癌、甲狀腺腫瘤、 抗膽鹼症候群、失語症、腦水腫、 更塞、腦缺血、舞蹈症、認知異 力不集中、姿勢性暈眩、發音困 amidal syndrome)、臉部麻痺、	
血管性異常 起立型低血壓症 耳朵與內耳迷路 (labyrinth) 異常 眩暈 代謝與營養異常 食慾增加 呼吸、胸部與縱隔膜異常 咳嗽	1 1 1	3 3 3	2 2 3	胃腫瘤、血管瘤、肝臟腫性肺癌、淋巴瘤、惡性黑性肺癌、淋巴瘤、惡性腫變腺腺瘤。假性淋巴瘤、肾空外原腺腺瘤。神經系統異常:味覺喪失、頸動脈阻塞、腕隧道症候常、昏迷、抽搐、協調異、難、書寫障攝(grand mac)大發作抽搐(grand mac),以表情,不是一个人。	血瘤 多審 隣 動、 に 結陽所 ・	區、結腸直腸鳴鳴。 這種瘤、結腸直腸 動腫腫瘤、 動腫腫瘤、 性膚、 性膚、 性膚、 性膚、 性膚、 性質、 性質、 性質、 性質、 性質、 性質、 性質、 性質	京、基底細胞癌、膀胱癌、乳癌、 子宮內膜癌、膽囊癌、胃癌、轉移 或口腔癌、惡性肺部腫瘤、轉移 轉移癌症、多發性骨髓瘤、與性 轉經瘤、卵巢癌、攝護腺癌、攝 於瘤、鱗狀細胞癌、甲狀腺腫瘤、 抗膽鹼症候群、失語症、腦水腫、 更塞、腦缺血、無野蹈症、 認知異 力無可は自。如便如此、 部所與 如明如, 過敏、運動機能亢進、 反力受損、 、 、 、 、 、 、 、 、 、 、 、 、 、 、 、 、 、 、	F
血管性異常 起立型低血壓症 耳朵與內耳迷路 (labyrinth) 異常 眩暈 代謝與營養異常 食慾增加 呼吸、胸部與縱隔膜異常 咳嗽 因為此研究係採彈性劑量調	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	3 4 3 3 因此無法評估劑量對不同	0 2 2 3 Q事件發生率的影響。	胃腫瘤、血管瘤、肝臟腫性肺癌、為性腫瘤、惡性腫態膜瘤。惡性腫態腺瘤。假性淋巴瘤、肾空腺腺瘤。一种經系統異常:味覺喪失、頸動脈阻塞、抽搐、肠影道症調異、整、書寫障礙、肌張力不全大發作抽搐(grand malc進、反射機体不足、則變化性偏頭痛 侧肉不全主擊擊,则是有人	血瘤 多裔 漢群 等之 企 的 不 不 不 不 不 不 不 不 不 不 不 不 不 不 不 不 不 不	語、結腸直腸鳴魚之 連腫瘤、患、肺部之 連腫瘤、患、肺部之 性膚腫瘤、患 性皮膚胃、頭肌 性皮膚胃、頭肌 性心 性心 性心 性心 性心 性心 性心 性心 性心 性心	、基底細胞癌、膀胱癌、乳癌、 子宫內膜癌、膽囊癌、胃癌、轉移 或口腔癌、惡性時間腫瘤、轉移 轉移癌症、多發癌、攝護腺癌 無經療、卵巢癌、甲狀腺腫瘤、 抗膽鹼症候群、失語症症、腦水腫、 更塞、腦缺血、舞蹈症、發育困 力不集中、姿勢性暈眩、診部育困 以過敏、運動機能亢、記憶力受損、 過過數、運動機能力、認節列受損、 過量、逐轉頭症(nystagmus)、 透過質、環難時症、感覺障礙、睡 、類環、鎮靜狀態、感覺障礙、睡 、緊張性頭痛、思想異常。	F
血管性異常 起立型低血壓症 耳朵與內耳迷路 (labyrinth) 異常 眩暈 代謝與營養異常 食慾增加 呼吸、胸部與縱隔膜異常 咳嗽 因為此研究係採彈性劑量調	1 1 1 1 1 1 1 1 整的設計,反	3 4 3 3 因此無法評估劑量對不良 或維持期。接受 MIRAP	0 2 2 3 §事件發生率的影響。 EX PR 治療者的某些不	胃腫瘤、血管瘤、肝臟腫黑性肺癌、瘤、腫瘤、惡性腫 護腺腺瘤、腫性淋巴瘤、影性腫 護腺腺瘤。腫性淋巴瘤、野子經系統理、時費喪失、 頸動脈腔基、肺療遊道症調 、香素原性、肌張力不足、 、原射機能不足、肌縮、 、反射機能不足、肌縮、 、原衛、 、原衛、 、原衛、 、原衛、 、 、 、 、 、 、 、 、 、	血瘤色瘤。 病、惡瘤, 養養 病、惡瘤, 養養 養養 養養 養養 養養 養養 養養 養養 養養 養養 養養 養養 養養	語、語、語、語、語、語、語、語、語、語、語、語、語、語、語、語、語、語、語、	、基底細胞癌、膀胱癌、乳癌、 子宮內膜癌、膽 養癌、胃癌、轉移 時經癌、乳蛋性 時經瘤、卵巢癌、 排性瘤、卵巢癌、 排性瘤、 排性瘤、 排性瘤、 排性瘤、 排性瘤、 排性瘤、 排性瘤、 排性瘤、 排性瘤、 排性瘤、 對性質症、 影缺血 與性質症、 影缺血 與性質症、 影缺血 與性質症、 影缺血 與性質症、 影如 是 與性 與 與 與 與 與 與 與 與 與 與 與 與 與	F
血管性異常 起立型低血壓症 耳朵與內耳迷路 (labyrinth) 異常 眩暈 代謝與營養異常 食慾增加 呼吸、胸部與縱隔膜異常 咳嗽 因為此研究係採彈性劑量調 最初的不良事件可能發生於 良事件於劑量調整期出現,	1 1 1 1 1 整的設計,D 劑量調整期項 並持續(≧)	3 4 3 因此無法評估劑量對不良或維持期。接受 MIRAP 7 天) 至維持期(亦即	2 2 2 3 良事件發生率的影響。 EX PR 治療者的某些不,MIRAPEX PR 組% -	胃腫瘤、血管瘤 密性腫 性肺癌、 為 是	血畜色 審解 運 学 常 症 の 過 に ない の は 、 窓 瘤 攝腫 動 、 、 に の 過 陣 理 不 優 と い の 過 陣 理 不 優 と い の 過 に し い の 過 に し い の 過 に し い の 過 に し い の 過 に し い の い の	語、輔語、 語、 語、 語、 語、 語、 語、 語、 語、 語、	不基底細胞癌、膀胱癌、乳癌、 子宫內膜癌、膽囊癌、胃癌、轉移 專移癌症、多發性骨髓瘤療癌 專移癌症、多發性骨髓腺癌癌 等經濟、鄉狀細胞癌、甲狀腺腫瘤、 抗膽鹼症候群、失語症症、醫水腫 更塞、腦缺血、勢性醫症症、醫水腫 更塞、際時理。 一個 一個 一個 一個 一個 一個 一個 一個 一個 一個 一個 一個 一個	ト F S A N F i i f i f i f i f i f i f i f i f i f
血管性異常 起立型低血壓症 耳朵與內耳迷路 (labyrinth) 異常 眩暈 代謝與營養異常 食慾增加 呼吸、胸部與縱隔膜異常 咳嗽 因為此研究係採彈性劑量調整期出現, 安慰劑組%=治療差異≥ 2	1 1 1 1 割整的設計,因 對量關整期寫 並持續(≧ご 2%);包括困	3 4 3 因此無法評估劑量對不應或維持期。接受 MIRAP 7天)至維持期(亦即 1億、噁心、便秘、疲勞	2 2 2 3 良事件發生率的影響。 EX PR 治療者的某些不,MIRAPEX PR 組 % - "與口乾。	胃腫瘤、血管瘤、惡性腫 性肺癌、減 医性腫 護脾腫瘤、惡性腫 護脾腺瘤。 一种經系統異常:味覺喪生 質宮肌瘤。 一种經系統異常:味覺喪失 質數脈昏迷、軸搐、協調 等、書寫 實質、體、調子 。 一种經 。 一 一 一 一 一 一 一 一 一 一 一 一 一 一 一 一 一 一	血畜色 審隊 運幹 常症の過陣理不信 大部	語 議 語 語 語 語 語 語 語 語 語 語 語 語 語	不基底細胞癌、膀胱癌、乳癌、乳癌、胃癌、腹癌、脂囊癌、胃癌、酶毒溶点、胃癌、酶毒移癌、种皮质癌、多發性骨髓瘤、癌癌、卵形癌、卵肠癌、卵形癌癌、卵胀肠癌癌、卵胀腺腫瘤、排泄腺肿瘤、瓣状细胞癌、等性蛋白、溶质、溶质、水质、水质、水质、水质、水质、水质、水质、水质、水质、水质、水质、水质、水质	ト F S A N F i i f i f i f i f i f i f i f i f i f
血管性異常 起立型低血壓症 耳朵與內耳迷路 (labyrinth) 異常 眩暈 代謝與營養異常 食慾增加 呼吸、胸部與縱隔膜異常 咳嗽 因為此研究係採彈性劑量調整期出現, 安慰劑組%=治療差異≥2 在 156 名早期帕金森氏症病	1 1 1 1 1 整的設計,即 並持續 整計 2%);包括困 5 2%);包括困或	3 3 3 因此無法評估劑量對不E 或維持期。接受 MIRAP 7 天)至維持期(亦即 1卷 噁心、便秘、疲勞 未使用左多巴)所進行	2 2 2 3 息事件發生率的影響。 EX PR 治療者的某些不,MIRAPEX PR 組% - ·與口乾。 一項雙盲、隨機分組、	胃腫瘤、血管瘤、惡暗瘤、惡性腫腫黑性肺癌、痛、恐性瘤瘤、惡性腫,體中腔腫瘤。。 神經系統異常:味覺喪生,以會內經系統異常:味覺遵定別瘤。。 神經系統異常:味覺道這調不至,不可以不可以不可以不可以不可以不可以不可以不可以不可以不可以不可以不可以不可以不	血瘤色瘤腎運鲜常、在COD過陣理不管與症人病、惡痛攝腫不腦失。能以高學性不管與症人格,也不可以不可以不可以不可以不可以不可以不可以不可以不可以不可以不可以不可以不可以不	為議無知 基種解 基種瘤 基達 基達 基達 基達 基達 基達 基達 基達 基達 基達	京、基底細胞癌、膀胱癌、乳癌、 界高、腹癌、腹癌、腹癌、胃癌、腺 身疼癌、脂囊癌、肿瘤 身疼癌症、多巢癌、摄護狀腺腫瘤、 神經癌、卵巢癌癌、 原塞、解缺缺血胞癌、 原塞、 脈缺症候群、失語蹈症、 發解、 療性血、 等移癌症、 等移癌症、 等移癌症、 等移癌症、 等移癌症、 等移癌症、 等原癌。 所能驗症候群、 等性量的。 等的。 等的。 等的。 等的。 等的。 等的。 等的。 等	
血管性異常 起立型低血壓症 耳朵與內耳迷路(labyrinth) 異常 眩暈 代謝與營養異常 食慾增加 呼吸、胸部與縱隔膜異常 咳嗽 因為此研究係採彈性劑量調 最初的不良事件可能發生於 良事件於劑量調整期出現之 全根前組 % = 治療差異之 至根劑組 % = 治療差異人 平行組別的試驗中,評估從	1 1 1 1 1 1 \$\frac{1}{2}\$ \$\	3 A A A A B B B B B B B B B	2 2 2 3 §事件發生率的影響。 EX PR 治療者的某些不,MIRAPEX PR 組% - "與口乾。 一項雙盲、隨機分組、轉用每日劑量相同的	胃腫瘤、血管瘤瘤、惡性腫腫腫腫腫腫腫腫瘤、淋巴瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤病硬性淋巴瘤瘤。假性淋巴瘤瘤。假性淋巴瘤瘤。假性淋巴瘤瘤。假性淋巴瘤肠膜瘤瘤。一种细胞体质,一种一种一种一种一种一种一种一种一种一种一种一种一种一种一种一种一种一种一种	血瘤鱼畜窝 運幣 · 在onder under seine	區、種類 基種 與 主主 主主 主主 主主 主主 主主 主主 主主 主主	不基底細胞癌、膀胱癌、乳癌、 界癌、腹癌、腹癌、 胃癌、腹癌、 胃癌、性质癌、 素溶性原癌、 素溶性原癌、 身移癌症、 多等癌症、 多等癌症、 多等癌症、 多等癌症、 多等癌症、 多等癌症、 多等癌症、 多等癌症、 多等癌症、 多等癌症、 多等癌症、 多等癌症、 多等癌症、 多等。 、 等移癌症、 等移癌症、 等移癌症、 等等癌症、 等移癌症、 等移癌症、 等等癌症、 等等癌症、 。 等等癌症、 。 等等癌症、 。 等等。 。 。 。 。 。 。 。 。 。 。 。 。 。	
血管性異常 起立型低血壓症 耳朵與內耳迷路 (labyrinth) 異常 眩暈 代謝與營養異常 食慾增加 呼吸、胸部與縱隔膜異常 咳嗽 因為此研究係採彈性劑量調整期出現, 安慰劑組%=治療差異≥2 在 156 名早期帕金森氏症病	1 1 1 1 1 1 1 8	3 A A A A A A A A A A A A A	2 2 2 3 息事件發生率的影響。 EX PR 治療者的某些不,MIRAPEX PR 組 % - "與口乾。 一項雙盲、隨機分組、轉用每日劑量相同的 xole 錠劑轉用 MIRAPEX	胃腫瘤、血管瘤瘤、惡性腫腫腫腫腫腫腫腫瘤、淋巴瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤瘤病硬性淋巴瘤瘤。假性淋巴瘤瘤。假性淋巴瘤瘤。假性淋巴瘤瘤。假性淋巴瘤肠膜瘤瘤。一种细胞体质,一种一种一种一种一种一种一种一种一种一种一种一种一种一种一种一种一种一种一种	血瘤色瘤 、 、 、 、 、 、 、 、 、 、 、 、 、 、 、 、 、 、	語、種類的 語、種類的 語、種類的 語、性質 語、性質 語、性質 語、性質 語、性質 語、性質 語、性質 語、性質 性質 語、性質 性質 性質 性質 性質 性質 性質 性質 性質 性質	京、基底細胞癌、膀胱癌、乳癌、 界高、胃癌、肿瘤、胃癌、胃癌、肿质 好可膜癌、脂囊癌、胃癌、神移 中經瘤、卵巢癌。 中間 中經瘤、卵巢癌 大瘤、鱗狀細胞 大瘤、鱗狀細胞 大瘤、鱗狀細胞 大瘤、瓣状細胞 大瘤、瓣状細胞 大瘤、瓣状細胞 大瘤、瓣状細胞 大瘤、瓣状細胞 大瘤、瓣状細胞 大瘤、瓣状細胞 大瘤、瓣状細胞 大瘤、瓣状細胞 大瘤、瓣状神细胞 大瘤、瓣状神细胞 大瘤、瓣状神细胞 大瘤、瓣状神细胞 大瘤、瓣状神细胞 大面、部面、形面、形面、 上面、一面、一面、一面、 是面、一面、一面、 是面、一面、一面、 是面、一面、一面、一面、 是面、一面、一面、一面、一面、 是面、一面、一面、一面、一面、 是面、一面、一面、一面、一面、一面、一面、一面、一面、一面、一面、一面、一面、一面	
血管性異常 起立型低血壓症 耳朵與內耳迷路 (labyrinth) 異常 眩暈 代謝與營養異常 食慾增加 呼吸、胸部與縱隔膜異常 咳嗽 因為此研究係採彈性劑量調整期出現, 安慰劑組 % = 治療金索於 平行組別的試驗中,評估從 MIRAPEX PR 錠劑時病人的	1 1 1 1 1 1 1 8	3 A A A A A A A A A A A A A	2 2 2 3 息事件發生率的影響。 EX PR 治療者的某些不,MIRAPEX PR 組 % - "與口乾。 一項雙盲、隨機分組、轉用每日劑量相同的 xole 錠劑轉用 MIRAPEX	胃腫瘤、感性性症、原性性性、原性性性、原性性性、原性性性、原体性性、原体性性、原体性性、原	血瘤色瘤腎 運鲜常、症的過化、心燥、ckz病、寒痛 臟 動、 ckxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	語、種類的 語、種類的 語、主、 主、 語、一、 、一、 、一、 、一、 、一、 、一、 、一、 、	京、基底細胞癌、膀胱癌、乳癌、 界高、胃癌、肿瘤、胃癌、胃癌、肿质 好可膜癌、脂囊癌、胃癌、神移 中經瘤、卵巢癌。 中間 中經瘤、卵巢癌 大瘤、鱗狀細胞 大瘤、鱗狀細胞 大瘤、鱗狀細胞 大瘤、瓣状細胞 大瘤、瓣状細胞 大瘤、瓣状細胞 大瘤、瓣状細胞 大瘤、瓣状細胞 大瘤、瓣状細胞 大瘤、瓣状細胞 大瘤、瓣状細胞 大瘤、瓣状細胞 大瘤、瓣状神细胞 大瘤、瓣状神细胞 大瘤、瓣状神细胞 大瘤、瓣状神细胞 大瘤、瓣状神细胞 大面、部面、形面、形面、 上面、一面、一面、一面、 是面、一面、一面、 是面、一面、一面、 是面、一面、一面、一面、 是面、一面、一面、一面、一面、 是面、一面、一面、一面、一面、 是面、一面、一面、一面、一面、一面、一面、一面、一面、一面、一面、一面、一面、一面	
血管性異常 起立型低血壓症 耳朵與內耳迷路(labyrinth) 異常 眩暈 代謝與營養異常 食慾增加 呼吸、胸部與縱隔膜異常 咳嗽 因為此研究係採彈性劑量調整期出現, 安慰劑組 % = 治療差疾氏症病 安慰劑組 % = 治療差疾氏症病 可行組別的試驗中,評估從 MIRAPEX PR 錠劑時因式	1 1 1 1 1 1 2%);因調整期頭整期頭。並持續包含性,因素的,可能力量,可能力量,可能力量,可能力量,可能力量,可能力量,可能力量,可能力量	3 A A A A A A A A A A A A A	2 2 2 2 2 3 息事件發生率的影響。 EX PR 治療者的某些不,MIRAPEX PR 組% - ·與口乾。 一項雙盲、隨機分組、轉用每日劑量相同的 xole 錠劑轉相 MIRAPEX 而中斷治療。	胃腫瘤、惡性瘤、惡性瘤、惡性腫腫無無性肺癌、瘤瘤、惡性瘤、惡性瘤、惡性瘤、惡性瘤、惡性瘤、假性性腫,質、神經動物。與實質、數學與不可以不可以不可以不可以不可以不可以不可以不可以不可以不可以不可以不可以不可以不	血畜鱼畜嘴 運鲜常、在加入、、向燥、(ckid 阿南、素、臟 動、、定心過陣理不侵知症人的症、尿病、恶痛攝腫 不腦失。此心高學性省略覺、格仍症、尿調器肝黑腺、 哌症等 凯人行爱易異加少失、 机量物 化氯化二甲基甲基甲基甲基甲基甲基甲基甲基甲基甲基甲基甲基甲基甲基甲基甲基甲基甲基甲基	語、難無相信 主、 主、 主、 主、 主、 主、 主、 主、 主、 主、	不基底細胞癌、膀胱癌、乳癌、 胃癌、腹癌、腹癌、胃癌、酶 对口腔癌、整黄癌性骨髓瘤瘤瘤癌 神經瘤、卵巢癌 中經瘤、卵巢癌 大瘤、瓣状細胞癌 、种瘤、瓣状细胞癌 、种性瘤、瓣状细胞癌 、种性瘤、瓣状细胞 、种性瘤、瓣状细胞 、种性。 、种性。 、种性, 、种性。 、种性。 、种性。 、种性。 、种性。 、种性。 、种性。 、种性。	
血管性異常 起立型低血壓症 耳朵與內耳迷路(labyrinth) 異常 眩暈 代謝與營養異常 食慾增加 呼吸、胸部與縱隔膜異常 咳嗽 因為此研究係採彈性劑量調 表別的不良事調整期與且之2 多限劑組% = 治療差疾於 是事件分別。	1 1 1 1 1 1 1 1 1 2 1 1 1 1	3 A A A A A A A A A A A A A	2 2 2 2 2 3 息事件發生率的影響。 EX PR 治療者的某些不,MIRAPEX PR 組% - ·與口乾。 一項雙盲、隨機分組、轉用每日劑量相同的 xole 錠劑轉相 MIRAPEX 而中斷治療。	胃腫腫黑腫、 開腫性性 原性性 原性性 原性性 原性性 原性性 原性性 原性性	血會色會等。運鲜等全の過階之、、向操、(尿頻經出陰病、素、臟、動、、定の過階性不慢知症、付症、不能失。此為學性不侵知症、付症、不應,以為學性不過,然應不能變,不應不可能,不能不可能,不能不可能,不可能 是不可能,不可能,不可能,不可能,不可能,不可能,不可能,不可能,不可能,不可能,	區、輔生 基種經濟 主達、意味。 基種經濟 主達、意味。 主達、意味。 一個 一個 一個 一個 一個 一個 一個 一個 一個 一個	· 基底細胞癌、磨脐胱癌、乳癌、 胃癌、腹癌、脂囊癌、脂肪癌、胃癌、胸肠癌、脂质癌、脂质癌、脂质癌、脂质癌、胸肠炎性原癌。 医性性肠炎 医生物 医皮受性 医皮肤	
血管性異常 起立型低血壓症 耳朵與內耳迷路(labyrinth) 異常 眩暈 (labyrinth) 異常 眩暈 (常數學營養異常 食慾增加 呼吸、胸部與縱隔膜異常 咳嗽 因為此研究係採彈性劑量調整期異與 最初的不良事情發現現。 長期的不於劑量調整期異與 ≥ 經濟期組 % = 對療金森許病人的 PR 錠劑的 104 名受知等流統在 在末期的齿球療在疾症在末期的間最常出現(發生羽物金森氏氏症病人(併名 週期則最常出現(發生 18 週期則 頭痛與食慾不振	1 1 1 1 1 1 1 1 1 1 1 1 1	3 A A A A A A A A A A A A A	2 2 2 3 息事件發生率的影響。 EX PR 治療者的某些不,MIRAPEX PR 組% - 「與口乾。 一項雙盲、隨機分組、轉用每日劑量相同的 xole 錠劑轉用 MIRAPEX 而中斷治療。 IRAPEX PR 錠劑治療 件為運動困難、噁心、便	胃腫瘤、瘤、溶、溶、溶、溶、溶、溶、溶、溶、溶、溶、溶、溶、溶、溶、溶、溶、溶、溶	血瘤色瘤等 運鲜等症の過陣状、向操、C尿頻經出陰:病、素、臟、動、、床の過陣理不侵知症人的症、不调(好吸、惡瘤攝腫、不腦失能以高、學性、管瘤、能動智體的感味,肌人行喪易異細少失、etc、病、病、病、病、病、病、病、病、病、病、病、病、病、病、病、病、病、病、病	感嫌短痛。 這種類性 動物 動物 動物 動物 動物 動物 動物 動物 動物 動物	· 基底細胞癌、磨脓癌、乳癌、胃癌、腹癌、腹癌、腹癌、腹癌、腹癌、腹癌、腹癌、内室内腹癌、整致性性肠炎、多生性原体、多样、一种原体,一种原体,一种原体,一种原体,一种原体,一种原体,一种原体,一种原体,	H F S A N F N A T 1 1 N F E F () Z () N T
血管性異常 起立型低血壓症 耳朵與內耳迷路 (labyrinth) 異常 眩暈 代謝與營養異常 食慾增加 呼吸、胸部與縱隔膜異常 咳嗽 因為此研究係採彈性劑量調整期出現, 安慰劑組 % = 治療金森所養與營養異常 平行組別的試驗中病病人的 PR 錠劑的 104名受訊等人。 被關和的金森氏症症 在末期帕金森氏氏症稅 MIRAPEX PR 錠劑時減分(供到 核等的 104名受訊, 全起劑的 104名受訊, 大規則的最高數則則最可以, 大規則的最高數則則 與期間最別所以, 大規則的。 於一致, 於一如, 於一致, 於一, 於一致, 於一致, 於一致, 於一致, 於一致, 於一致, 於一致, 於一致, 於一致,	1 1 1 1 1 1 1 1 1 1 1 1 22%) 读函数 (包围型 下层 (包围型 下层 (包围型 下层 (包围型 下层)	3 A A A A A A A A A A A A A	2 2 2 2 2 2 3 息事件發生率的影響。 EX PR 治療者的某些不,MIRAPEX PR 組% - 與口項雙言、隨機分組、 轉用每日劑量相同的 xole 錠劑轉用 MIRAPEX 而中斷治療。 (RAPEX PR 錠劑治療 件為運動困難、噁心、便 (5%) 因不良事件而中	胃腫腫黑腫、 無性性性 無性性性 無性性性 無性性性 無性性性 無性性性 無性性性 無性性性 無性性性 無性性性 無性性性 無性性性 無性性性 無性性性 無性性性 無性性性 無性性性 無性性 無性性 無性性 無性性 無疑 無性 無疑 無疑 無疑 無疑 無疑 無疑 無疑 無疑 無疑 無疑	血瘤色瘤等 運鲜等症の過犯之、向操、CRR质徑出陰:生病、素、臟、動、、症心過呼性質的症、CRB(对吸吸、惡痛攝腫、不腦失雖Isio感嗜肉手覺另、格on少失、在道呼吸以情性、護瘤、能動智體isio感嗜肉事為失醒常证尿禁乳tro物等難,與原及使性、脈症外的覺眠變為,與實際,以應於外別	區、種類學 基達 基達 基達 基達 基達 基達 基達 基達 基達 基達	京基底細胞癌、療胱癌、乳癌、胃癌、腹癌、腹癌、腹癌、腹癌、腹癌、腹癌、胃癌、胃癌、胃癌、胃癌、胃癌、胃癌、胃癌、胃癌、胃癌、肾癌、肾癌、肾癌、肾癌、肾癌、肾癌、肾癌、肾癌、原性原癌、卵巢肠炎癌、肾髓量、肾虚、肾虚、肾虚、肾虚、肾虚、肾虚、肾虚、肾虚、肾虚、肾虚、肾虚、肾虚、肾虚、	H F S A N F N A T 1 1 N F E F () Z () N T
血管性異常 起立型低血壓症 耳朵與內耳迷路(labyrinth) 異常 眩暈 代謝與營養異常 食慾增加 呼吸、胸部與縱隔膜異常 咳嗽 因為此研究係採彈性劑量調 要被劑組 % = 的多數。 長事件於劑量 % 等。 長事件於劑量 % 等。 長事件於劑量 % 等。 是不行為 名早期帕金, 安慰劑組 % 等。 是不行為 名早期帕金, 安慰劑組 % 等。 於實劑的 104 名受試費的 所以實劑的 104 名受試費的 104 名受試費的 104 名受試費的 104 名受試費的 104 名受試費的 104 名受法期的金森氏症病人 後生素 期間最頭常與食慾不完, 接受 MIRAPEX PR 錠劑治療 接受 MIRAPEX PR 錠劑治療,接受 安慰劑的 178	1 1 1 1 1 1 1 1 1 1 1 1 1	3 A A A A A A A A A A A A A	2 2 2 2 2 2 2 3 §事件發生率的影響。 EX PR 治療者的某些不,MIRAPEX PR 組% - 與口較。 一項雙盲、隨機分組、轉用每日前 時用每日轉用 MIRAPEX 而中斷治療。 RAPEX PR 錠劑治療 件為運動困難、噁心、便 (5%) 因不良事件而中 劑型 pramipexole 錠劑	胃腫腫黑腫、	血畜鱼畜腎 運鲜常定的過阻之、、向操、Cra镇經出陰:生草病、素、臟 動、、定心過阻理不侵知症人的症、不無(分吸吃乾結性、護瘤 能動智體的感味用人行觉易異加少失、en必暂困燥腸肝黑腺、、脈症變的慢能 水,肌人行爱易異如少失、en必暂困燥腸肝黑腺、促枕、外)覺眠避,為失醒常时病,持吃、等,真	語鍵無種膚 定塞意候半退神時 無極的 無極的 無極的 一次 一次 一次 一次 一次 一次 一次 一次 一次 一次 一次 一次 一次	· 基底細胞癌 · 基底細胞癌 · 大喜 · 大。 · 大 · 大 · 大 · 大 · 大 · 大 · 大 · 大	H F S A N F N A T 1 1 N F E F () Z () N T
血管性異常 起立型低血壓症 耳朵與內耳迷路(labyrinth) 異常 眩暈 代謝與營養異常 食慾增加 呼吸、胸部與縱隔膜異常 咳嗽 因為此研究係採彈性劑量調整期是至稅。 最初的不良事件的發生於良事件於則與會數學,等與劑組。 等與數學,對於與數學,對於與數學,對於與數學,對於與數學,對於數學,對於數學,對於數學,對於數學,對於數學,對於數學,對於數學,對於	1 1 1 1 1 1 1 1 1 1 1 1 1	3 A A A A A A A A A A A A A	2 2 2 2 2 2 2 3 §事件發生率的影響。 EX PR 治療者的某些不,MIRAPEX PR 組% - 與口較。 一項雙盲、隨機分組、轉用每日前 時用每日轉用 MIRAPEX 而中斷治療。 RAPEX PR 錠劑治療 件為運動困難、噁心、便 (5%) 因不良事件而中 劑型 pramipexole 錠劑	胃腫瘤、惡密 會不 一	血畜鱼畜腎 運鲜常、在D過阿米、CR環境經血陰:生量商族 系素 臟 動、、左心過阿理不侵知症人Ch症、不過 道呼呼子痰、惡瘤攝腫 不腦失 能以高學性省略覺、格仍、尿網(对吸吸乾、結性、護瘤 能動智體的感 机人行费易異和少失、m症增弱吸收咳,肌人行费易異和少失、mox暂困燥咳,解暑暑暑肢 废格、外)覺眠避,事為失醒常时症、衰衰,病疾,	· 整理 · · · · · · · · · · · · · · · · · ·	不是底細胞癌、膀胱癌、胃癌、腺糖体瘤、原子宫内膜癌、腹癌性肠癌、腹癌、脂囊的原癌、脂囊的原癌、卵巢肠癌、胃癌、乳毒性原癌、卵巢肠癌、肠肠癌、肠肠癌、肠肠癌、肠肠癌、肠肠癌、肠肠癌、肠肠癌、肠肠癌、肠肠癌、	H F S A N F N A T 1 1 N F E F () Z () N T
血管性異常 起立型低血壓症 耳朵與內耳迷路(labyrinth) 異常 眩暈 代謝與營養異常 食慾增加 呼吸、胸部與縱隔膜異常 咳嗽 因為此研究係採彈性劑量調整期景 衰初的不良事件可能發生於 良事件於則分數,與對於一方。 安慰劑組%=治療差疾氏症, 好別的不見事調整期之之 安慰劑組%=治療差疾氏症, 好別的不見事問數。 是事件的金森時期的 可以表面的 104 名 是事件的。 是事件的。 是事件的。 是事件的。 是事件的。 是事件, 是事件, 是事件, 是事件, 是事件, 是事件, 是事件, 是事件,	1 1 1 1 1 1 1 1 1 1 1 1 1	3 A A A A A A A A A A A A A	2 2 2 2 3 录事件發生率的影響。 EX PR 治療者的某些不,MIRAPEX PR 組 % - 與口乾。 一項雙盲、隨機分組、轉用每日劑轉用 MIRAPEX 而中斷治療。 RAPEX PR 錠劑治療 件為運動困難、噁心、便 (5%) 因不良事件而中 劑型 pramipexole 錠劑 EX PR 錠劑治療中斷的	胃腫腫黑腫、 原性性瘤、 原性性瘤、 原性性瘤、 原性性瘤、 原性性瘤、 原性性瘤、 原性性瘤、 原性性瘤、 原性性瘤、 原性性瘤、 原性性瘤、 原性性瘤、 原性性瘤、 原性性瘤、 原性性瘤、 所述性瘤、 一种質道的形子 是不自動。 是在一种。 是在一种。 是在一种。 是在一种。 是在一种。 是在一种。 是有。 是有。 之。 是有。 之。 是有。 之。 是有。 之。 是有。 之。 是有。 之。 是有。 之。 是有。 之。 是一种	血畜鱼畜腎 運鲜常、在D過阿米、CR環境經血陰:生量商族 系素 臟 動、、左心過阿理不侵知症人Ch症、不過 道呼呼子痰、惡瘤攝腫 不腦失 能以高學性省略覺、格仍、尿網(对吸吸乾、結性、護瘤 能動智體的感 机人行费易異和少失、m症增弱吸收咳,肌人行费易異和少失、mox暂困燥咳,解暑暑暑肢 废格、外)覺眠避,事為失醒常时症、衰衰,病疾,	· 整理 · · · · · · · · · · · · · · · · · ·	· 基底細胞癌 · 基底細胞癌 · 大喜 · 大。 · 大 · 大 · 大 · 大 · 大 · 大 · 大 · 大	H F S A N F N A T 1 1 N F E F () Z () N T
血管性異常 起立型低血壓症 耳朵與內耳迷路(labyrinth) 異常 眩暈 代謝與營養異常 食慾增加 呼吸、胸部與縱隔膜異常 咳嗽 因為此研究係採彈性劑量調整期 長期的不良事件可能發現, 安慰劑組%=治療養疾氏症病 分別的試驗之, 安慰劑組%=治療養疾氏症症 分別的試驗之, 安慰劑的 104 名 平利K和APEX PR 錠劑時受試者 任末期帕金森氏症症 份PR 錠劑的 104 名 末期帕金森氏症 在末期帕量原常與食慾不計 後受 MIRAPEX PR 錠劑的 178 6 数 到覺、現餘與食慾不能 形容,接受安慰劑的 178 6 数 175 名病人中有 8 人 (5 不良事件為為末期帕金森氏症 表 2 所列為末期帕金森氏症	1 1 1 1 1 1 1 1 1 1 1 1 1	3 A A A A A A A A A A A A A	2 2 2 2 2 3 录事件發生率的影響。 EX PR 治療者的某些不,MIRAPEX PR 組 % -	胃性性原性。 療力 所動性 所動性 所動性 所動性 所動性 所動性 所動性 所動性	血會色會勞。運鲜常公の過阻之、、向躁、Co录頻經引陰:性量商過病、素、臟、動、、症の過陣理不侵知症人的症、不面道呼呼子痰敏、惡瘤攝腫、不腦失。此高學性不侵知症人的症、不調(分吸吸乾、性結性、護瘤 能動智體ISI感 机人行喪易異面少失、他泌暫困燥咳鼻腸肝黑腺、 、脈症治的侵眠炎,人行喪易其面及禁乳t的停難、 家炎系解暑服皮、 假术,外)覺眠避、、失症、,后、、,真有、	感聽經濟度。全意底、減病度迷煩解情精的是、原格的學學學學學學學學學學學學學學學學學學學學學學學學學學學學學學學學學學學學	不是 基底細胞癌 素素 素素 素素 素素 素素 素素 素素 素素 素素 素	H F S A N F N A T 1 1 N F E F () Z () N T
血管性異常 起立型低血壓症 耳朵與內耳迷路(labyrinth) 異常 眩暈 代謝與營養異常 食慾增加 呼吸、胸部與縱隔膜異常 咳嗽 因為此研究係採彈性劑量調於 吸、胸部與縱隔膜異常 咳嗽 因為此研究係採彈性劑量對與良數劑的 因表對的的不於則量 湯納療金森評病人的 MIRAPEX PR 錠劑的 104 名 受 表 到 的 175 名 病 所 以 與 经 数 例 版 到 贵 次 的 175 名 病 成 以 與 经 表 到 所 的 175 名 病 成 以 與 经 表 2 所 列 為 末 期 帕 全 索 氏 症 不良 事 件 為 序 表 1 所 的 2% 日 的 175 名 病 於 以 與 经 表 2 所 列 為 末 期 帕 全 索 氏 近 不良 事 件 為 序 表 1 所 分 為 末 期 帕 全 至 少 2% 且 高 於 安 慰 自 於 安 慰 自 於 安 慰 自 於 安 慰 自 於 安 慰 自 於 安 慰 可 的 178 的 175 名 病 於 可 178 的 178 的 175 名 病 於 可 178 的 178	1 1 1 1 1 1 1 1 1 1 1 1 1	3 A A A A A A A A A A A A A	2 2 2 2 3 §事件發生率的影響。 EX PR 治療者的某些不,MIRAPEX PR 組% - · · · · · · · · · · · · · · · · · ·	胃性性的原性的原性的原性的原性的原性的原性的原性的原性的原性的原性的原性的原性的原	血瘤色瘤等 運鲜等症の過阻平、向操、C尿頻經出陰:生毒商员系素、臟、動、、症以過阻平、向操、C尿頻經出陰:性等商员、惡痛攝腫、不腦失。此為學性、質質、人的症、不 通呼呼子痰敏 玩器用黑腺、 、 脈症場的 實際的人行喪易異細少失、 配泌暫困燥咳鼻、冷腸肝黑腺、 、 肠症外的 曼眠速, 、 原、 、 , , , , , , , , , , , , , , , ,	感嫌短庸。全意候半退、病腹迷煩解情精的是尿疹和性性的鼻息痰流上、結瘤胞、癌症、臟性半退、神活走流離緒神,排死痛寫道內出肉、鼻、性肠、腹、腹、腹、腹、腹、腹、腹、腹、腹、腹、腹、腹、腹、腹、腹、腹、腹、腹、	· 基底細胞癌 · 基底細胞癌 · 大疱性皮膚 · 大丸 · 大力 · 大丸 · 大丸	
血管性異常 起立型低血壓症 耳朵與內耳迷路(labyrinth) 異常 眩暈 代謝與營養異常 食慾增加 呼吸、胸部與縱隔膜異常 咳嗽 因為此研究係採彈性劑量調整病 最初的不於劑量調整病是不可能的不於劑量調整病是不可能的的, 是不可能的。 是一种。 是一种。 是一种。 是一种。 是一种。 是一种。 是一种。 是一种	1 1 1 1 1 1 1 1 1 1 1 1 1	3 A A A A A A A A A A A A A	2 2 2 2 3 §事件發生率的影響。 EX PR 治療者的某些不,MIRAPEX PR 組% - · · · · · · · · · · · · · · · · · ·	胃性性的 開性性的 開性性的 開性性的 開生性的 開生性的 開生性的 開生性的 開生性的 開生性的 開生性的 開生性的 開生性的 開生性的 開生性的 開生性的 用等 用等 是不知 是不知 等。 一等 是不知 等。 是不知 等。 是不知 等。 是不知 等。 是不知 等。 是不知 等。 是不知 等。 是不知 等。 是是不知 是是是是。 是是是是是是是是是是是是是是是是是是是是是是是是是是是是是是	血畜鱼畜等 運鲜常症的過陣工人的操、CRX槓徑引急:生真商员、东斑、、、、、、、、、、、、、、、、、、、、、、、、、、、、、、、、、、、	語、種細瘤 高、種細瘤 高、性 生 生 生 生 生 生 生 生 生 生 生 生 生	· 基底細胞癌 · 基底細胞癌 · 大海性 · 大海性皮膚炎 · 大海性皮膚炎 · 大海性皮膚 · 大海性皮膚皮 · 大海性皮膚 · 大海球 · 大海性皮膚 · 大海球 · (livedo reticularis) · (livedo reticularis)	下
血管性異常 起立型低血壓症 耳朵與內耳迷路(labyrinth) 異常 眩暈 (labyrinth) 異常 眩暈 (常) (大) (大) (大) (大) (大) (大) (大) (大) (大) (大	1 1 1 1 1 1 1 1 1 1 1 1 1	3 A A A A A A A A A A A A A	2 2 2 2 2 2 3 Q事件發生率的影響。 EX PR 治療者的某些不,MIRAPEX PR 組% -	胃性性瘤、疾病、治學、治學、治學、學、學、學、學、學、學、學、學、學、學、學、學、學、學、學	血畜鱼畜寮、運鲜常、在沙湖、、、、、、、、、、、、、、、、、、、、、、、、、、、、、、、、、、、	· 建二醇 · · · · · · · · · · · · · · · · · · ·	· 基底細胞癌 · 基底細胞癌 · 大疱性皮膚 · 大丸 · 大力 · 大丸 · 大丸	1
血管性異常 起立型低血壓症 耳朵與內耳迷路(labyrinth) 異常 眩暈 代謝與營養異常 食慾增加 呼吸、胸部與縱隔膜異常 食慾增加 呼吸、胸部與縱隔膜異常 咳嗽 因為此所究係採彈性劑量調整期 長事件於劑量場所,沒數劑對。 以致動劑對。 以致動劑對對。 以致動劑對對。 以致動劑對對	1 1 1 1 1 1 1 1 1 1 1 1 1	3 A A A A A A A A A A A A A	2 2 2 2 2 2 2 2 3 Q事件發生率的影響。 EX PR 治療者的某些不,MIRAPEX PR 組%	胃性口髓等。 爾密爾爾斯特 所 所 所 所 所 所 所 所 所 所 所 所 所	血會色密等、運洋学会の過陣で、「冷、くの環境では陰:性量商量、斑域青皮病、素、臓・動、、症の障理性質性質、格で、尿調(分吸吸乾、性・頭、性炎膚、惡瘤攝腫・不腦失・此の障壁性質性質、格で、尿調(分吸吸乾、性・頭、性炎膚、唇、腫、腫、腫、腫、腫、腫、腫、腫、腫、腫、腫、腫、腫、腫、腫、腫、腫、腫、	感嫌然腫膚 定塞意症、减病度迷煩解情精。 素腫細瘤 定塞意候半退神活走渦離結神,頻液痛度道內出肉、鼻 皮慢、感腐肠、癌 症、髓候半退神活走涮離緒神,頻液痛弱道內出肉、鼻 皮腹牛、感胃唇、膚皮 靜出降(水水,神骨昏智(認亞),用。吸咳塞塞鼻 塵狀、變常、兩與部瘤頭 能 N 意识 與神子,於與常,不、注,以神骨昏智(18亞),如今, 與一人, 與一人, 與一人, 與一人, 與一人, 與一人, 與一人, 與一人	· A E E E E E E E E E E E E E E E E E E	1
血管性異常 起立型低血壓症 耳朵與內耳迷路(labyrinth) 異常 眩暈 (labyrinth) 異常 眩暈 (常) (大) (大) (大) (大) (大) (大) (大) (大) (大) (大	1 1 1 1 1 1 1 1 1 1 1 1 1	3 A A A A A A A A A A A A A	2 2 2 2 2 2 2 2 3 Q事件發生率的影響。 EX PR 治療者的某些不,MIRAPEX PR 組%	胃性口膜。 爾瘤。 爾瘤。 爾瘤。 爾瘤。 一种頸前、 一种 一种頸前、 一种頸前、 一种頸前、 一种頸前、 一种頸前、 一种頸前、 一种頸前、 一种頸前、 一种頸前、 一种頸前、 一种一种一种 一种一种一种一种	血會至會 運鲜等在の過阻之、向操、C尿頻經出陰:生鳥角圖、死斑感費皮病病、素、臟、動、、定心局理生得知症人的症、不血道呼呼子痰敏、无斑感,是變為性、護瘤、振動智體ISI感味用人行喪易異細少失、e的質 困燥咳鼻、冷膚過皮小動腸肝黑腺、、脈症患的臭眠皮,具有人,原皮,以下,原皮,以下,原皮,以下,原皮,以下,,原皮,,则是胀,外,是,有,,则是胀,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	感嫌經濟。全意候上、減病度迷煩解情精)是、尿疹肝陰肺鼻息痰流上比應熱皮梗化結瘤的、癌、症、髓性肾炎神活走流離緒神,頻液痛寫道內出肉、鼻、性度、中皮、腸、脂、皮、水、腹、骨、外、骨、外、骨、外、骨、外、骨、外、骨、外、骨、外、骨、外、骨、外、骨	基底細胞癌 素素 素素 素素 素素 素素 素素 素素 素素 素素 素	- X- 1 - X - 1 - X - X - X - X - X - X -
血管性異常 起立型低血壓症 耳朵與內耳迷路(labyrinth) 異常 眩暈 代謝與營養異常 食慾增加 呼吸、胸部與縱隔膜異常 咳嗽 因為此研究係採彈性劑量調 吸嗽 因為此研究係採彈性劑量調 等 咳嗽 因為此研究係採彈性劑量調 發數對劑組%=約億差 最初的不良事間整期差 是事門組 與對的。 是事門組 與對的。 是事門的。 是事門的。 是事門的。 是事門的。 是事門的。 是不行組 的。 是事門的。 是不行組 的。 是不行組 的。 是不行 是 是 的。 是 是 的。 是 的。 是 的。 是 的。 是 的。 是 的。	1 1 1 1 1 1 1 1 1 1 1 1 1	3 A A A A A A A A A A A A A	2 2 2 2 2 2 2 2 3 Q事件發生率的影響。 EX PR 治療者的某些不,MIRAPEX PR 組%	胃性口膜。 爾瘤。 爾瘤。 爾瘤。 爾瘤。 一种頸前、 一种 一种頸前、 一种頸前、 一种頸前、 一种頸前、 一种頸前、 一种頸前、 一种頸前、 一种頸前、 一种頸前、 一种頸前、 一种一种一种 一种一种一种一种	血畜鱼畜等(運鲜学会20過加入、、向操、CRX槓徑引盒呼呼子痰動局、光斑處青皮病、素素、臟、動、、、心障性不侵知症人下。不血道呼呼子痰敏、性炎膚變熱、惡痛攝腫、不腦失。此高學性省略覺、格如、宋而(分吸吸乾、性、頭、性炎膚變熱結性、護瘤、能動智體的感情和事為失極常、此次等國人等數,會數層瘤脈、腸肝黑腺、、脈症等的過程,與人行變易異和火失、由於暫困燥咳鼻、冷膚敏膚瘤脈、腸肝黑腺及、像枕、外)覺眠避、為失醒常、成為、其60、、鼻衣、汗角反灼、预滞	語彙經濟 高雄經濟 高雄經濟 高雄經濟 高雄經濟 高雄經濟 高雄經濟 高雄經濟 高極。 高速 一位 一位 一位 一位 一位 一位 一位 一位 一位 一位	基底與癌、 東國 東國 東國 東國 東國 東國 東國 東國 東國 東國	- X- 1 - X - 1 - X - X - X - X - X - X -

n=178

%

1

申經系統異常

量眩(姿勢性)

運動困難

n=164

%

2

n=175

6.1 臨床試驗經驗

劑型 pramipexole
11
6
0
1
7
4
1
3
良事件發生率的影響。 PEX PR 治療者的某些不 ,MIRAPEX PR 組 % -

劑型 pramipexole 錠劑臨床試驗期間所觀察到的其他不良事件

ramipexole 錠劑的因果關係如何,所有通報事件均予以納入。 與淋巴系統異常:貧血、缺鐵性貧血、白血球增多症、白血球減少症、淋巴結發炎、後的生長受到抑制 結病變、血小板增多症、血小板減少症。 動脈阻塞、發紺、期外收縮、左心室衰竭、心肌梗塞、結性心律不整、竇性心律不開研究顯示,pramipexole 會抑制人類與兔子之泌乳激素的分泌。 · 、家族性與遺傳性病症:心房中隔缺損、先天性足部畸形、脊椎畸形。

型内耳迷路異常:耳聾、耳朵疼痛、聽力受損、聽力減退、動量症、前庭性共濟失 8.4 在兒童之使用 分泌病症:甲狀腺腫、甲狀腺機能亢進、甲狀腺機能不足。 情病症:眼調節異常、暫時性黑矇症(amaurosis fugax)、眼瞼炎、眼瞼痙攣、白內障、 天性淚管狹窄、複視、乾眼症、眼睛出血、眼睛刺激不適、眼睛疼痛、眼瞼水腫、眼 下垂、青光眼、角膜炎、黃斑部退化、近視、畏光、視網膜剝離、視網膜血管異常、 增至 12 小時。在早期帕金森氏症病人所進行以安慰劑對照的 MIRAPEX PR 錠劑臨床 用五是不可能發生,但力捷期、視力降低、系動性。 、視力異常、視力模糊、視力降低、飛蚊症。 月炎、直腸出血、逆流性食道炎、舌頭腫大、舌頭潰瘍、牙痛、臍疝氣。 身性病症:胸部不適、冷顫、死亡、停藥症候群、臉水腫、感覺冷、感覺熱、緊張不 9. 藥物濫用與 9.1 管制物質 發燒、步態不穩、聽力受損、類似流感症狀、焦躁易怒、局部水腫、水腫、身體不 *病症*:膽絞痛、膽囊炎、慢性膽囊炎、膽石症。

低鈉血症、維生素缺少症、肌酸 PK 增加、代謝性鹼毒症。

走、低納血症、維生素缺少症、肌酸 PK 唱加、代謝性廠等症。

为骨骼與結締組織異常:骨頭痛、黏液囊炎、筋膜炎、腹侧疼痛、脊椎盤異常、脊椎
突出、關節積液腫脹、關節僵直、調節腫大、單關節炎、肌肉僵硬、肌肉骨骼僵直、
肉無力、肌肉病變、肌炎、頸背僵硬、骨關節炎、骨壞死、骨質疏鬆症、四肢疼痛、
用20分子量爲 302.26。 性肌痛症、類風濕性關節炎、肩膀疼痛、脊椎骨關節炎、肌腱炎、肌腱鞘炎、抽痛。化學結構 惡性與未指明之腫瘤:腹部腫瘤、腺癌、良性腺瘤、基底細胞癌、膀胱癌、乳癌、 f瘤、慢性淋巴性白血病、結腸癌、結腸直腸癌、子宮內膜癌、膽囊癌、胃癌、腸 四管瘤、肝臟腫瘤、惡性肝臟腫瘤、唇部與/或口腔癌、惡性肺部腫瘤、轉移 · 高、淋巴瘤、惡性黑色素瘤、黑素細胞痣、肺部之轉移癌症、多發性骨髓瘤、良性 <mark></mark> 空腫瘤、腫瘤、惡性腫瘤、攝護腺腫瘤、皮膚腫瘤、神經瘤、卵巢癌、攝護腺癌、攝 泉腺瘤、假性淋巴瘤、腎臟腫瘤、皮膚癌、皮膚乳頭狀瘤、鱗狀細胞癌、甲狀腺腫瘤、 ·統異常:味覺喪失、運動不能、健忘症、靜坐不能、抗膽鹼症候群、失語症、腦水腫、

書寫障礙、肌張力不全症、錐體外症候群(extrapyramidal syndrome)、臉部麻痺、分解。Pramipexole dihydrochloride 在水中的溶解度超過 20%,在甲醇中大約 8%,遂作抽搐(grand mal convulsion)、半身不遂、感覺過敏、運動機能亢進、反射亢(在乙醇中大約 0.5%,但幾乎不溶於二氯甲烷(dichloromethane)。 京村機館、Qrand mar conversion)

一方(1)

「大方(2)

「大 頭痛 肌肉不自主攣縮 肌陣攣 嗜眠病 神經痛 神經病變 眼球震顫症(nystagmus),覺倒錯(parosmia)、心理性肌肉過度活動、坐骨神經痛、鎮靜狀態、感覺障礙、睡 間位節律混亂、說夢話、不省人事、迷走神經性昏厥、緊張性頭痛、思想異常。 神異常:不穩度性影響、侵略行為、煩調不安、智力遲鈍、磨牙、自殺、精神錯亂、 損症。始寒刑妄相症、方向知覺藥生、經難狀態(discociation)、結集困情、治驗結果 痛 肌肉不自主攣縮 肌陣攣 嗜眠病 神經痛 神經病變 眼球震顫症(nystagmus) 度が、小穏反に影音・区でロリックスペース 日本の大学 12.1 年間 12.1 年 困難、性慾增高、狂躁症、易醒、情緒改變、惡夢、妄想、妄想性強迫症、恐慌反 藥理治療分類:多巴胺促效劑,ATC code:N04BC05。 、偏執反應、睡中異常、人格異常、精神異常、心神不定、夢遊、自殺意念。 腎結石 *韓與尿道異常*:色尿症(chromaturia),排尿困難、葡萄糖尿、血尿、急尿感、腎結石 ,對專一性,亦有完全的內在活性,對 D₃ 受體亞型的結合親和力高於 D₂ 或 D₄ 亞型。 偏執反應、睡中異常、人格異常、精神異常、心神不定、夢遊、自殺意念。 性膀胱功能異常、夜尿症、少尿症、頻尿、蛋白尿、腎動脈狹窄、腎絞痛、腎囊腫、 Pramipexole 用於治療帕金森氏症的確切作用機轉未知,但應該與其對紋狀體 竭、腎功能受損、尿頻、尿失禁、尿液滯留、尿道發炎。

」 原準線、子宮出皿、医垣ブルグツ | 陸垣田皿。 ₹、胸腔與縱隔膜異常:呼吸暫停、肺內異物吸入、氣喘、哽噎、慢性阻塞性肺疾、 直乾、發聲困難、運動性呼吸困難、鼻出血、咳血、打嗝、換氣過度、支氣管分泌物 在 60 名健康的男性與女性自願受試者進行一項臨床試驗,以評估 pramipexole 對 口、喉頭痙攣、鼻塞、鼻子乾燥、鼻息肉、阻塞性氣管病症、咽喉痛、胸膜炎、肺炎、心電圖 QT 間隔的影響。所有的受試者均先接受一天一次 0.375 mg MIRAPEX PR 人性肺炎、氣胸、鼻後滴痰、咳嗽有痰、肺栓塞、肺水腫、呼吸性鹼中毒、呼吸窘迫、錠劑治療,然後每三天調升一次劑量,直至一天分別為 2.25 mg 與 4.5 mg。結果 注意場、呼吸道充血、過敏性鼻炎、流鼻涕、鼻竇充血、睡眠窒息症、打噴嚏、打呼、並未發現 MIRAPEX PR 對 QT 間隔平均值有任何與劑量或暴露量有關的影響,但此 及急促、喘鳴。 實與皮下組織異常: 粉刺 秃頭、冷汗、上皮性囊腫、皮膚炎、大疱性皮膚炎、接觸性皮膚炎、 實與皮下組織異常: 粉刺 秃頭、冷汗、上皮性囊腫、皮膚炎、大疱性皮膚炎、接觸性皮膚炎、 症師性tidine)、腎功能受損或較高劑量而在體內較高暴露量,但目前尚未經過一個系統 質乾燥、淤血、濕疹、紅斑、皮膚角化過度、網狀青斑(livedo reticularis)、夜間盗汗 性的評估此一情況對 QTc 間隔的影響。

aynaud's phenomenon)、休克、血栓性靜脈炎、血栓形成、靜脈曲張。

以下為速放劑型 pramipexole 錠劑獲核准使用後所發現的不良反應,主要發生於帕金 線性藥物動力學性質。一天服用一次之 MIRAPEX PR 錠劑所緩慢釋放的 pramipexole **森氏症病人。** | RA になたがスプログラス | RA になっています。 | Pramipexole 血漿濃度(C_{max}、C_{min}) 與藥物暴露的因果關係。是否將這些反應納入藥物標示通常須根據一項或多項以下因
吸收 素決定:(1)反應嚴重程度,(2)通報頻率,或(3)與 pramipexole 錠劑的因果關 Pramipexole 的絕對生體可用率超過 90%,顯示其吸收完全,且體循環前的代謝 係強度。以 MedDRA 專用術語將相近類型的事件歸類成項目較少的標準化類別:異常 (presystemic metabolism) 極低 行為、異常夢境、意外事件(包括摔倒)、昏倒、心衰竭、強迫性購物、疲勞、幻覺 (所有種類)、頭痛、低血壓症(包括姿勢性低血壓症)、抗利尿素分泌異常、食量増加

因為是否可能發生藥物交互作用,主要取決於活性藥物 pramipexole 本身而非其配 方,因此並未針對 MIRAPEX PR 錠劑進行藥物交互作用研究。目前已有速放劑型 pexole 錠劑配方的資料。

因為 pramipexole 為多巴胺致效劑,因此多巴胺拮抗劑 例如,抗精神疾病藥物 [phenothiazines、butyrophenones、thioxanthenes] 或 netoclopramide)可能降低 MIRAPEX PR 錠劑的療效。 不建議將抗精神病藥物與 MIRAPEX 併用,例如:當多巴胺拮抗效果可被預期時 (請參 | plasma ratio)約為 2 顯示。

閱「警語與特別注意事項」欄)。 7.3 藥物/實驗室檢測交互作用 Pramipexole 與實驗室檢測之間無已知的交互作用存在。

8. 在特定族群的使用

時,才可在懷孕期間使用 MIRAPEX PR。 於整個懷孕期間接受 pramipexole 的大鼠,其受精卵的著床會受到 2.5 mg /公斤/天 子或人類則否)。因為在這些研究中出現的事件為懷孕中斷與早期胚胎流失,因此無法 適當評估 pramipexole 的致畸胎性。在器官生成期間給予懷孕兔子最高 10 mg /公斤

動脈阻塞、發紺、期外收維、左心至多物、心即收塞、四压心性工程、具体心性、同時先顯小,pidinipexole 自到的人及之外。因為許多藥物均會從人類乳汁分泌,而且同本評估所以能不定到 pidinipexole 《宋初期》以子に及り可能,因此以為此數學的有 90% 為藥物原型,肝功能受損對 pramipexole 的清除應無顯著的影響。 pramipexole 在哺乳嬰兒可能引發嚴重的不良反應,因此必須在考量此藥物對母親的重 腎功能受損

要性之後,決定是否中斷哺乳或中斷用藥。 尚未評估 MIRAPEX PR 錠劑在兒童病人使用的藥物動力學狀況、安全性與療效。

9. 藥物濫用與成癮

ipexole 尚未在動物或人體進行系統性的藥物濫用、耐受性或成癮狀況研究,但在 的清除率。

$$H_2N$$
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昏迷、抽搐、協調異常、失智症、意識下降、注意力不集中、姿勢性暈眩、發音困 Pramipexole dihydrochloride 為白色至黃白色粉末,在 296° C 至 301° C

衰竭、腎功能受損、尿頻、尿失禁、尿液滯留、尿道發炎。 直系統與乳房異常:月經不調、乳房疼痛、經痛、附睪炎、男性女乳化、陽萎、更年 支持,這些研究顯示,pramipexole 可藉由活化紋狀體與黑質體(substantia nigra) 定狀、月經過多子宮出血(metrorrhagia)、卵巢囊腫、陰莖持續勃起症、攝護腺炎、 (此為神經細胞傳送訊號至紋狀體的部位)中之多巴胺受體而影響紋狀體的神經激發速 率(neuronal firing rates)。D3 受體的結合與帕金森氏症的關聯性目前不明。

> 12.3 藥物動力學 與一天使用三次之速放劑型 pramipexole 錠劑可產生相同的每日最大與最小

「包括暴飲暴食、強迫進食症與過度攝食症)、性慾異常(包括性慾增高與降低以及性 | 慾過高 (hypersexuality))、病態性賭博、搔癢、暈厥、嘔吐與體重增加。 在藥物流行病學的研究中,和未使用者相比使用 pramipexole,顯示與增加心衰竭的危 | 險有相關性。

願者進行的多劑研究中,一天服用一次的 MIRAPEX 錠劑(4.5 mg),其 24 小時期間 均未發現類似的病灶。此病灶在人體的重要性目前不明。 的 C_{max} 及 AUC 會與一天服用三次的速放劑型 pramipexole 錠劑(1.5 mg / 次)達到 生體相等性。MIRAPEX 錠劑達到最高濃度的平均時間為 6 小時。相較於空腹狀態服用,協床藥物動力學資料(*請參閱臨床藥理學 [12.3]*)以及在早期與末期帕金森氏症病人 大約 20%,T_{max} 則延遲大約 2 小時,但這些差異不具臨床相關性。

Pramipexole 的組織分佈極廣,分佈體積約為 500 L(變異係數 [coefficient of variation,CV] = 20%),大約有 15% 與血漿蛋白質結合。 Pramipexole 會分布至紅血球細胞內,這可由紅血球對血漿比值(erythrocyte-to-

性的特定代謝物質。 Pramipexole 主要經由尿液排除,約可從尿液回收使用劑量的 90%,而且幾乎都是未 I-III 期)的有效性,已在一項隨機分組、雙盲、以安慰劑對照、3 個平行組別的臨床 改變的原型藥物形式。Pramipexole 的腎臟清除速率約為 400 mL /分鐘(CV=25%),試驗中獲得確立。受試者接受 MIRAPEX PR 錠劑、速放劑型 pramipexole 錠劑或安慰

在特殊族群之藥物動力學 於整個懷孕期間接受 pramipexole 的大鼠,其受精卵的著床會受到 2.5 mg /公斤/天 劑量(為以 mg / m² 為準之人體最大建議劑量 [MRHD] 的 5 倍)所抑制。於器官生 時期間(檢及第 7 至 16 王),绘予懷及未聞 1 5 mg /公斤/天劑量的 pramipexole, 以獲致最理想的療效。初始劑量的調整無須考量性別、體重、人種或年齡,但腎功能不療。主要療效評估指標為:相較於安慰劑,以 MIRAPEX PR 錠劑治療 18 週後 UPDRS

> 女性的 pramipexole 清除率約較男性低 30%,但此差異為體重差異所致。 Pramipexole 在男性與女性血漿中的半衰期並無差異。

相較於健康的年輕自願受試者(< 40 歲),老年人(≧ 65 歲)的 pramipexole 清除 率約降低 30%,此差異極可能為腎功能隨年齡下降所致,因為 pramipexole 清除率與 第 18 與 33 週時,MIRAPEX PR 錠劑的平均劑量約為 3 mg /天。在最後評估之前,

肝功能受損 尚未評估肝功能不足對 pramipexole 之藥物動力學性質有何影響。因為經由尿液排出 末期帕金森氏症

因為是否可能發生藥物交互作用,主要取決於活性藥物 pramipexole 本身而非其配方, ¦因此並未針對 MIRAPEX PR 錠劑進行具體的藥物動力學藥物交互作用試驗。以下交互 ■用資料係來自速放劑型 pramipexole 錠劑。

多巴/左多巴的吸收(AUC)或清除率,但可使左多巴的 C_{max} 增加約 40%, T_{max} 則 從 2.5 小時縮短為 0.5 小時。 第 33 週時,接受 MIRAPEX PR 錠劑治療者(n=177)UPDRS 第 II+III 部分之分數平 位 2.5 小時縮短為 0.5 小時。 Selegiline:在健康的自願受試者(N=11),selegiline 不會影響 pramipexole 的藥物 動力學性質。 Amantadine:族群藥物動力學分析顯示,amantadine 可小幅降低口服 pramipexole 多巴胺不良事件而降低左多巴每日劑量。依據性別、年齡、人種(白人或亞洲人)或 Cimetidine:cimetidine 會經由陽離子運輸系統抑制有機鹼在腎小管的分泌作用,

metidine 會使 pramipexole AUC 增加 50%,半衰期增加 40%(N=12)。 Probenecid: probenecid 會經由陰離子運輸系統抑制有機酸在腎小管的分泌作用, probenecid 不會明顯影響 pramipexole 的藥物動力學性質。(N=12)。 經由腎臟清除的其他藥物:族群藥物動力學分析顯示,併用經由陽離子運送系統清 除的藥物(例如 cimetidine、ranitidine、diltiazem、triamterene、vera

ramipexole 清除率的影響則可能極小 CYP 交互作用:細胞色素 P450 酵素的抑制劑應不致影響 pramipexole 的 清除率,因為無論在體內或體外,pramipexole 均不受這些酵素的明顯影 響。Pramipexole 對 CYP 酵素 CYP1A2、CYP2C9、CYP2C19、CYP2E1 與 CYP3A4 均無抑制作用。對 CYP2D6 之抑制作用的表觀 Ki 值(apparent Ki) 為 30μM,顯示在使用臨床劑量(4.5 mg / 天)之後所觀察到的血漿濃度下, pramipexole 對 CYP 酵素不具抑制作用。

影響腸胃蠕動或胃部 pH 值的藥物: 族群藥物動力學分析顯示,併用制酸劑(N=6)會使口服 pramipexole 的清除率 大約降低 25%,但 H2- 阻斷劑(N=5)、抗膽鹼劑(anticholinergics)(N=27)、 propulsive(N=7)與質子幫浦抑制劑(N=16)對口服 pramipexole 清除率的影響可

物中既良小鼠(取向用里 10 IIIg / A/I / A/ / Ca / UIg / III / Will / All / A/ / Ca / UIg / III / Will / All / A/ / A/ / Ca / UIg / III / Will / All /

在體外(細菌逆突變 [reverse mutation]、V79/HGPRT 基因突變、CHO 細胞中的染 性 在體外(細菌逆突變 [reverse mutation]、V79/HGPRT 基因突變、CHO 細胞中的染 請告知病人與其照護者,使用 Mirapex 時,病人可能出現強烈的花錢慾望、賭博衝動、色體變異)與體內(小鼠徵核 [micronucleus])的微核檢測中,pramipexole 均不具性慾增加、暴飲暴食與/或其他強烈慾望,而且無法控制這些衝動。 致突變性或誘變性。 在大鼠的繁殖力研究中,2.5 mg/公斤/天劑量的 pramipexole(以 mg/m² 請告知病人,服藥可能導致產生幻覺,而且老年帕金森氏症病人的發生風險高於較年為準,大約為 MRHD 的 5 倍)可延長發情期並抑制著床。這些作用與血清中泌較的病人。

乳激素濃度降低有關,因為泌乳激素為大鼠著床與維持早期懷孕所必需的荷爾蒙。 13.2 動物毒物學與/或藥理學 在大鼠的研究中觀察到性發育延遲的現象(即包皮分離與陰道開口)。在人類相對的影

變化(感光細胞的退化與喪失)。在接受 2 或 8mg /公斤/天劑量(血漿 AUC 分別 因為尚未在實驗動物完全確認 pramipexole 是否具有致畸胎,而且在人體的經驗亦有 相當於一天三次 1.5 mg 之 MRHD 在人體所產生之 AUC 的 2.5 與 12.5 倍)的動物, 限,若女性病人於治療期間懷孕或打算懷孕,請即告知醫生。 這些發現最先於第76週期間觀察到,且與劑量相關。在有色大鼠接受 pramipexole 17.6 餵哺母乳的母親 (2 或 8mg/公斤/天)治療 2 年的類似研究中,並未發現視網膜退化現象,但相較 因為 pramipexole 可能從母乳中排出 若女性病人打算或正在餵哺母乳 請即告知醫生。 於對照組大鼠,藥物治療組動物視網膜外核層變薄的幅度稍大。 研究顯示,在白化大鼠,pramipexole 可降低視盤從視網膜之柱狀感光細胞

(photoreceptor rod cells)剝離(此與對光的破壞作用較為敏感有關)的發生率。在

0.5 或 2.0 mg /公斤/天劑量(以 mg / m² 為準時,分別為最高臨床劑量的 0.4、2.2 台灣百靈佳般格翰股份有限公司 與速放劑型 pramipexole 錠劑一樣,MIRAPEX PR 錠劑在整個臨床劑量範圍內均呈現 與 8.6 倍)的 pramipexole 治療 12 個月,以及給予迷你豬 0.3、1 或 5 mg /公斤/ 天劑量的 pramipexole 治療 13 週時,均未在視網膜偵測到任何變化。 雖然此作用在人體具有何種重要性尚未確立,但不能忽視,因為這可能為一種普遍存在 脊椎動物的機制(亦即視盤剝離 [disk shedding])受到破壞。

與食物一起使用時(亦即高脂肪餐),MIRAPEX 錠劑的 AUC 不受影響,但 C_{max} 增加 進行的兩項隨機分組、雙盲、以安慰劑對照、多中心的臨床試驗均證實,MIRAPEX PR 錠劑對帕金森氏症具有治療效果。在這兩項隨機分組試驗中,均以帕金森氏症統 一量表(Unified Parkinson's Disease Rating Scale,UPDRS)作為主要評估指標。 UPDRS 量表共分四個部分,含有多個項目,旨在評估心理活動(第 I 部分)、日常活 動(第 II 部分)、運動功能(第 III 部分)與治療的併發症(第 Ⅳ 部分)。 UPDRS 第II 部分包含13個與日常活動有關的問題分數從0分(正常)至4分(最嚴重) 總分最高為 52 分(最嚴重)。UPDRS 第 III 部分包含 14 個項目,旨在評估帕金森氏 症病人的主要運動徵狀(例如,顫抖、僵直、動作遲緩、姿勢不穩定等)的嚴重程度, 僅極少量(<10%)- 的 pramipexole 被代謝。在人體血漿或尿液中並未找到任何具有活一針對身體不同部位進行評分,總分最高為 108 分(最嚴重)。

MIRAPEX PR 錠劑對未曾接受左多巴治療之早期帕金森氏症病人(Hoehn 與 Yahr 第 | 優学親別で | 尚未在懷孕婦女進行有良好對照組的適當研究。僅在可能的益處超過對胎兒的可能風險 | 職子運送系統分泌。 | 職子運送系統分泌。 0.375 mg /天,再根據療效與耐受性,將劑量彈性調升,最高至 4.5 mg /天。研究 期間允許使用左多巴作為救援藥物,亦允許受試者同時接受穩定劑量之單胺氧化酶

治療 18 週後,接受 MIRAPEX PR 錠劑治療者(n=102)UPDRS 第 II+III 部分之分數 與基準點的平均差異為 -8.1 分,安慰劑組(n=50)則為 -5.1 分,兩者的差異具有統計顯著性(p<0.03)。安慰劑組與 MIRAPEX PR 錠劑組分別有 7 名 (14%)與 3 名 (3%)受試者接受左多巴救援藥物治療。第 18 週時,MIRAPEX PR 的平均劑量為 3 mg / 天。 第 33 週時,在接受 MIRAPEX PR 錠劑治療的受試者(n=213),UPDRS 第 II+III 部 分之校正後分數平均較基準點改善-8.6 分,安慰劑組(n=103)則為-3.8 分。 安慰劑組與 MIRAPEX PR 錠劑組分別有 22-名(21%)與 15 名(7%)受試者接受左 多巴救援藥物治療。

B(MAOB-I)抑制劑藥物、抗膽鹼劑或 amantadine 等藥物治療的病人,與未接受這 藥物治療者均具有相近的反應。

MIRAPEX PR 錠劑對併用左多巴療法(最適劑量)於出現運動功能波動(每天的累積「關」時間至少 2 小時)之末期帕金森氏症病人(其「開」時間屬於 Hoehn 與 Yahr 相較於健康的自願受試者,重度腎功能受損者(肌酸酐清除率約為 20 mL / 分鐘)的 第 II-IV 期)的有效性,已在一項隨機分組、雙盲、以安慰劑對照、3 個平行組別的速放劑型 pramipexole 清除率約降低 75%,中度腎功能受損者(肌酸酐清除率約為 臨床試驗中獲得確立。受試者接受 MIRAPEX PR 錠劑、速放劑型 pramipexole 錠劑 40 mL / 分鐘)則約降低 60%。在各種程度之腎功能受損者,pramipexole 清除率與 或安慰劑治療。接受 MIRAPEX PR 錠劑或速放劑型 pramipexole 錠劑治療的初始 至 4.5 mg /天,接著為 26 週的維持期。僅在出現多巴胺不良事件時,才可降低左 多巴劑量。主要療效評估指標為:相較於安慰劑,以 MIRAPEX PR 錠劑治療 18 週後 UPDRS 第 II+III 部分之分數與基準點的平均差異(校正後)。 治療 18 週後,接受 MIRAPEX PR 錠劑治療者(n=161)UPDRS 第 II+III 部分之分數 平均較基準點改善 −11.0 分(校正後),安慰劑組(n=174) 則為 −6.1 分(p=0.0001)。

> 第 18 與 33 週時,MIRAPEX PR 錠劑的平均每日劑量均為 2.6 mg/天。第 18 週時, 目較於基準點,安慰劑組與 PPX ER 組分別有 4 名(3%)與 14 名(11%)受試者因 併用其他抗帕金森氏症藥物(MAOB-I amantadine 或抗膽鹼劑)所進行的子分析中並未觀察到其有效性出現具有臨床重要性的差異。 15. 藥物外觀、形狀及標示:

樂伯克 持續性藥效錠 0.375 毫克為白色、圓形、具斜邊之錠劑。錠劑正面刻有"P1", 樂伯克 持續性藥效錠 0.75 毫克為白色 圓形 具斜邊之錠劑。錠劑正面刻有"P2", 反面刻有 百靈佳殷格翰公司標誌。 樂伯克 持續性藥效錠 1.5 毫克為白色、橢圓形之錠劑。錠劑正面刻有"P3",反面刻有 百靈佳殷格翰公司標誌。

儲存於 30° C 以下。避免暴露於高濕氣。請存放在孩童無法取得的安全位置。 「保存期限 : 標識於外盒。 17. 用藥說明

請病人遵循處方服用 MIRAPEX PR 錠劑 若錯過一劑藥物 請病人勿將下一劑劑量加倍。 MIRAPEX PR 錠劑可空腹或與食物一起服用。若出現噁心症狀請告知病人,將 MIRAPEX PR 錠劑與食物一起服用,可能有助減少噁心的發生。 MIRAPEX PR 錠劑必須整顆吞服,不可嚼碎、壓碎或切割。

MIRAPEX PR 錠劑與速放劑型 pramipexole 錠劑的主要成分均為 pramipexole。請病 人切勿同時服用速放劑型 pramipexole 與 MIRAPEX PR。

可能性。因為困倦為可能造成嚴重後果的常見不良事件,病人在有足夠的使用經驗可 供判斷 MIRAPEX PR 錠劑是否會影響其精神與/或運動功能之前,請勿開車或從事其 3.1 致癌性、致失妄性、工身刀支援。

3.在小鼠與大鼠進行為期兩年的 pramipexole 致癌性研究。將 pramipexole 添加於食
动中餵食小鼠(最高劑量 10 mg /公斤/天)(若以 mg / m² 為準,大約為最大建議
刺中餵食小鼠(最高劑量 10 mg /公斤/天)(若以 mg / m² 為準,大約為最大建議
期間出現睡著的新狀况時,在與醫生聯絡之前,請勿開車或從事可能具有危險性的活動。

174姿勢性(起立型)低血壓症 請告知病人 服用 MIRAPEX PR 可能導致發生姿勢性 (起立型) 低血壓症 可能出現量眩、

噁心、昏倒,有時也會有盜汗等症狀,但亦可能無症狀。剛開始治療時,可能較常出 現低血壓症。因此,請病人勿從坐著或躺著的姿勢快速起身,尤其在久坐或久躺之後 以及在剛開始接受 MIRAPEX PR 治療時

製造廠: Rottendorf Pharma GmbH Ostenfelder Straße 51-61, 59320 Ennigerloh, Germany (德國)

臺北市民生東路三段 2 號 12 樓

修訂時間: 2019 年 12 月

Mirapex® **Prolonged-Release Tablets** 0.375 mg & 0.75 mg & 1.5 mg FULL PRESCRIBING INFORMATION 1 INDICATIONS AND USAGE DOSAGE AND ADMINISTRATION General Dosing Consideration MIRAPEX PR tablets are taken orally once daily, with or without food. MIRAPEX PR tablets must be swallowed whole and must not be chewed, crushed, or divided If a significant interruption in therapy with MIRAPEX PR tablets has occurred, re-titration of therapy 2.2 Dosing for Parkinson's Disease

The starting dose is 0.375 mg given once per day. Based on efficacy and tolerability, dosages may be increased gradually, not more frequently than every 5 to 7 days, first to 0.75 mg per day and then by 0.75 mg increments up to a maximum recommended dose of 4.5 mg per day. In clinical trials, dosage was initiated at 0.375 mg/day and gradually titrated based on individual therapeutic response and tolerability. Doses greater than 4.5 mg/day have not been studied in clinical trials. Patients should be assessed for therapeutic response and tolerability at a minimal interval of 5 days or longer after each dose increment. Due to the flexible dose design used in clinical trials, specific dose-response information could not

When discontinuing therapy with MIRAPEX PR, taper the dose gradually over a period of one week (see Warnings and Precautions). In some studies with immediate-release pramipexole tablets, however, abrupt discontinuation was uneventful. Dosing in Patients with Renal Impairment

The elimination of pramipexole is dependent on renal function [see Clinical Pharmacology (12.3)]. Patients with mild renal impairment (a creatinine clearance above 50 mL/min) require no reduction

In patients with moderate renal impairment (creatinine clearance between 30 and 50 mL/min) MIRAPEX PR tablets should initially be taken every other day. Caution should be exercised and daily dosing after one week, and before any additional titration in 0.375 mg increments up to 2.25 mg per day. Dose adjustment should occur no more frequently than at weekly intervals. MIRAPEX PR tablets have not been studied in patients with severe renal impairment (creatinine clearance <30 mL/min) or patients on hemodialysis, and are not recommended in these patients 2.3 Switching from Immediate-Release Pramipexole Tablets to MIRAPEX PR Patients may be switched overnight from immediate-release pramipexole tablets to MIRAPEX PR

3 DOSAGE FORMS AND STRENGTHS 0.375mg white to off-white, round, biconvex, bevel-edged, extended-release tablets debossed with "P1" on one side and the Boehringer Ingelheim company symbol on the other side.

0.75mg white to off-white, round, biconvex, bevel-edged, extended-release tablets debossed with "end on a regular basis when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX pround, biconvex, bevel-edged, extended-release tablets debossed with "end on a regular basis when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX PR tablets for any indication. Ideally, periodic skin when using MIRAPEX PR tablets for any indication with "P2" on one side and the Boehringer Ingelheim company symbol on the other side.

1.5mg white to off-white, oval, biconvex, extended-release tablets debossed with "P3" on one Patients with Parkinson's disease may present with axial dystonia such as antecollis, camptocormic side and the Boehringer Ingelheim company symbol on the other side.

- - WARNINGS AND PRECAUTIONS -

Falling Asleep During Activities of Daily Living living, including the operation of motor vehicles, which sometimes resulted in accidents. Although augmentation. initiation of treatment. In placebo-controlled clinical trials in Parkinson's disease, the sudden onset of sleep or sleep attacks were reported in 8 of 387 (2%) patients treated with MIRAPEX PR tablets showed no significant difference between pramipexole (N = 152) and placebo groups (N = 149).

compared to 2 of 281 (1%) patients on placebo. compared to 2 of 281 (1%) patients on placebo.

In early Parkinson's disease, somnolence was reported in 36% of 223 patients treated with MIRAPEX Some patients have reported the occurrence of remnants in faeces which may resemble intact PR modified does 3.0 mg/day compared to 15% of 103 patients on placebo. In advanced Parkinson's loss and the occurrence of remnants in faeces which may resemble intact dose 3 mg/day, compared to 16% of 178 patients on placebo. Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of preexisting iolence, although patients may not give such a history. For this reason, prescribers should

Before initiating treatment with MIRAPEX PR tablets, advise patients of the potential to develop drowsiness, and specifically ask about factors that may increase the risk such as the use of concomitant sedating medications or alcohol, the presence of sleep disorders, and concomitant medications that increase pramipexole plasma levels (e.g., cimetidine). If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.), MIRAPEX PR tablets should ordinarily be discontinued. If a decision is made to continue MIRAPEX PR tablets, advise patients not to drive and Inappropriate antidiuretic hormone secretion to avoid other potentially dangerous activities. While dose reduction reduces the degree of somnolence, there is insufficient information to establish that dose reduction will eliminate

episodes of falling asleep while engaged in activities of daily living. 5.2 Symptomatic Orthostatic Hypotension Dopamine agonists, in clinical studies and clinical experience, appear to impair the systemic egulation of blood pressure, with resulting orthostatic hypotension, especially during dose escalation. Parkinson's disease patients, in addition, appear to have an impaired capacity to respond Hallucinations dopaminergic agonists, including MIRAPEX PR, ordinarily require careful monitoring for signs and symptoms of orthostatic hypotension, especially during dose escalation, and should be informed of this risk. In placebo-controlled clinical trials in Parkinson's disease, symptomatic orthostatic

5.3 --- Impulse Control/Compulsive Behaviors --

Case reports and the results of cross-sectional studies suggest that patients can experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge eating, and/or other intense urges, and the inability to control these urges while taking one or more of the medications, including MIRAPEX PR, that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease. In some cases, although not all, these urges were reported to have Somnolence stopped when the dose was reduced or the medication was discontinued. Because patients may not Systems recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with MIRAPEX PR. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking Cardiac disorders

A total of 1056 patients with Parkinson's disease who participated in two MIRAPEX PR placebocontrolled studies of up to 33 weeks duration were specifically asked at each visit about the occurrence of these symptoms. A total of 14 of 387 (4%) treated with MIRAPEX PR tablets, 12 of 388 (3 %) treated with immediate-release pramipexole tablets, and 4 of 281 (1%) treated with placebo

Respiratory, thoracic and mediastinal disorders reported compulsive behaviors, including pathological gambling, hypersexuality, and/or compulsive

In placebo-controlled clinical trials in Parkinson's disease, hallucinations (visual or auditory or nixed) were reported in 25 of 387 (6%) patients treated with MIRAPEX PR tablets compared to 5 of - Nausea 281 (2%) patients receiving placebo. Hallucinations led to discontinuation of treatment in 5 of 387 (1%) patients on MIRAPEX PR tablets. Age appears to increase the risk of hallucinations attributable to pramipexole. In placebo-controlled Hypersensitiv linical trials in Parkinson's disease, hallucinations were reported in 15 of 162 (9%)patients ≥

65 years of age taking MIRAPEX PR tablets compared to 10 of 225 (4%)patients <65 years of age

MIRAPEX PR tablets may potentiate the dopaminergic side effects of levodopa and may cause or exacerbate preexisting dyskinesia.

5.6 Renal Impairment

The elimination of pramipexole is dependent on renal function [see Clinical Pharmacology (12.3)]. Patients with mild renal impairment (a creatinine clearance above 50 mL/min) require no reduction in daily dose. MIRAPEX PR tablets have not been studied in patients with moderate to severe renal Weight decrease including decreased appetite Weight increase rment (creatinine clearance <50 mL/min) or on hemodialysis.

Boehringer 5.7 Rhabdomyolysis

Boehringer 5.7 Rhabdomyolysis
Ingelheim In the clinical development program for immediate-release pramipexole tablets, a single case of rhabdomyolysis occurred in a 49-year-old male with advanced Parkinson's disease. The patient was Advise patients to contact a physician if they experience any unexplained muscle pain, tenderness, or During the premarketing development of MIRAPEX PR tablets, patients with early Parkinson's disease weakness, as these may be symptoms of rhabdomyolysis.

5.8 Retinal Changes in Albino Rat

Pathologic changes (degeneration and loss of photorecentor cells) were observed in the retina of albino reveal similar changes. The potential significance of this effect for humans has not been established. but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (i.e., disk shedding) may be involved.

5.9 Patients with psychotic disorders ents with psychotic disorders should be treated with dopamine agonists only if the potential nefits outweigh the risks. Co-administration of antipsychotic medicinal products with pramipexolo

5.10 Events Reported with Dopaminergic Therapy development program, they are associated with the use of other dopaminergic drugs. The expected incidence of these events, however, is so low that even if pramipexole caused these events at rates similar to those attributable to other dopaminergic therapies, it would be unlikely that even a single case would have occurred in a cohort of the size exposed to pramipexole in studies to date.

Although not reported with pramipexole in the clinical development program, a symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been orted in association with rapid dose reduction, withdrawal of, or changes in anti-Parkinsonian herapy (see section Dosage and Administration). Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, pleural thickening, pericardi

and cardiac valvulopathy have been reported in patients treated with ergot-derived dopamine agents. While these complications may resolve when the drug is discontinued, complete resolutio Although these adverse events are believed to be related to the ergoline structure of these compour whether other, non-ergot derived dopamine agonists can cause them is unknown. Cases of possible fibrotic complications, including peritoneal fibrosis, pleural fibrosis, and pulmon fibrosis have been reported in the postmarketing experience with immediate-release pramipexole tablets. While the evidence is not sufficient to establish a causal relationship between pramipexole

these fibrotic complications, a contribution of pramipexole cannot be completely ruled out. Epidemiologic studies have shown that patients with Parkinson's disease have a higher risk (2- to ablets at the same daily dose. When switching between immediate-release pramipexole tablets and approximately 6-fold higher) of developing melanoma than the general population. Whether the MIRAPEX PR tablets, patients should be monitored to determine if dosage adjustment is necessary. observed increased risk was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear. For the reasons stated above, patients and providers are advised to monitor for melanomas freque

> pleurothotonus (Pisa Syndrome). Dystonia has occasionally been reported following initiation of dopamine agonists including pramipexole, although a clear causal relationship has not been established. Dystonia may also occur several months following medication initiation or adjustmen dystonia occurs, the dopaminergic medication regimen should be reviewed and an adjustment

uamentation in RLS nts treated with pramip exole have reported falling asleep while engaged in activities of daily Reports in the literature indicate that treatment of RLS with dopaminergic medications can result in many of these patients reported somnolence while on pramipexole tablets, some perceived that Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), incre they had no warning signs such as excessive drowsiness, and believed that they were alert in symptoms, and spread of symptoms to involve other extremities. Augmentation was specifically immediately prior to the event. Some of these events had been reported as late as one year after the investigated in a controlled clinical trial over 26 weeks. 11.8% of patients in the pramipexole group

PR, median dose 3.0 mg/day, compared to 15% of 103 patients on placebo. In advanced Parkinson's MIRAPEX prolonged-release tablets. If patients report such an observation, the physician should disease, somnolence was reported in 15% of 164 patients treated with MIRAPEX PR tablets, median reassess patient's response to therapy. 5.12 Drug withdrawal syndrome A drug withdrawal syndrome has been reported during or after discontinuation of dopamine agoni nually reassess patients for drowsiness or sleepiness, especially since some of the events occur including pramipexole. Risk factors may include high cumulative dopaminergic exposure. Withdrax

well after the start of treatment. Prescribers should also be aware that patients may not acknowledge symptoms do not respond to levodopa, and may include apathy, anxiety, depression, fatigue, sweat drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific and pain. Prior to discontinuation, patients should be informed about potential withdrawal sympt and closely monitored during and after discontinuation. In case of severe withdrawal symptoms, temporary re-administration of a dopamine agonist at the lowest effective dose may be consider ADVERSE REACTIONS Infections and infestations

Endocrine disorders

Psychiatric disorders binge eating, compulsive shopping, hypersexuality and pathological gambling

sion was reported in 10 of 387 (3%) patients treated with MIRAPEX PR tablets compared to Restlessness 3 of 281 (1%) patients on placebo. One patient of 387 on MIRAPEX PR tablets discontinued Nervous system disorders

Eye disorders Visual impairment including diplopia, vision blurred and visual acuity reduced

Vascular disorders

Gastrointestinal disorders

Skin and subcutaneous tissue disorders

General disorders and administration site conditions

Peripheral oedema Drug withdrawal syndrome (Dopamine agonist withdrawal syndrome) (see section Special Warni and Precautions)

moderate (41%) in intensity.

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in on the incidence of adverse events the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug (or Adverse events can initially occur in either the titration or maintenance phase. Some adverse events hospitalized with an elevated CPK (10,631 IU/L). The symptoms resolved with discontinuation of the development program of a different formulation of the same drug) and may not reflect the developed in MIRAPEX PR-treated patients during the titration phase and persisted (≥7 days) into the 8.1 Pregnancy rates observed in practice.

were treated with MIRAPEX PR tablets, placebo, or immediate-release pramipexole tablets. In addition, LaboratoryTesting a randomized, double-blind, parallel group trial was conducted in 156 early Parkinson's disease patients (Hoehn & Yahr Stages I-III) to assess overnight switching of immediate-release pramipexole tablets to MIRAPEX PR tablets. In this latter study, concomitant treatment with stable doses of ration a 2-year carcinogenicity study. While retinal degeneration was not diagnosed in pigmented rats in a 2-year carcinogenicity study. While retinal degeneration was not diagnosed in pigmented rats individually or in combination, was allowed. In a third trial, advanced Parkinson's disease patients treated for 2 years, a thinning in the outer nuclear layer of the retina was slightly greater in rats given drug compared with controls. Evaluation of the retinas of albino mice, monkeys, and minipigs did not the layer of the retinas of albino mice, monkeys, and minipigs did not the layer of the retinas of albino mice, monkeys, and minipigs did not the layer of the retinas of albino mice, monkeys, and minipigs did not the layer of the retinas of albino mice, monkeys, and minipigs did not the layer of the retinas of albino mice, monkeys, and minipigs did not the layer of the retinas of albino mice, monkeys, and minipigs did not the layer of the retinas of albino mice, monkeys, and minipigs did not the layer of the retinas of albino mice, monkeys, and minipigs did not the layer of the retinas of albino mice, monkeys, and minipigs did not the layer of the retinas of albino mice, monkeys, and minipigs did not the layer of the retinas of albino mice, monkeys, and minipigs did not the layer of the retinas of albino mice, monkeys, and minipigs did not the layer of the retinas of albino mice, monkeys, and minipigs did not the layer of the retinas of albino mice, monkeys, and minipigs did not the layer of the retinas of albino mice, monkeys, and minipigs did not the layer of the retinas of albino mice, monkeys, and minipigs did not the layer of the retinas of albino mice, monkeys, and minipigs did not the layer of the retinas of albino mice, monkeys, and minipigs did not the layer of the retinas of the retinas of the layer of the retinas of the retinas of the layer of the

The most commonly observed adverse events (25% and more frequent than placebo) after 33 weeks of treatment with MIRAPEX PR tablets in the trial of early Parkinson's disease patients were somnolence, due to adverse events compared to 4 of 103 (4%) patients who received placebo and approximately 20 of 213 (9%) patients who received immediate-release pramipexole tablets. The adverse event most only causing discontinuation of treatment with MIRAPEX PR tablets was nausea (2%). Although the events enumerated below may not have been reported with the use of pramipexole in its Table 1 lists adverse events that occurred with a frequency of at least 2% with MIRAPEX PR and were more frequent than with placebo during 33 weeks of treatment in a double-blind, placebo-controlled study in early Parkinson's disease. In this study, patients did not receive concomitant levodopa however, levodopa was permitted as rescue medication. Adverse events were usually mild (38%) or

Treatment-Emergent Adverse-Event Incidence in a Double-Blind, Placebo-Controlled

PR and greater than wit	h Placebo)			dacryostenosis acquired, diplopia, dry eye, eye hemorrhage, eye irritation, eye pain, eyelid edema,	8.4 Pediatric Use
Body System / Adverse Event	Placebo	MIRAPEX PR	Immediate Release Pramipexole	eyelid ptosis, glaucoma, keratitis, macular degeneration, myopia, photophobia, retinal detachment,	The pharmacokinetics, safety, an
	(n=103)	(n=223)	(n=213)	retinal vascular disorder, scotoma, vision abnormalities, vision blurred, visual acuity reduced, vitreous floaters	evaluated. 8.5 Geriatric Use
	%	%	%	Gastrointestinal disorders: abdominal distension, aphthous stomatitis, ascites, cheilitis, colitis, colitis	Pramipexole total oral clearance
Nervous system disorders				ulcerative, dyspepsia, dysphagia, duodenal ulcer, duodenal ulcer hemorrhage, enteritis, eructation,	with younger subjects, because of
Somnolence	15	36	33	fecal incontinence, gastric ulcer, gastric ulcer hemorrhage, gastritis, gastrointestinal hemorrhage,	reduction in renal function. This r
Dizziness	7	12	12	gastroesophageal reflux disease, gingivitis, haematemesis, haematochezia, hemorrhoids, hiatus hernia,	
Tremor	T	3	3	hyperchlorhydria, ileus, inguinal hernia, intestinal obstruction, irritable bowel-syndrome, esophageal -	disease, 47% of the 259 patients
Balance disorder	1	2	0	spasm, esophageal stenosis, esophagitis, pancreatitis, periodontitis, rectal hemorrhage, reflux esophagitis, tongue edema, tongue ulceration, toothache, umbilical hernia	hallucinations were more commo
Gastrointestinal disorders				sesophagius, tongue edema, tongue uiceration, toothache, umbilicar hernia General disorders: chest discomfort, chills, death, drug withdrawal syndrome, face edema, feeling cold,	compared to 2% of the patients < 8.6 Patients with Renal Impa
Nausea	9	22	24	feeling hot, feeling jittery, fever, gait disturbance, impaired healing, influenza-like illness, irritability,	The elimination of pramipexole is
Constipation	2	14	12	localized edema, edema, malaise, pitting edema, thirst	low in dialysis patients, as a negli
Dry mouth	1	5	4	Hepatobiliary disorders: biliary colic, cholecystitis, cholecystitis chronic, cholelithiasis	9 DRUG ABUSE AND DEPE
Vomiting	0	4	4	Immune system disorders: drug hypersensitivity	9.1 Controlled Substance
Upper abdominal pain	1	3	4	Infections and infestations: abscess, acute tonsillitis, appendicitis, bronchiolitis, bronchitis,	Pramipexole is not a controlled si
Dyspepsia	2	3	3	bronchopneumonia, cellulitis, cystitis, dental caries, diverticulitis, ear infection, eye infection, folliculitis, fungal infection, furuncle, gangrene, gastroenteritis, gingival infection, herpes simplex,	9.2 Abuse and Dependence
Abdominal discomfort	0	2	1	homeunus, rungar infection, rundricle, gangrene, gastroentenus, gingivar infection, nerpes simplex,	Pramipexole has not been system
General disorders and				onychomycosis, oral candidiasis, orchitis, osteomyelitis, otitis externa, otitis media, paronychia,	tolerance, or physical dependenc
administration site conditions				pyelonephritis, pyoderma, sepsis, skin infection, tonsillitis, tooth abscess, tooth infection, upper	had little or no effect.
Fatigue	4	6	6	respiratory tract infection, urethritis, vaginal candidiasis, vaginal infection, viral infection, wound	10 OVERDOSAGE
Peripheral edema	4	5	8	infection	There is no clinical experience wi
Asthenia	2	3	1	Injury, poisoning, and procedural complications: accidental falls, drug toxicity epicondylitis, road traffic	for 2 days in a clinical trial for an
Musculoskeletal and connective				accident, sunburn, tendon rupture Metabolism and nutrition disorders: cachexia, decreased appetite, decreased weight, dehydration,	rate increased to between 100 and the increased dose.
tissue disorders				diabetes mellitus, fluid retention, gout, hypercholesterolemia, hyperglycemia, hyperlipidemia,	There is no known antidote for o
Muscle spasms	3	5	3	hyperuricemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, hypovitaminosis, increased	stimulation are present, a phenoi
Psychiatric disorders				creatine PK, metabolic alkalosis	the efficacy of such drugs in reve
Hallucinations, including	1	5	6	Musculoskeletal and connective tissue disorders: bone pain, bursitis, fasciitis, flank pain, intervertebral	of overdose may require general :
visual, auditory and mixed				disc disorder, intervertebral disc protrusion, joint effusion, joint stiffness, joint swelling, monarthritis,	electrocardiogram monitoring.
Insomnia	3	4	4	muscle rigidity, musculoskeletal stiffness, myasthenia, myopathy, myositis, nuchal rigidity,	11 DESCRIPTION
Sleep attacks or sudden	1	3	6	osteoarthritis, osteonecrosis, osteoporosis, pain in extremity, polymyalgia, rheumatoid arthritis,	MIRAPEX PR tablets contain pran
onset of sleep				shoulder pain, spinal osteoarthritis, tendonitis, tenosynovitis, twitching heoplasms benian, malianant, and unspecified: abdominal neoplasm, adenocarcinoma, adenoma	pramipexole dihydrochloride is (S
Sleep disorder	1	2	3	benign, basal cell carcinoma, bladder cancer, breast cancer, breast neoplasm, chronic lymphocytic	dihydrochloride monohydrate. It weight is 302.26.
Depression	0	2	0	leukemia, colon cancer, colorectal cancer, endometrial cancer, gallbladder cancer, gastric cancer,	The structural formula is:
Injury, poisoning and procedural				gastrointestinal neoplasm, hemangioma, hepatic neoplasm, hepatic neoplasm malignant, lip and/or	
complications				oral cavity cancer, lung neoplasm malignant, lung cancer metastatic, lymphoma, malignant melanoma,	
Fall	1	4	4	melanocytic naevus, metastases to lung, multiple myeloma, oral neoplasm benign, neoplasm,	
Vascular disorders				neoplasm malignant, neoplasm prostate, neoplasm skin, neuroma, ovarian cancer, prostate cancer,	NI -
Orthostatic hypotension	1	3	0	prostatic adenoma, pseudo lymphoma, renal neoplasm, skin cancer, skin papilloma, squamous cell	/N
Ear and labyrinth disorders				carcinoma, thyroid neoplasm, uterine leiomyoma Nervous system disorders: ageusia, akinesia, amnesia, akathisia, anticholinergic syndrome, aphasia,	H_2N
Vertigo	1	4	2	brain edema, carotid artery occlusion, carpal tunnel syndrome, cerebral artery embolism, cerebral	
Metabolism and nutrition				hemorrhage, cerebral infarction, cerebral ischemia, chorea, cognitive disorder, coma, convulsion,	`s \
disorders				coordination abnormal, dementia, depressed level of consciousness, disturbance in attention,	1
Increased appetite	1	3	2	dizziness postural, dysarthria, dysgraphia, dystonia, extrapyramidal syndrome, facial palsy, grand mal	
ricopii atorij, tiroracio arra				convulsion, hemiplegia, hyperaesthesia, hyperkinesia, hyperreflexia, hyporeflexia, hypertonia,	Pramipexole dihydrochloride is a
modiactinal disorders				nynestnesia nynotonia lethargy loss of consciolisness memory impairment migraine muscle	

Because this study used a flexible dose titration design, it was not possible to assess the effects of dose on the incidence of adverse events.

Sleep talking, stupor, syncope vasovagal, tension headache, thinking abnormalities.

Psychiatric disorders: affect lability, aggression, agitation, bradyphrenia, bruxism, suicide, delirium, Adverse events can initially occur in either the titration or maintenance phase. Some adverse events delusions, delusional disorder persecutory type, disorientation, dissociation, emotional distress, developed in MIRAPEX PR-treated patients during the titration phase and persisted (27 days) into the euphoric mood, initial insomnia, libido increased, mania, middle insomnia, mood altered, nightmare, maintenance phase (i.e., MIRAPEX PR % - placebo % = treatment difference ≥2%); persistent adverse obsessive thoughts, obsessive-compulsive disorder, panic reaction, paranoid reaction, parasomnia, A double-blind, randomized, parallel group trial evaluated the tolerability of an overnight switch from Renal and urinary disorders; chromaturia, dysuria, glycosuria, hematuria, urgency, nephrolithiasis.

release pramipexole tablets to MIRAPEX PR tablets discontinued due to adverse events (vertigo and tract infection

levodopa. Adverse events were usually mild (32%) or moderate (17%) in intensity.

Table 2 Treatment-Emergent Adverse-Event Incidence in a Double-Blind, Placebo-Controlled Trial hypertrophy, skin irritation, skin nodule, skin odor abnormal, skin ulcer, urticaria greater than with Placebo)

Body System/Adverse Event	Placebo	MIRAPEX PR	Immediate-release pramipexo
	n = 178	n = 164	n = 175
	%	%	%
Nervous system disorders			
Dyskinesia	8	17	18
Headache	3	7	4
Dizziness (postural)	1	2	3
Gastrointestinal disorders			
Nausea	10	11	11
Constipation	5	7	6
Salivary hypersecretion	0	2	0
Diarrhea	1	2	1
Psychiatric disorders			
Hallucinations, including visual, auditory and mixed	2	9	7
Insomnia	2	4	4
Metabolism and nutrition disorders			
Anorexia	2	5	1
Musculoskeletal and connective tissue disorders			
Back pain	1	2	3

Because this flexible dose study used a titration design, it was not possible to assess the effects of dose 7.3 Drug/LaboratoryTest Interactions

naintenance phase (i.e., MIRAPEX PR % - placebo % = treatment difference ≥2%); persistent adverse events were dyskinesia and insomnia.

During the development of MIRAPEX PR tablets, no systematic abnormalities on routine laboratory testing were noted. Therefore, no specific guidance is offered regarding routine monitoring; the practitioner retains responsibility for determining how best to monitor the patient in his or her care. Other adverse events observed during clinical trials of immediate-release pramipexole tablets Adverse events not listed above but reported on at least two occasions (one occasion if the event was serious) in clinical studies involving 2509 individuals who received pramipexole immediate-release due to the prolactin-lowering effect of pramipexole, since prolactin is necessary for implantation and lationship to pramipexole immediate-release tablets.

Blood and lymphatic system disorders: anemia, iron deficiency anemia, leukocytosis, leukopenia, extrasystoles, left ventricular failure, myocardial infarction, nodal arrhythmia, sinus arrhythmia, sinus 8.3 Nursing Mothers bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, tachycardia, ventricular fibrillation, ventricular extrasystoles, ventricular hypertrophy Congenital, familial, and genetic disorders: atrial septal defect, congenital foot malformation, spine

Ear and labyrinth disorders: deafness, ear pain, hearing impaired, hypoacusis, motion sickness, ocrine disorders: goiter, hyperthyroidism, hypothyroidisn

33 Week Trial in Early Parkinson's Disease (Events ≥2% of Patients Treated with MIRAPEX | Eye disorders: accommodation abnormalities, amaurosis fugax, blepharitis, blepharospasm, cataract, PR and greater than with Placebo acryostenosis acquired, diplopia, dry eye, eye hemorrhage, eye irritation, eye pain, eyelid edema, velid ptosis, glaucoma, keratitis, macular degeneration, myopia, photophobia, retinal detachment, tinal vascular disorder, scotoma, vision abnormalities, vision blurred, visual acuity reduced, vitreous evaluated

astrointestinal disorders: abdominal distension, aphthous stomatitis, ascites, cheilitis, colitis, colitis Pramipexole total oral clearance is approximately 30% lower in subjects older than 65 years compared ulcerative, dyspepsia, dysphagia, duodenal ulcer, duodenal ulcer hemorrhage, enteritis, eructation, with younger subjects, because of a decline in pramipexole renal clearance due to an age-related ecal incontinence, gastric ulcer, gastric ulcer hemorrhage, gastritis, gastrointestinal hemorrhage, astroesophageal reflux disease, gingivitis, haematemesis, haematochezia, hemorrhoids, hiatus hernia, 8,5 hours to 12 hours. In a placeho-controlled clinical trial of MIRAPEX PR tablets in early Parkin yperchlorhydria, ileus, inguinal hernia, intestinal obstruction, irritable bowel syndrome, esophageal - disease, 47% of the 259 patients were 265 years of age. Armong patients receiving MIRAPEX PR tablets, pasm, esophageal stenosis, esophagitis, pancreatitis, periodontitis, rectal hemorrhage, reflux hallucinations were more common in the elderly, occurring in 13% of the patients ≥ 65 years of age sophagitis, tongue edema, tongue ulceration, toothache, umbilical hernia compared to 2% of the patients <65 years of age. eneral disorders: chest discomfort, chills, death, drug withdrawal syndrome, face edema, feeling cold, 8.6 Patients with Renal Impairment eling hot, feeling jittery, fever, gait disturbance, impaired healing, influenza-like illness, irritability, calized edema, edema, malaise, pitting edema, thirst

ervous system disorders: ageusia, akinesia, amnesia, akathisia, anticholinergic syndrome, aphasia, brain edema, carotid artery occlusion, carpal tunnel syndrome, cerebral artery embolism, cerebral hemorrhage, cerebral infarction, cerebral ischemia, chorea, cognitive disorder, coma, convulsion, pordination abnormal, dementia, depressed level of consciousness, disturbance in attention izziness postural, dysarthria, dysgraphia, dystonia, extrapyramidal syndrome, facial palsy, grand mal onvulsion, hemiplegia, hyperaesthesia, hyperkinesia, hyperreflexia, hyporeflexia, hypertonia, ypesthesia, hypotonia, lethargy, loss of consciousness, memory impairment, migraine, muscle contractions involuntary, myoclonus, narcolepsy, neuralgia, neuropathy, nystagmus, parosmia, psychomotor hyperactivity, sciatica, sedation, sensory disturbance, sleep phase rhythm disturbance

personality disorder, psychotic disorder, restlessness, sleep walking, suicidal ideation immediate-release pramipexole tablets to MIRAPEX PR tablets at the same daily dose in 156 early neurogenic bladder, nocturia, oliguria, pollakiuria, proteinuria, renal artery stenosis, renal colic, renal activity at the D₂ subfamily of dopamine receptors, binding with higher affinity to D₃ than to D₂ or Parkinson's disease patients with or without levodopa. One of 104 patients switched from immediate- cyst, renal failure, renal impairment, urinary frequency, urinary incontinence, urinary retention, urinary <u>D</u>₄ receptor subtypes.

Reproductive system and breast disorders: amenorrhea, breast pain, dysmenorrhea, epididymitis, The most commonly observed adverse events (25% and greater frequency than in placebo) during 18 weeks of treatment with MIRAPEX PR tablets in the trial of advanced Parkinson's disease patients with concomitant levodopa were dyskinesia, nausea, constipation, hallucinations, headache, and with concomitant levodopa were dyskinesia, nausea, constipation, hallucinations, headache, and with concomitant levodopa were dyskinesia, nausea, constipation, hallucinations, headache, and with concomitant levodopa were dyskinesia, nausea, constipation, hallucinations, headache, and with concomitant levodopa were dyskinesia, nausea, constipation, hallucinations, headache, and with concomitant levodopa were dyskinesia, nausea, constipation, hallucinations, headache, and with concomitant levodopa were dyskinesia, nausea, constipation, hallucinations, headache, and with concomitant levodopa were dyskinesia, nausea, constipation, hallucinations, headache, and with concomitant levodopa were dyskinesia, nausea, constipation, hallucinations, headache, and with concomitant levodopa were dyskinesia, nausea, constipation, hallucinations, headache, and with concomitant levodopa were dyskinesia, nausea, constipation, hallucinations, headache, and with concomitant levodopa were dyskinesia, nausea, constipation, asthmac distinction, uterine hemorrhage, vaginal hemorrhage, va pyperventilation, increased bronchial secretion, laryngospasm, nasal congestion, nasal dryness, nasal 12.2 Pharmacodynamics Eight of 164 (5%) patients treated with MIRAPEX PR tablets for 18 weeks discontinued treatment due to adverse events compared to 7-of 178 (4%) patients who received placebo and 8 of 175 (5%) patients aspiration, pneumoniay edema; 60 healthy male and female volunteers. All subjects initiated treatment with 0.375 mg MIRAPEX PR -Eight of 164 (5%) patients treated with MIRAPEX PX tablets up 10 weeks upscriminated realization approach to 70 f178 (4%) patients who received placebo and 8 of 175 (5%) pati disease treated with MIRAPEX PR tablets. In this study, MIRAPEX PR tablets, or placebor was administered to patients with each season and the placebor was administered to patients with advanced Parkinson's was active and the united with advanced parkinson's with advanced parkinson's with advanced parkinson's was expensively and placebor with advanced parkinson's was administered to parkinson's wit

burning sensation, skin discoloration, skin disorders, skin exfoliation, skin hyperpigmentation, skin blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate for subjects treated with in Advanced Parkinson's Disease* (Events ≥2% of Patients Treated with MIRAPEX PR and Vascular disorders: aneurysm, angiopathy, arteriosclerosis, circulatory collapse, deep vein thrombosis, 10 bpm higher than placebo, respectively. Higher SBP, DBP, and pulse rates compared to placebo were embolism, hematoma, hot flush, hypertensive crisis, lymphoedema, pallor, phlebitis, Raynaud's phenomenon, shock, thrombophlebitis, thrombosis, varicose vein. Postmarketing Experience

The following adverse reactions have been identified during post-approval use of immediate-release pramipexole tablets, primarily in Parkinson's disease patients. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in administration results in the same daily administration of immediate-release pramipexole tablets.

[Caption of reporting, or (3) strength of causal connection to pramipexole tablets. Similar types of events were grouped into a smaller number of standardized categories using the MedDRA terminology:

[Chark, Cmin] as three times daily administration of immediate-release pramipexole tablets.

[Absorption]

[abnormal behavior, abnormal dreams, accidents (including fall), blackouts, cardiac failure, compulsive undergoes little presystemic metabolism: shopping, fatigue, hallucinations (all kinds), headache, hypotension (including postural hypotension), inappropriate antidiuretic hormone secretion, increased eating (including binge eating, compulsive eating, and hyperphagia), libido disorders (including increased and decreased libido, and hypersexuality), pathological gambling, pruritus, syncope, vomiting, and weight increase. In a pharmacoepidemiological study, pramipexole use was associated with an increased risk of cardiac

failure compared with non-use of pramipexole. DRUG INTERACTIONS No drug interaction studies were conducted with MIRAPEX PR tablets since the potential for drug interactions mainly depends on the active drug substance pramipexole and not the formulation. Data (i.e., high-fat meal) did not affect AUC but increased C_{max} by approximately 20% and delayed T_{max} by disease (e.g., tremor, rigidity, bradykinesia, postural instability, etc.), scored for different body regions are available for the immediate-release pramipexole tablet formulation. 7.1 Dopamine Antagonists Since pramipexole is a dopamine agonist, it is possible that dopamine antagonists, such as the

7.2 Antipsychotic Medicinal Products Co-administration of antipsychotic medicinal products with pramipexole is not recommended, e.g. if dopamine-antagonistic effects can be expected. (see section Warnings and Precautions)

There are no known interactions between pramipexole and laboratory tests USE IN SPECIFIC POPULATIONS

There are no adequate and well-controlled studies in pregnant women. MIRAPEX PR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. When pramipexole was given to female rats throughout pregnancy, implantation was inhibited at a dose of 2.5 mg/kg/day [5 times the maximum recommended human dose (MRHD) on a mg/m² basis] Administration of 1.5 mg/kg/day of pramipexole to pregnant rats during the period of organogenesis (gestation days 7 through 16) resulted in a high incidence of total resorption of embryos. The plasma AUC in rats at this dose was 4 times the AUC in humans at the MRHD. These findings are thought to be maintenance of early pregnancy in rats (but not rabbits or humans). Because of pregnancy disruption and early embryonic loss in these studies, the teratogenic potential of pramipexole could not be adequately evaluated. There was no evidence of adverse effects on embryo-fetal development

A single-dose, radio-labeled study showed that drug-related material was present in rat milk at ations three to six times higher than in plasma at equivalent time points. Studies have shown that pramipexole treatment resulted in an inhibition of prolactin secretion in

humans and rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from pexole, a decision should be made as to whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother

Pediatric Use The pharmacokinetics, safety, and efficacy of MIRAPEX PR tablets in pediatric patients have not been

8.5 Geriatric Use reduction in renal function. This resulted in an increase in elimination half-life from approximately

The elimination of pramipexole is dependent upon renal function. Pramipexole clearance is extremel low in dialysis patients, as a negligible amount of pramipexole is removed by dialysis. DRUG ABUSE AND DEPENDENCE

Controlled Substance Pramipexole is not a controlled substance. 9.2 Abuse and Dependence

Praminexole has not been systematically studied in animals or humans for its potential for abuse. tolerance, or physical dependence. However, in a rat model of cocaine self-administration, pramipexole oral clearance of pramipexole. had little or no effect.

10 OVERDOSAGE e is no clinical experience with significant overdosage. One patient took 11 mg/day of pramipexole Probenecid: Probenecid, a known inhibitor of renal tubular secretion of organic acids via the anionic njury, poisoning, and procedural complications: accidental falls, drug toxicity epicondylitis, road traffic for 2 days in a clinical trial for an investigational use. Blood pressure remained stable, although pulse transporter, did not noticeably influence pramipexole pharmacokinetics (N=12). rate increased to between 100 and 120 beats/minute. No other adverse events were reported related to Other drugs eliminated via renal secretion: Population pharmacokinetic analysis suggests that There is no known antidote for overdosage of a dopamine agonist. If signs of central nervous system ranitidine, diltiazem, triamterene, verapamil, quinidine, and quinine) decreases the oral clearance of

> 11 DESCRIPTION MIRAPEX PR tablets contain pramipexole, a non-ergot dopamine agonist. The chemical name of pramipexole dihydrochloride is (S)-2-amino-4,5,6,7-tetrahydro-6-(pr dihydrochloride monohydrate. Its empirical formula is C₁₀ H₁₇ N₃ S • 2HCl•H₂O, and its molecular

$$H_2N$$
 H_2N
 H_2N
 H_2N
 H
 H

exole dihydrochloride is a white to off-white powder substance. Melting occurs in the range of 296°C to 301°C, with decomposition. Pramipexole dihydrochloride is more than 20% soluble in water, V79/HGPRT gene mutation, chromosomal aberration in CHO cells) and in vivo (mouse micronucleus) about 8% in methanol, about 0.5% in ethanol, and practically insoluble in dichloromethane. APEX PR tablets, for oral administration, contain 0.375 mg, 0.75 mg, or 1.5 mg of pramipexole dihydrochloride monohydrate. Inactive ingredients are hypromellose, corn starch, carbomer homopolymer, colloidal silicon dioxide, and magnesium stearate

CLINICAL PHARMACOLOGY

rmacotherapeutic group: dopamine agonist, ATC code: N04BC05. ole is a non-ergot dopamine agonist with high relative *in vitro* specificity and full intrinsic

The precise mechanism of action of pramipexole as a treatment for Parkinson's disease is unknown. although it is believed to be related to its ability to stimulate dopamine receptors in the striatum. This conclusion is supported by electrophysiologic studies in animals that have demonstrated that

pramipexole generally increased during the rapid up-titration phase, by 10 mmHg, 7 mmHg, and maintained until the pramipexole doses were tapered; values on the last day of tapering were generally | because disruption of a mechanism that is universally present in vertebrates (i.e., disk shedding) may | Binger Strasse 173, 55216 Ingelheim am Rhein, Germany similar to baseline values. Such effects have not been observed in clinical studies with Parkinson's disease patients, who were titrated according to labeled recommendations.

12.3 Pharmacokinetics MIRAPEX PR tablets, like immediate-release pramipexole tablets, display linear pharmacokinetics over treated for 2 years with 0.3, 2.0, or 10 mg/kg/day (0.3, 2.2, and 11 times the highest clinical dose on a 12F, 2, Min Sheng E. Road, Sec. 3, Taipei, Taiwan, 104, R.O.C. the entire clinical dosage range. Slow release of pramipexole from MIRAPEX PR tablets with once-daily administration results in the same daily maximum and minimum pramipexole plasma concentrations male mice or rats and monkeys of either sex that were treated chronically with pramipexole. The

Increase in systemic exposure of pramipexole following oral administration of 0.375 mg to 4.5 mg of MIRAPEX PR tablets was dose-proportional. For MIRAPEX PR tablets, steady state of exposure is reached within 5 days of continuous dosing. Relative bioavailability of MIRAPEX PR tablets compared with immediate-release tablets was

approximately 100%. In a repeat-dose study in healthy, normal volunteers, MIRAPEX PR tablets 4.5 mg therapy (Part IV) administered once daily was bioequivalent with regard to Cmax and AUC over 24 hours to immediate | Part II of the UPDRS contains 13 questions related to activities of daily living, which are scored from 0 release pramipexole tablets 1.5 mg administered three times daily. The average time-to-peak concentration for MIRAPEX PR tablets is 6 hours. Administration of MIRAPEX PR tablets with food approximately 2 hours compared with dosing under fasted conditions; these differences are not sidered to be clinically relevant.

cells as indicated by an erythrocyte-to-plasma ratio of approximately 2.

identified in human plasma or urine.

Urinary excretion is the major route of pramipexole elimination, with 90% of a pramipexole dose wered in urine, almost all as unchanged drug. The renal clearance of pramipexole is approximately mL/min (CV=25%), approximately three times higher than the glomerular filtration rate. Thus, receiving placebo (n=50), a difference that was statistically significant (p<0.03). Seven patients 400 mL/min (CV=25%), approximately three times higher than the glomerular filtration rate. Thus, pramipexole is secreted by the renal tubules, probably by the organic cation transport system. rmacokinetics in Specific Populations Because therapy with MIRAPEX PR tablets is initiated at a low dose and gradually titrated upward

according to clinical tolerability to obtain the optimum therapeutic effect, adjustment of the initial dose based on gender, weight, race, or age is not necessary. However, renal insufficiency causes a large patients receiving placebo (n=103). decrease in the ability to eliminate pramipexole. This will necessitate dosage adjustment in patients At 18 and 33 weeks, the mean dose of MIRAPEX PR tablets was approximately 3 mg/day with moderate to severe renal impairment

Pramipexole clearance is about 30% lower in women than in men, but this difference can be accounted No. differences in effectiveness based on age or gender were detected. Patients receiving s for by differences in body weight. There is no difference in plasma half-life between males and females. MAOB-I, anticholinergics, or amantadine had responses similar to patients not receiving these

After multiple-dose administration of Mirapex tablets 0.375 mg or 1.5 mg, the Cmax in Japanese was Patients were treated with MIRAPEX PR tablets, immediate-release pramipexole tablets, or 40-50% higher than in Caucasian while there was no significant difference seen in AUC, which could be placebo; those treated with MIRAPEX PR tablets or immediate-release pramipexole tablets had attributed to weight differences.

The influence of hepatic insufficiency on pramipexole pharmacokinetics has not been evaluated.

Because approximately 90% of the recovered dose is excreted in the urine as unchanged drug, hepatic

The primary efficacy endpoint was the adjusted mean change from baseline in the UPDRS Parts pairment would not be expected to have a significant effect on pramipexole elimination.

Clearance of immediate-release pramipexole was about 75% lower in patients with severe renal mpairment (creatinine clearance approximately 20 mL/min) and about 60% lower in patients with moderate impairment (creatinine clearance approximately 40 mL/min) compared with healthy volunteers. In patients with varying degrees of renal impairment, pramipexole clearance correlates well

At 33-weeks the adjusted mean improvement from baseline UPDRS Parts II+III score was with creatinine clearance. Therefore, creatinine clearance can be used as a predictor of the extent of -11.1 points in patients receiving MIRAPEX PR tablets (n=117) and -6.8 points in patients decrease in pramipexole clearance.

potential for drug interactions mainly depends on the active drug substance pramipexole and not the Carbidopa/levodopa: Carbidopa/levodopa did not influence the pharmacokinetics of pramipexole in amantadine or anticholinergics). healthy volunteers (N=10). Pramipexole did not alter the extent of absorption (AUC) or the elimination 15 HOW SUPPLIED

f carbidopa/levodopa, although it caused an increase in levodopa C_{max} by about 40% and a decrease MIRAPEX PR tablets are available as follows Γ_{max} from 2.5 to 0.5 hours. Selegiline: In healthy volunteers (N=11), selegiline did not influence the pharmacokinetics o

Amontadine: Population pharmacokinetic analyses suggest that amantadine may slightly decrease the 0.75mg white to off-white, round, biconvex, bevel-edged, extended-release tablets Cimetidine: Cimetidine, a known inhibitor of renal tubular secretion of organic bases via the cationic transport system, caused a 50% increase in pramipexole AUC and a 40% increase in half-life (N=12). 1.5mg white to off-white, oval, biconvex, extended-release tablets debossed with "P3" on

co-administration of drugs that are secreted by the cationic transport system (e.g., cimetidine, hypocuricemia, hypocalcemia, h

uloskeletal and connective tissue disorders: bone pain, bursitis, fasciitis, flank pain, intervertebral of overdose may require general supportive measures along with gastric lavage, intravenous fluids, and the oral clearance of pramipexole. CYP interactions: Inhibitors of cytochrome P450 enzymes would not be expected to affect pramipexole elimination because pramipexole is not appreciably metabolized by these enzymes in vivo or in vitro. Pramipexole does not inhibit CYP enzymes CYP1A2, CYP2C9, CYP2C19, CYP2E1, and CYP3A4. Inhibition of CYP2D6 was observed with an apparent Ki of 30 μ M, indicating that pramipexole will not hibit CYP enzymes at plasma concentrations observed following the clinical dose of 4.5 mg/day. Drugs affecting gastrointestinal motility or gastric pH:

oral clearance of pramipexole by about 25%, while H2-blockers (N=5), anticholinergics (N=27), propulsive (N=7), and proton pump inhibitors (N=16) are likely to have little effect on the oral clearance 17.1 Sedating Effects

13 NONCLINICALTOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

was administered in the diet to mice at doses up to 10 mg/kg/day [or approximately 10 times the maximum recommended human dose (MRHD) of 1.5 mg TID on a mg/m 2 basis]. Pramipexole was administered in the diet to rats at doses up to 8 mg/kg/day. These doses were associated with plasma occurred in either species. exole was not mutagenic or clastogenic in a battery of in vitro (bacterial-reverse mutation

In rat fertility studies, pramipexole at a dose of 2.5 mg/kg/day (5 times the MRHD on a mg/m² basis) prolonged estrus cycles and inhibited implantation. These effects were associated with reductions in serum levels of projectin, a hormone necessary for implantation and maintenance of early pregnancy

17.3 Hallucinations 13.2 Animal Toxicology and/or Pharmacology A delay in sexual development (i.e., preputial separation and vaginal opening) was observed in rats. The

relevance for humans is unknown Retinal Pathology in Albino Rats Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in the 2-year carcinogenicity study with pramipexole. These findings were first observed during week 76 and were dose-dependent in animals receiving 2 or 8 mg/kg/day (plasma AUCs equal to 2.5 and 12.5 times that in humans at the MRHD of 1.5 mg TID). In a similar study of pigmented rats with 2-years exposure to pramipexole at 2 or 8 mg/kg/day, retinal degeneration was not observed. Animals given drug had thinning in the outer nuclear layer of the retina that was only slightly greater

than that seen in control rats. nvestigative studies demonstrated that pramipexole reduced the rate of disk shedding from the photoreceptor rod cells of the retina in albino rats, which was associated with enhanced sensitivity to the damaging effects of light. In a comparative study, degeneration and loss of photoreceptor cells occurred in albino rats after 13 weeks of treatment with 25 mg/kg/day of pramipexole (54 times the - - - Because of the possibility that pramipexole may be excreted in breast milk, advise women to highest clinical dose on a mg/m² basis) and constant light (100 lux), but not in pigmented rats exposed notify their physicians if they intend to breast-feed or are breast-feeding an infant. m² basis) for 12 months and minipigs given 0.3, 1, or 5 mg/kg/day of pramipexole for 13 weeks also

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detected no changes.
For
The potential significance of this effect in humans has not been established, but cannot be disregarded Boehringer Ingelheim International GmbH

be involved. Fibro-osseous Proliferative Lesions in Mice An increased incidence of fibro-osseous proliferative lesions occurred in the femurs of female mice

Boehringer Ingelheim Taiwan Limited.

clinical pharmacokinetic data [see Clinical Pharmacology (12:3)] and two randomized, double-blind, outcome assessment measure. The UPDRS is a four-part multi-item rating scale intended to evaluate mentation (Part I), activities of daily living (Part II), motor performance (Part III), and complications of

(normal) to 4 (maximal severity) for a maximum (worst) score of 52. Part III of the UPDRS contains 14 items designed to assess the severity of the cardinal motor findings in patients with Parkinson's and has a maximum (worst) score of 108.

The effectiveness of MIRAPEX PR tablets in early Parkinson's disease patients (Hoehn & Yahr Stages neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, may diminish the effectiveness of MIRAPEX PR tablets.

| Pramipexole is extensively distributed, having a volume of distribution of about 500 L (coefficient of variation [CV] = 20%). It is about 15% bound to plasma proteins. Pramipexole distributes into red blood controlled, 3-parallel-group clinical study. Patients were treated with MIRAPEX PR tablets, immediaterelease pramipexole tablets, or placebo; those treated with MIRAPEX PR tablets or immediate-release pramipexole tablets had a starting dose of 0.375 mg/day followed by a flexible up-titration, based on efficacy and tolerability, up to 4.5 mg/day. Levodopa was permitted during the study as rescue

medication. Stable doses of concomitant MAO-B inhibitors, anticholinergics, or amantadine, Pramipexole is metabolized only to a negligible extent (<10%). No specific active metabolite has been individually or in combination, were allowed. The primary efficacy endpoint was the mean change from baseline in the UPDRS Parts II+III score for MIRAPEX PR tablets versus placebo following 18 weeks of treatment

At 18 weeks of treatment, the mean change from baseline UPDRS Parts II+III score was treated with placebo (14%) and 3 patients treated with MIRAPEX PR tablets (3%) received levodopa rescue medication. At 18 weeks, the mean dose of MIRAPEX PR was 3 mg/day. At 33-weeks the adjusted mean improvement from baseline UPDRS Parts II+III score was -8.6 points in patients receiving MIRAPEX PR tablets (n=213), compared to -3.8 points in

Twenty-two patients treated with placebo (21%) and 15 patients treated with MIRAPEX PR blets (7%) received levodopa rescue medication before the final assessment.

dose) and who had motor fluctuations (at least 2 cumulative hours of OFF time per day) was

stablished in a randomized, double-blind, placebo-controlled, 3-parallel group clinical study. a starting dose of 0.375 mg/day followed by a flexible up-titration over 7 weeks, based on efficacy and tolerability, up to 4.5 mg/day, followed by a 26 week maintenance period. II+III score for MIRAPEX PR tablets versus placebo following 18 weeks of treatment.
At 18 weeks of treatment, the adjusted mean improvement from baseline UPDRS Parts II+III score was -11.0 points in patients receiving MIRAPEX PR tablets (n=161) and -6.1 points in patients receiving placebo (n=174), (p=0.0001). At week 18, the adjusted mean improvement

receiving placebo (n=136) (p=0.0135). At both 18 and 33 weeks the mean daily dose of MIRAPEX PR was 2.6 mg/day. At week 18. No specific pharmacokinetic drug interaction trials were conducted with MIRAPEX PR tablets since the 4 patients (3%) in the placebo group and 14 patients (11%) in the PPX ER group had decreased their levodopa daily dose compared to baseline due to dopaminergic adverse events. No clinically relevant difference in effectiveness was observed in the sub-group analyses based o gender, age, race (White vs. Asian), or concomitant use of antiparkinsonian treatment (MAOB-I

0.375mg white to off-white, round, biconvex, bevel-edged, extended-release tablets debossed with "P1" on one side and the Boehringer Ingelheim company symbol on the other side.

debossed with "P2" on one side and the Boehringer Ingelheim company symbol on one side and the Boehringer Ingelheim company symbol on the other side.

STORAGE Store under 30°C. Protect from exposure to high humidity. Store in a safe place out of the reach

Expiry Date: Please refer outside box. Instruct patients to take MIRAPEX PR tablets only as prescribed. If a dose is missed, advise

MIRAPEX PR tablets can be taken with or without food. If patients develop nausea, advise that taking MIRAPEX PR tablets with food may reduce the occurrence of nausea. MIRAPEX PR tablets should be swallowed whole. They should not be chewed, crushed, or Pramipexole is the active ingredient that is in both MIRAPEX PR tablets and immediate-release

oulation pharmacokinetic analysis suggests that co-administration of antacids (N=6) decreased the pramipexole tablets. Ensure that patients do not take both immediate-release pramipexole and

Alert patients to the potential sedating effects of MIRAPEX PR tablets, including somnolence and the possibility of falling asleep while engaged in activities of daily living. Since somnolenc is a frequent adverse event with potentially serious consequences, patients should neither drive Two-year carcinogenicity studies with pramipexole have been conducted in mice and rats. Pramipexole was administered in the diet to mice at doses up to 10 mg/kg/day [or approximately 10 times the was administered in the diet to mice at doses up to 10 mg/kg/day [or approximately 10 times the was administered in the diet to mice at doses up to 10 mg/kg/day [or approximately 10 times the was administered in the diet to mice at doses up to 10 mg/kg/day [or approximately 10 times the was administered in the diet to mice at doses up to 10 mg/kg/day [or approximately 10 times the was administered in the diet to mice at doses up to 10 mg/kg/day [or approximately 10 times the was administered in the diet to mice at doses up to 10 mg/kg/day [or approximately 10 times the was administered in the diet to mice at doses up to 10 mg/kg/day [or approximately 10 times the was administered in the diet to mice at doses up to 10 mg/kg/day [or approximately 10 times the was administered in the diet to mice at doses up to 10 mg/kg/day [or approximately 10 times the was administered in the diet to mice at doses up to 10 mg/kg/day [or approximately 10 times the was administered in the diet to mice at doses up to 10 mg/kg/day [or approximately 10 times the was administered in the diet to mice at doses up to 10 mg/kg/day [or approximately 10 times the was administered in the diet to mice at doses up to 10 mg/kg/day [or approximately 10 times the was administered in the diet to mice at doses up to 10 mg/kg/day [or approximately 10 times the was administered in the diet to mice at doses up to 10 mg/kg/day [or approximately 10 times the was administered in the diet to mice at doses up to 10 mg/kg/day [or approximately 10 times the was administered in the diet to mice at doses up to 10 mg/kg/day [or approximately 10 times the was administered in the diet to mice at doses up to 10 mg/kg/day [or approximately 10 times the was administered in the diet to mice at doses up to 10 mg/kg/day [or approximately 10 times the was administered in the di falling asleep during activities of daily living (e.g., conversations or eating) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities until they have contacted their physician. Because of possible additive effects, caution should be advised when patients are taking other sedating medications or alcohol in combination with MIRAPEX PR and when taking concomitant medications that increase

plasma levels of pramipexole (e.g., cimetidine). 17.2 Impulse Control Symptoms Including Compulsive Behaviors Patients and their caregivers should be alerted to the possibility that they may experience intense urges to spend money, intense urges to gamble, increased sexual urges, binge eating and/or other intense urges and the inability to control these urges while taking MIRAPEX.

Inform patients that hallucinations can occur and that the elderly are at a higher risk than younger patients with Parkinson's disease 17.4 Postural (Orthostatic) Hypotension Advise patients that they may develop postural (orthostatic) hypotension, with or without symptoms such as dizziness, nausea, fainting, or blackouts, and sometimes, sweating. Hypotension may occur more frequently during initial therapy. Accordingly, caution patient against rising rapidly after sitting or lying down, especially if they have been doing so for

17.5 Pregnancy Because the teratogenic potential of pramipexole has not been completely established in laboratory animals, and because experience in humans is limited, advise women to notify their physicians if they become pregnant or intend to become pregnant during therapy.

17.6 Nursing Mothers

prolonged periods and especially at the in

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