可致律錠

25 公絲
100 公絲

CLOZARIL® Tablets 25 mg
100 mg

NOVARTIS

衛署藥輸字第 018541 號
衛署藥輸字第 018542 號

抗精神病製劑

Clozaril® 會造成顆粒性白血球缺乏症。其使用應限於下列的患者：
- 對於傳統抗精神病類藥物治療無反應或無耐受性的精神分裂症患者。具有復發性自殺傾向的精神分裂症或情感性分裂症患者 (見 " 適應症 ")。
- 初始之白血球檢查結果正常 (白血球數 (WBC) ≧ 3500/mm^3 (3.5×10^9L)，和絕對嗜中性細胞球數 (ANC) ≧ 2000/mm^3 (2.0×10^9/L))。
- 定期接受白血球與絕對嗜中性細胞球檢查者，其檢查如下：(在治療的前十八週應每週檢查一次，之後的療程應至少每四週檢查一次。治療全程以及結束 Clozaril 治療之後的四個星期都要持續進行追蹤監控。)

開立處方之醫師應遵守必需之安全規定。於每次門診應提醒有使用 Clozaril 患者，如果發生任何感染的現象，應立即與主治醫師聯絡。對於出現類似於感冒的症狀，如發燒、喉嚨痛、及其他可能表現出嗜中性白血球減少症之感染現象，應特別注意。
Clozaril 藥品的分裝都必須在符合制式規定的嚴格監督下進行。

成份
含有 25 毫克與 100 毫克 clozapine 之錠劑。

劑型
錠劑

適應症
其他藥物治療失效的精神分裂症病患。
降低精神分裂症或情感性分裂症的復發性自殺行為。
帕金森氏症期間的精神疾病。
< 說明 >
帕金森氏症期間的精神疾病
Clozaril 亦適用於帕金森氏症期間之精神疾病，經標準治療仍無效者。
標準治療的失敗定義為，在經過以下方式的治療後，仍然無法控制精神疾病的症狀及 / 或開始出現功能上無法忍受之運動功能惡化者：
- 停止服用抗副交感神經治療藥物，包括三環抗抑鬱藥物。
- 嘗試減少具有多巴胺作用之帕金森氏症治療藥物的劑量。

對治療具有抗性之精神分裂症患者
Clozaril 適用於對治療具有抗性之精神分裂症患者，也就是對於傳統的抗精神病類藥物無反應或無法忍受之精神分裂症患者。
無反應定義為，儘管已給予兩種其使用劑量與期間均足夠的抗精神病類藥物後，仍然無法獲得令人滿意之臨床上的改善。
無法忍受則定義為，因為嚴重及無法治療的神經性副作用 (錐體外徑副作用或遲發性運動困難)，而無法使用抗精神病類藥物以達到應有的臨床效果。
發生復發性自殺行為的風險
Clozaril 可以降低精神分裂症或情感性分裂症患者的復發性自殺行為。根據病史與最近的臨床狀況，這些病人都有再犯自殺行為的長期危險性。自殺行為指的是患者讓自身處於死亡的高危險境地。

用法用量
劑量應隨個人而加以調整。對每個患者均應自最低有效劑量開始使用。
Clozaril 起始治療的適用對象必須嚴格限定於 WBC ≧ 3500/mm^3 (3.5×10^9/L) 及 ANC ≧ 2000/mm^3 (2.0×10^9/L)，而且數值在標準正常範圍之內的病患。
劑量的調整應視病患是否同時使用會與 clozapine 產生藥物動力學交互作用的藥物，如 benzodiazepines，或選擇性的血清素再回收抑制劑 (見 " 與其它藥物的交互作用以及其它形式的交互作用 ") 而定。
對治療具有抗性之精神分裂症患者
開始治療
第一天給予一次或兩次 12.5 毫克 (1/2 顆 25 毫克之錠劑)，接著第二天給予一或兩顆 25 毫克錠劑，如果耐受性良好，則每日劑量可緩緩逐漸增加，可將所給予的錠劑由 25 毫克增加為 50 毫克，以在二到三個星期內將劑量調整至每日 300 毫克。此後如果有需要，每日劑量可以每半個星期，或盡量每星期，增加 50 到 100 毫克。
使用於老年患者
建議以特別低的劑量開始治療 (第一天給予一次 12.5 毫克)，並限制之後劑量的增加最多只能到每日 25 毫克。
使用於兒童患者
Clozaril 對於兒童的安全性與藥效尚未被確定。
治療劑量範圍
對於大多數的患者，每日分次給予 300 到 450 毫克將可預期達到抗精神病的效果。有些患者可能以較低劑量治療即可，有些則可能需要到每日 600 毫克。每日總劑量可以不平均分配給予，大部分的量分配於睡前服用。關於維持劑量，則參見下述。
最大劑量
為達到最佳治療效果，一些患者可能需要較大劑量，對於這類患者可允許每日劑量謹慎地追加 (也就是每次追加量不超過 100 毫克) 到每天 900 毫克。必須牢記在心的是，副作用的增加 (尤其是癲癇) 可能會在超過每日 450 毫克的劑量時發生。
維持劑量
在達到最佳治療效果之後，很多患者即能以較低的劑量有效地維持。因此建議小心地逐漸減少劑量。治療至少應持續六個月。如果每日劑量不超過 200 毫克，則可以每日一次給藥，而給藥時間可能在晚上會較適當。
治療結束
計畫結束 Clozaril 的治療時，建議在一到兩個星期間逐漸降低劑量。如果有必要突然停藥 (例如因為白血球減少)，應謹慎地觀察病患是否有精神病症狀，以及與膽鹼類藥物反彈相關的症狀，如大量出汗、頭痛、噁心、嘔吐、腹瀉。
再次開始治療
對於與最後一次給與 Clozaril 間距超過兩天的患者，應該再次由每日一到兩次 12.5 毫克 (25 毫克錠劑半顆) 開始。如果對於這個劑量的耐受良好，則可以比初始治療中所建議的方式更快速地調到治療劑量。然而對於任何曾經在使用初始劑量時發生呼吸或心跳停止 (見 " 特別警告與使用注意事項 ")，但之後仍成功地將劑量調整至治療劑量的患者，於重新調整劑量時，需要極度地小心謹慎。
由先前之抗精神病類藥物療法轉換至 Clozaril
通常建議 Clozaril 不應與其它抗精神病類藥物併用。當正在接受口服抗精神病類藥物治療的患者要開始進行 Clozaril 的治療時，建議降低原本其它抗精神病類藥物的劑量，或逐漸減少劑量至停用。根據臨床情況而定，在開始使用 Clozaril 治療之前，開立處方的醫師必須決定是否終止其它抗精神病類藥物的使用。
降低精神分裂症或情感性分裂症患者發生自殺行為的風險
前面 " 用法用量 " 所敘述之用藥方式與劑量的建議 (對治療具有抗性之精神分裂症患者，使用 Clozaril 之用量與用法)，在治療具有復發性自殺行為傾向的精神分裂症或情感性分裂症患者的時候，也都要遵循。
建議 Clozaril 的一個療程最少要有兩年的時間，以維持自殺行為發生風險的降低。經過兩年的治療之後，建議重新評估病患發生自殺行為的風險。之後，根據治療期間對病人發生自殺行為風險所進行的評估，做出是否繼續 Clozaril 定期治療的決定。
當標準治療失敗時，發生於帕金森氏症期間的精神疾病
起始的劑量不能超過 12.5 毫克 / 日 (25 毫克錠劑半顆)，且於夜間服用。之後的劑量增加必須以 12.5 毫克逐量增加，一週最多只能增加二次劑量，直到最大劑量為 50 毫克，在第二個星期結束之前，都不可以達到這個最大劑量。每日總劑量最好是於夜間服用的單一劑量。
平均有效劑量通常介於 25 和 37.5 毫克 / 日之間。如果以 50 毫克治療至少一個星期後，仍無法提供令人滿意的治療反應，則劑量可以謹慎地增加 12.5 毫克 / 週。只有在特殊情況才可超過 50 毫克 / 日的劑量，絕對不可以超過每日 100 毫克的最大劑量。
如果發生直立時的低血壓、過度的鎮靜效果或意識混亂，應限制或延遲劑量的增加。在治療的第一個星期應監測血壓。
當精神疾病症狀完全解除至少 2 個星期後，可以依據患者的運動狀態而增加治療帕金森氏症的藥物。如果這種方法導致精神疾病症狀再度出現，Clozaril 的劑量可以從 12.5 毫克 / 週增加至最大劑量 100 毫克 / 日，分一次或二次服用 (參見上述資訊)。
當治療結束，劑量應以每次 12.5 毫克的劑量逐漸減少，且降低時藥量的時間至少一個星期 (最好是二個星期)。
如果發生如 " 特殊警告和使用時的特殊注意事項 " 中所描述的嗜中性白血球減少或粒性白血球缺乏，則應立即中斷治療。在這種情況下，小心地監控患者的精神疾病是必要的，因為他們的症狀可能會很快地復發。

禁忌症
- 已知對 clozapine 或 Clozaril 的其他成分過敏者
- 無法定期接受血液檢查者
- 曾有毒性或特異性的顆粒性白血球減少 / 顆粒性白血球缺乏症病史者 (除了因之前的化學治療引起之顆粒性白血球減少 / 顆粒性白血球缺乏症)
- 骨髓功能受損
- 未控制之癲癇
- 酗酒者以及其他毒癮精神病、藥物中毒、昏迷等狀況
- 任何原因造成之循環性虛脫和 / 或中樞神經抑制
- 嚴重的腎臟、或心臟疾患 〔 例如：心肌炎 〕
- 伴隨噁心、厭食、黃疸之活動性肝疾病；進行性肝疾病，肝衰竭
- 麻痺性腸阻塞

特別警告與使用注意事項
特別預防措施
由於 Clozaril 與顆粒性白血球缺乏症的關連性，下列為必要之預防措施：
已知具有相當潛在性骨髓抑制效果的藥物，不可與 Clozaril 併用。此外，應避免與長效型抗精神病藥物合併使用，因為這些藥可能具有潛在性的骨髓抑制效果，而且由無法在必要的時候，快速排出體外，例如顆粒性白血球缺乏症發生時。
具有原發性骨髓異常病史的患者，只有在益處大於危險性時，才可施予此治療。在開始使用 Clozaril 之前，應先由血液學家仔細地評估這些患者。
因良性的種族性嗜中性白血球減少症而造成白血球數目低下的患者，應予以特別考量，並在取得血液學家的同意後，開始進行 Clozaril 的治療。
白血球 (WBC) 與絕對嗜中性白血球 (ANC) 監測
在開始 Clozaril 治療前的十天內，必須進行白血球計數與血球分類計數的檢驗，以確保只有白血球與絕對嗜中性白血球計數正常 (WBC ≧ 3500/mm^3 和 ANC ≧ 2000/mm^3) 的患者才能使用此藥。在開始 Clozaril 的治療後十八個星期內，白血球以及絕對嗜中性白血球計數，必須每個星期檢測一次。此後在整個療程中，至少每四週檢查一次。在完全停止 Clozaril 治療後的四週內再做一次。於每次門診時應提醒患者，如果有開始發生任何的感染、發燒、喉嚨痛或類似於感冒的症狀時，應立即與主治醫師聯繫。如果有任何感染的徵兆或症狀發生，應立即進行血球分類計數檢驗。
白血球和 / 或絕對嗜中性白血球低下時
如果在以 Clozaril 治療的前十八個星期中，白血球計數降到 3500/mm^3 到 3000/mm^3 之間，和 / 或絕對嗜中性白血球計數降到 2000/mm^3 到 1500/mm^3 之間，就必須接受每星期至少兩次的血液學評估。
在十八個星期之後，如果白血球計數降到 3000/mm^3 到 2500/mm^3 之間，和 / 或絕對嗜中性白血球計數降到 1500/mm^3 到 1000/mm^3 之間，就必須接受每星期至少兩次的血液學評估。
此外，在 Clozaril 的治療期間，與基準值相較，白血球有相當的程度下降時，就必須重複進行白血球與血球分類計數檢驗。所謂相當程度的下降定義為白血球一次下降大於等於 3000mm^3，或是在三個星期中累積下降的量大於等於 3000mm^3。
在前十八個星期中，如果白血球計數低於 3000/mm^3 或絕對嗜中性白血球計數低於 1500/mm^3 時，以及在十八個星期後如果白血球計數低於 2500/mm^3 或絕對嗜中性白血球計數低於 1000/mm^3 時，就必須立刻強制停止 Clozaril 的治療。如果患者有類似感冒或是其他類似感染的症狀，就必須加以仔細觀察並每日檢查白血球總數及分類計數。在 Clozaril 停止給藥後，仍需要血液學的評估，直到有血液檢查值好轉為止。
如果 Clozaril 已經停止使用，而白血球仍進一步降到 2000/mm^3 以下，和 / 或 ANC 降到 1000/mm^3 以下時，就必須由有經驗的血液學家來負責引導整個情況的處置。如果可能的話，患者應轉介到特殊的血液治療單位，以進行保護性的隔離，並給予 GM-CSF (granulocyte-macrophage colony stimulating factor) 或 G-CSF (granulocyte colony stimulating factor)。建議當嗜中性顆粒白血球恢復到 1000/mm^3 以上時，可停止 G-CSF (granulocyte colony stimulating factor) 的治療。
由於白血球缺乏而導致停止使用 Clozaril 的患者，不可以再度接受 Clozaril 的治療。
建議藉由連續兩日進行兩次血球計數，來加以確認血液學檢查值。然而在第一次血球計數時，即應停止給予 Clozaril。

表一　Clozaril 前 18 週治療期間的血液檢查

血球細胞數		必須採取的動作
WBC/mm^3 (/L)	ANC/mm^3 (/L)	
≧ 3500 (> 3.5×10^9)	≧ 2000 (> 2.0×10^9)	繼續 Clozaril 的治療
3000~3500 (3.0×10^9~3.5×10^9)	1500~2000 (1.5×10^9~2.0×10^9)	繼續 Clozaril 的治療。每週抽血檢查兩次，直到血球數穩定或增加為止。
< 3000 (< 3.0×10^9)	< 1500 (< 1.5×10^9)	立即停止 Clozaril 的治療。每天抽血檢查，直到血液檢查異常情況解決為止，要監控是否發生感染。不要再使用該藥。

表二　Clozaril 治療 18 週之後的血液檢查

血球細胞數		必須採取的動作
WBC/mm^3 (/L)	ANC/mm^3 (/L)	
≧ 3000 (> 3.0×10^9)	≧ 1500 (> 1.5×10^9)	繼續 Clozaril 的治療
2500~3000 (2.5×10^9~3.0×10^9)	1000~1500 (1.0×10^9~1.5×10^9)	繼續 Clozaril 的治療。每週抽血檢查兩次，直到血球數穩定或增加為止。
< 2500 (< 2.5×10^9)	< 1000 (< 1.0×10^9)	立即停止 Clozaril 的治療。每天抽血檢查，直到血液檢查異常情況解決為止，要監控是否發生感染。不要再使用該藥。

因非血液學因素而中斷治療時
接受超過十八個星期 Clozaril 的治療的病患，曾中斷治療超過三天，但不超過四個星期者，應該接受額外六週的每週白血球以及絕對嗜中性白血球計數檢驗。如果沒有血液學異常情形發生，定時監測不超過四個星期者可以再度開始。如果 Clozaril 的治療中斷超過四個星期，在下一次治療的十八週內即必須每週加以監測。
其他注意事項
當發生嗜伊紅性白血球增多症時，如果嗜伊紅性白血球的數量超過 3000/mm^3 時建議停用 Clozaril，並且只有在嗜伊紅性白血球數降到低於 1000/mm^3 時，才可再度開始療程。
當發生血小板減少情況時，如血小板數量降至 50,000/mm^3 以下，則建議停止 Clozaril 的治療。
伴隨或不伴隨昏厥情況發生之直立性低血壓，可能會在 Clozaril 的治療期間發生。很少 (約每三千個接受 Clozaril 的治療的患者會有一位) 病人會有心跳和 / 或呼吸停止的狀況發生。這樣的情況較常發生在劑量調整初始期，與快速地升高劑量有關。在極少的情況下甚至發生在第一個劑量給予後。因此，接受 Clozaril 治療患者需要密切的醫療監測。很少數病人會在治療的第一個月發生於休息時持續的心跳過速，並伴隨心律不整、呼吸急促或心臟衰竭的症狀與徵候 (第一個月之後發生上述的情況的機會更為減少)。當發生這些症狀與徵候時，就必須緊急診斷評估心肌炎的可能性，尤其是在劑量調整期間。如果心肌炎的診斷是確定的，就必須停止使用 Clozaril。治療晚期，相同的徵兆及症狀可能非常罕見，但可能與心肌病變有關聯，應該做進一步的檢查評估。同時，假如該項診斷被確定，除非很清楚地顯示對病人的效益勝過其它的風險，否則需要立即停藥。
在治療的第一個星期中，必須監控帕金森氏症患者的站立和仰臥血壓。
對於曾有癲癇病史的患者或患有腎或心血管疾病者 (註：嚴重腎或心血管疾病為禁忌症)，其初始劑量應在第一天時給予一次 12.5 毫克，且劑量應該緩慢的小量地增加。
先前患有穩定的肝疾病患者可以接受 Clozaril 的治療，但是需要定期的肝功能檢驗。在 Clozaril 的治療期間，對於出現可能為肝功能障礙症狀如噁心、嘔吐和 / 或厭食時，必須立即進行肝功能測試。如果肝功能數值的升高有臨床上的相關性，或如果有黃疸症狀的發生，就必須中斷 Clozaril 的治療。只有在肝功能檢驗均回歸正常值時，才可再開始使用 (見 " 用法用量 "，再次開始治療)。在這些情況下，再度開始 Clozaril 治療之後，必須要密切監測肝功能。
Clozapine 會激發抗膽鹼作用，而引起全身性副作用。發生前列腺腫大和狹角青光眼時，就必須加以小心謹慎地監測。可能因為其抗膽鹼作用的特質，Clozaril 會伴隨產生不同程度的腸蠕動功能受損，從便秘到腸阻塞、糞便緊壓以及麻痺性腸阻塞 (見 " 副作用 ")。在極少數之情況下這些狀況可能導致死亡。
接受 Clozaril 的治療中患者，可能會經歷短暫的體溫上升超過攝氏 38℃。尤其是治療的前三個星期為發生之高峰期。這種發燒的情況一般是良性的，偶爾可能與白血球的增加或減少有關，應對發燒的患者加以小心謹慎地評估，以便將潛在性感染或顆粒性白血球缺乏症發生的可能性排除。如有高燒的情況，就必須考慮是否有發生抗精神病藥物惡性症候 (NMS) 類。
本品為一種非典型抗精神病藥品，使用非典型抗精神病藥物會出現高血糖及增加罹患葡萄醣耐受性不良或糖尿病風險。少數嚴重之案例有可能出現酮酸血症 (ketoacidosis) 和高血糖高滲透壓非酮體性症候群 (Hyperglycemic Hyperosmolar Nonketotic Coma) 等急症導致昏迷甚至死亡。
所有接受非典型抗精神病藥品之病人，應密切留意高血糖症狀 (如：多食、劇渴、多尿或無力)，若出現高血糖症狀時，應立刻測量血糖值。有糖尿病或糖尿病危險因子 (如：肥胖、有糖尿病家族史等) 之病人，用藥前應監測血糖，用藥中也應定期監測血糖。對於出現明顯需要緊急治療高血糖的病患，應考慮停藥，有些病患停藥後仍須使用抗糖尿病藥品治療。
碳水化合物代謝平衡可能會受到改變而造成葡萄糖恆定狀況受損，因此可能會讓糖尿病前期徵狀顯現，或是造成既有的糖尿病病情惡化。
Clozaril 可能造成鎮靜作用以及體重增加，因而增加血栓性栓塞症的危險性。無法活動的患者應避免使用。
在某些接受非典型抗精神病藥品的失智症族群中，曾觀察到腦血管不良事件的風險增加。風險增加的機轉目前仍不明。無法在其他抗精神病藥品或其他病患族群中排除腦血管不良事件風險增加的可能。Clozaril 在具有中風風險因子的病患中應謹慎使用。
如同其他的抗精神病藥品，對於已知有心血管疾病或 QT 延長家族病史的病患

應特別謹慎。

如同其他的抗精神病藥品，當 Clozaril 與已知會延長 QT 間隔的藥物併用時應特別謹慎。

老年人的使用

建議以特別低的劑量開始治療（第一天給予 12.5 毫克，一天一次），並限制往後劑量的增加只能到每日 25 毫克。

Clozaril 的臨床研究六十五歲以上患者數不足，因此無法確定他們的反應是否與年輕人有異。

Clozaril 的治療可能伴隨委婉性低血壓，以及服用 Clozaril 的患者，有少數的報告指出心跳過速的發生，這種情況可能是特別嚴不斷的。年老患者，特別是那些心血管功能有異者，可能更容易發生這些反應。

年老患者也可能特別容易出現 Clozaril 的抗膽鹼效果，例如尿液滯留和便秘。

老年失智症病患

依據隨機分派，有對照組的臨床試驗(Randomized controlled trial，RCT)及回溯性世代研究(retrospective cohort study)發現，抗精神病藥品，包括傳統（Conventional）與非典型(Atypical)之抗精神病藥品用於治療老年失智症病患(dementia-related psycosis)的死亡率與安慰劑組比較，其死亡之相對危險性較高。

與其它藥品的交互作用以及其它形式的交互作用

藥物效力學相關之交互作用

已知具有相當潛在性骨髓抑制效果的藥物，不可與 Clozaril 併用 (見 " 特別警告與使用注意事項 ")。

Clozaril 可能增強酒精、單胺氧化酶 (MAO) 抑制劑以及中樞神經抑制劑，如麻醉藥 (narcotics)、抗組織胺以及 benzodiazepines 對中樞的作用。

當有使用 (或最近曾使用)benzodiazepines 或任何其他抗精神病藥物的患者，開始接受 Clozaril 的治療時建議應加以特別注意，因為這些患者可能會有較高的循環系統崩潰的危險性，在少數時候，這些情況可能會導致心跳和 / 或呼吸停止。因為有加成作用的可能性，在和具有抗膽鹼、低血壓或呼吸抑制等作用的物質併用時，必須特別注意。

與鋰鹽或其他中樞神經興奮劑併用時，可能會增加抗精神病藥物惡性症候 (NMS) 出現的危險性。

由於其抗甲型釋上腺素的特質，clozapine 可能會降低血壓－增加正釋上腺素或其他主要甲型釋上腺素物質的效果，並逆轉釋上腺素增高血壓的效果。

應警發作的可能性相當低，但有一些系列個案報告，包括在非癲癇的患者出現應警發作。也有罕見的個案報告顯示與 valproic acid 併用時出現譫妄。這些效果可能來自於藥效學的交互作用，這些機轉尚未被確認。

如同其他的抗精神病藥品，當 Clozaril 與已知會延長 QT 間隔或造成電解質失衡的藥物併用時應特別謹慎。

藥物動力學相關交互作用

Clozapine 是許多 CYP450 同功酵素的受質，特別是 1A2 與 3A4。由作用在個別的同功酵素所造成的代謝交互作用危險性，因此會被降至最低。體管如此，當病患同時接受其他物質治療，不論是這些酵素的抑制劑或誘導劑，仍須加以注意。

至今尚未觀察到與 P450 2D6 結合的三環抗鬱劑、苯磺醯胺、或 Ic 型抗心律不整藥物，有臨床上的相關交互作用。

與已知會誘導 cytochrome P450 酵素的物質併用，可能會降低血漿中 clozapine 的含量。

- 已知會誘導 3A4 作用，且有報告指出會與 clozapine 有交互作用的物質，例如 carbamazepine、phenytoin 和 rifampicin。
- 已知之 1A2 的誘導物，例如 omerprazole 和 nicotine。在突然中止尼古丁濫用的個案，血漿中 clozapine 的濃度會增加而導致副作用的增加。

與已知具有抑制 cytochrome P450 同功酵素作用的物質併用，可能增加血漿中 clozapine 的濃度。

- 已知具有抑制 clozapine 代謝中主要酵素活性的物質，以及有報告指出具有交互作用的，例如包括 cimetidine，紅黴素 (3A4) 和 fluvoxamine (1A2)。
- 有效的 CYP3A 抑制劑，例如 azole antimycotics，蛋白酶抑制劑，可能也會潛在地增加 Clozapine 血漿濃度；然而迄今仍沒有報告指出有交互作用。
- Clozapine 的血漿濃度會因為咖啡因 (1A2) 的攝取而增加，而在五天不攝取咖啡因之後，會大約降低 50%。
- 同時使用選擇性血清素回收抑制劑 (SSRIs)，如 paroxetine (1A2), sertraline，fluoxetine and citalopram 的患者，也曾報告過 clozapine 的血清濃度增加的例子。

懷孕與授乳時的使用

懷孕

對動物的生殖實驗中，沒有證據顯示 Clozapine 對生育力或胎兒有害。然而，Clozaril 對懷孕婦女使用的安全性尚未建立。因此，只有在預期益處遠超過潛在危險時，才可將 Clozaril 使用於懷孕婦女身上。

非畸形影響

在懷孕第 7-9 個月時曾暴露於抗精神病藥品的新生兒，具有分娩後發生錐體外徑症狀和 / 或停藥症狀的風險。這些新生兒曾出現激動、張力抗進、張力減退、顫抖、困倦、呼吸窘迫和餵食障礙等情況。這些併發症的嚴重程度各不相同；在一些案例中症狀可自行緩解，而在其他案例中曾有新生兒需要在加護病房中接受治療以及延長住院的情形。

僅有當藥物潛在效益超過對胎兒的潛在風險時，才應於懷孕期間使用抗精神病藥品 (包括 Clozaril)。

授乳

動物實驗顯示，clozapine 會分泌至乳汁中，因此接受 Clozaril 治療的母親不應該授乳。

有懷孕可能性的婦女

有些接受 Clozaril 以外的其它抗精神病藥物治療的婦女病人，可能會造成無月經。從其它抗精神病藥劑轉換到 Clozaril，可能就可以使月經恢復正常。因此，有懷孕可能性的婦女必須採取適當的避孕措施。

對於開車和操作機器的影響

由於 Clozaril 會產生鎮靜和陣症癲癇發作閾值的作用，因此患者應避免進行一些活動，例如開車、操作機器，尤其是在治療一開始的幾個星期中。

副作用

根據其藥理學特性，除了顆粒性白血球減少症 (agranulocytosis) 以外，clozapine 的大部分副作用都是可預期的 (見 " 特別警告與使用注意事項 ")。

表三　因治療而造成的急性副作用發生頻率，從自發性與臨床試驗的報告估計而來

依下面的原則將副作用的發生頻率依序排列：很常見 (≧ 1/10)，常見 (≧ 1/100， < 1/10)，不 常 見 (≧ 1/1,000， < 1/100)，罕 見 (≧ 1/10,000， < 1/1,000)，很罕見 (< 1/10,000)。包括個別的報告在內。

血液與淋巴系統異常	
常見	白血球減少 / WBC 減少 / 嗜中性白血球過多，嗜伊紅性白血球過多，白血球過多症
不常見	顆粒性白血球缺乏
罕見	貧血
很罕見	血小板減少，血小板增生
代謝與營養異常	
常見	體重增加
罕見	葡萄糖耐受性功能缺損，新發生之糖尿病，糖尿病病情惡化
很罕見	酮體中毒症，高滲透性昏迷，嚴重高血糖，高膽固醇，高三酸甘油脂
精神疾病	
常見	發音困難
不常見	口吃
罕見	坐立不安，激動
神經系統疾病	
很常見	昏昏欲睡 / 鎮靜作用，暈眩
常見	視覺模糊，頭痛，癲狗，身體僵硬，步態困難，錐體外徑症狀，癲痛 / 抽搐 / 肌陣型抽搐
罕見	困惑，譫妄
很罕見	遲發性不自主運動症，強迫症
心臟疾病	
很常見	心跳過快
常見	心電圖異常
罕見	循環系統虛脫，心律不整，心肌炎，心包膜炎
很罕見	心肌病變
血管系統異常	
常見	高血壓，姿勢性低血壓，昏厥
罕見	血栓性栓塞症
呼吸異常	
常見	吸入食物，可能致命的肺炎和下呼吸道感染
很罕見	呼吸壓抑 / 停頓
腸胃道疾病	
很常見	便秘，嗯液過多
常見	嗯心，嘔吐，口乾
罕見	吞嚥困難
很罕見	耳下腺腫大，腸道阻塞 / 腸阻塞症 / 糞便壓緊
肝臟疾病	
常見	肝臟酵素升高
罕見	肝炎，膽汁滯留性黃膽，膽腦炎
很罕見	猛暴性肝組織壞死
皮膚與皮下組織疾病	
很罕見	皮膚反應
腎臟與排尿系統疾病	
常見	尿失禁，尿液滯留
很罕見	間質性腎炎
生殖系統疾病	
很罕見	陰莖持續勃起症
一般疾病	
常見	疲勞，良性體溫過高，排汗障礙 / 體溫控制
不常見	抗精神病藥劑惡性症候群
很罕見	不明原因猝死
研究報告	
罕見	CPK 值增加

曾觀察到很罕見的可能與 Torsades De Pointes 相關之心室性心博過速、心跳停止和 QT 延長事件，但與藥物使用間並無確切的因果關係。

過量

當發生急性故意或意外的 Clozaril 使用過量時，相關結果的資訊是可取得的，迄今死亡率約為 12%。大部分的死亡與心衰竭或吸入性肺炎有關，發生在劑量超過 2000 毫克時。曾有報告顯示，患者在使用的超過 10000 毫克後仍復原。然而在某些大部分之前未使用 Clozaril 的成人個案中，使用低到 400 毫克的劑量，即會導致致命的昏迷，且有一個個案死亡。兒童服用 50 到 200 毫克，會導致強烈的鎮靜作用或非致命性的昏迷。

症狀與徵候

顫倦、嗜眠、無反射、昏迷、溫亂、幻覺、躁動、譫妄、錐體外徑症狀、過度反射、抽搐、嘔液分泌過多、瞳孔放大、親緣模糊、不耐熱；低血壓、虛脫、心搏過速、心律不整、吸入性肺炎、呼吸困難、呼吸抑制或衰竭。

治療

在服下 Clozaril 的六小時內洗胃和 / 或給予活性碳 (讓腸逐析與血液透析未必有效)。在持續監測心肺功能以及電解質與酸鹼平衡下，進行症狀治療。由於有 " 反轉性腎上腺素 " 效果產生的可能性，應避免使用腎上腺素來治療低血壓。

因為有延遲反應出現的可能性，因此密切的醫療監測需至少持續五天。

藥理學特性

藥效學特性

藥理療效類別：抗精神病藥物 (ATC code NO5A H02)

Clozaril 與傳統的抗精神病藥物不同。

在藥理學實驗中，這個化合物不會引起強直性昏厥，或抑制 Apomorphin 的或安非他命誘導的常同行為。它只有微弱的多巴胺受體 D_1、D_2、D_3 及 D_5 的阻斷效果，但對多巴胺受體 D_4 及抗甲型腎上腺素、抗膽鹼、抗組織胺和激醒反應抑制等作用，曾顯示有強大的親和力或效果。它也有抗血清升壓素的特質。

臨床上 Clozaril 可產生快速且顯著的鎮靜作用，且對其它藥物有抗性的精神分裂症患者，也有抗精神病的治療效果。在這樣的情況下，Clozaril 經很多短期與長期的臨床試驗證實，在緩解精神分裂症症性和負性症狀上均有效。在一個以 319 個對藥物治療具有抗性的精神分裂症患者參雙盲的臨床試驗裡面，臨床上觀察到 Clozaril 治療組有 30% 的患者，在前六週的治療中會獲得改善。在兩個開放性的臨床試驗中，治療病人 12 個月之後發現，有 37% 的患者在前六週的治療中獲得臨床症狀的改善，十二個月之後，更有另外的 39-44% 患者獲得改善。改善的定義為：根據簡易精神病學評量分數 (Brief Psychiatric Rating Scale)，和臨於基準線獲得至少 20% 的降低幅度。此外，也發現對於某些方面的敵知功能受損也能改善。

流行病學研究顯示，相較於沒有接受 clozapine 治療的精神分裂症或情感性分裂症患者，使用 clozapine 的患者其自殺企圖降低了大約七倍，而自殺致死率則降低四到六倍。在一個以 980 個病人為對象的多中心雖機臨床試驗中，與 olanzapine 相較之下，在二年內 Clozaril 減少自殺行為的風險 26%（測量方式為自殺傾向及住院避免自殺者）。即使接受 olanzapine 治療的病人併用敵多的抗抑鬱藥物及抗焦慮劑，Clozaril 仍能遂到與其相當的療效。

Clozaril 是幾乎不會產生雖體外徑的反應，例如急性肌張力不足與遲發性不自主運動。另外，類帕金森氏症副作用和酮坐困難也是很少發生的。相較於傳統抗精神病藥物，Clozapine 只產生輕微或甚至沒有催乳激素上升的反應，因此可以避免如男性女乳症、閉經、泌乳與陽萎的副作用產生。

因 Clozaril 治療而造成的潛在嚴重副作用是顆粒性白血球減少和顆粒性白血球缺乏症，其發生率分別是 3% 和 0.7% (見 " 特別警告與使用注意事項 ")。

藥動學特性

經口投予 clozapine 的吸收率是 90% 到 95%，其遞率與吸收度不會受食物影響。

Clozapine 容易遷受中度的首渡代謝 (first-pass metabolism)，造成絕對生體可用率為 50% 到 60%。在穩定的狀態中每天兩次給藥，血中最高濃度會在平均 2.1 小時出現 (範圍：0.4 到 4.2 小時)，其分佈體積為每公斤 1.6 升。clozapine 與血清蛋白的結合率約 95%。其排出方式為雙相，平均半衰期為 12 小時 (範圍：6 到 26 小時)。在單次給予 75 公克的劑量後，平均半衰期為 7.9 小時。當每日劑量穩定給予至少七天後，其半衰期會增加至 14.2 個小時。每天兩次給予由 37.5 毫克到 75 毫克以及 150 毫克的劑量，結果顯示在穩定的狀態下，血清濃度 / 時間曲線下方的區域 (AUC) 依劑量比例呈線性增加，且最高與最低的血清濃度也增加。

Clozapine 在排出前幾乎是完全代謝，主要的代謝物中只有去甲基代謝物是具活性的。其藥理作用類似於 clozapine，但是較弱且時間較短。在尿液與糞便中，只有存在微量未改變的藥物。代謝物大約 50% 經尿液排除，而 30% 經糞便排除。

臨床前安全性數據

根據傳統的安全性藥理學、重複給藥毒性、基因毒性、以及致癌可能性等研究，這些臨床前的數據顯示，對人體並沒有特別的危害性 (有關生殖毒性請參看 " 懷孕與授乳時的使用 ")。

急性毒性

由小鼠、大鼠、與天竺鼠的急性毒性研究得知，口服時的 LD_{50} 值為每公斤體重 190 到 681 毫克 (190–681 mg/kg)。狗的口服 LD_{50} 則為每公斤體重 145 毫克 (145 mg/kg)；藥物過量的跡象包括肌肉顫抖、攻擊行為與嘔吐。

致突變性

在被視基因突變、染色體異常、與致使 DNA 損壞的一些活體外致突變性試驗發現，Clozapine 與其代謝產物完全不具基因毒性 (genotoxic)。在活體的研究也沒有發現會造成染色體的斷裂 (clastogenic activity)(小鼠骨髓微核測試 [micronucleus test])。

致癌性

在 Sprague-Dawley (CD) 大鼠的飼料中加入其最大容忍劑量，每天 35 mg/kg，24 個月之後發現，clozapine 並不具致癌性。同樣地，在兩個為期 78 週的 Charles River (CD) 小鼠最先研究中，也沒有出現任何致腫瘤作用的證據。在第一個研究中，雌於雄鼠與雌鼠的最高口服劑量分別為 64 mg/kg 與 75 mg/kg。在第二個研究中，雄鼠與雌鼠的最高口服劑量都達每天 61 mg/kg。

生殖毒性

Clozapine 並不會造成大鼠或兔子胚胎毒性或畸形的形成。在公鼠交配前的餵食 70 天，對其生殖能力並無影響。

在母鼠方面，交配前口服 clozapine 對生育力及生產前後幼鼠的發展並無任何不良的影響。於懷孕後期及哺乳期有被餵食的母鼠，若服用劑量高於每公斤體重 40 毫克，其幼鼠的存活率會降低且有通動現象。然而，這些影響將不會發生於哺乳期之後。

賦形劑

Clozaril 錠劑：鎂硬酯酸鹽；二氧化矽；無水矽膠；聚維酮；滑石；玉米澱粉；單水合乳糖。

不相容性

因為缺乏不相容性的研究，本藥劑產品不得與其它藥劑產品混合。

貯存時特別注意事項

貯存於 30°C 以下。

Clozaril 在超過包裝上的使用期限後不可再使用。

使用 / 處置指示

任何殘留產品或廢棄物質都必須依照當地規定處理。

® = 註冊商標

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Info: 24-May-2011, DOH 19-Aug-2008, DOH 29-Aug-2008
TWI-120711

NOVARTIS

Clozaril®

Antipsychotic agent

Clozaril can cause agranulocytosis. Its use should be limited to patients:

- **with schizophrenia who are non-responsive to or intolerant of classical antipsychotic agents, or with schizophrenia or schizoaffective disorder who are at risk of recurrent suicidal behaviour (see section INDICATIONS)**
- **who have initially normal leukocyte findings (white blood cell count (WBC) ≥ 3500/mm^3 (3.5 x 10^9/L), and absolute neutrophil counts (ANC) ≥ 2000/mm^3 (2.0 x 10^9/L)),**
- **and in whom regular white blood cell counts and absolute neutrophil counts can be performed as follows: weekly during the first 18 weeks of therapy, and at least every 4 weeks thereafter throughout treatment. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of Clozaril.**

Prescribing physicians should comply fully with the required safety measures. At each consultation, a patient receiving Clozaril should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia.

Clozaril must be dispensed under strict medical supervision in accordance with official recommendations.

Composition and pharmaceutical form

Tablets containing 25 mg and 100 mg clozapine.

For a full list of excipients, see section EXCIPIENTS.

Certain dosage strengths may not be available in all countries.

Indications

Treatment-resistant schizophrenia

Clozaril is indicated in patients with treatment-resistant schizophrenia, i.e. patients with schizophrenia who are non-responsive to or intolerant of classic antipsychotics.

Non-responsiveness is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two marketed antipsychotics prescribed for adequate durations.

Intolerance is defined as the impossibility of achieving adequate clinical benefit with classic antipsychotics because of severe and untreatable neurological adverse reactions (extrapyramidal side effects or tardive dyskinesia).

Risk of recurrent suicidal behaviour

Clozaril is indicated for reducing the risk of recurrent suicidal behaviour in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for re-experiencing suicidal behaviour, based on history and recent clinical state. Suicidal behaviour refers to actions by a patient that put him/herself at high risk for death.

Psychosis during the course of Parkinson's disease

Clozaril is indicated in psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed.

The failure of standard treatment is defined as the lack of control of the psychotic symptoms and/or the onset of functionally unacceptable motoric deterioration occurring after the following measures have been taken:

- Withdrawal of anti-cholinergic medication including tricyclic anti-depressants
- Attempt to reduce the dose of antiparkinsonian medication with dopaminergic effect

Dosage and administration

The dosage must be adjusted individually. For each patient the lowest effective dose should be used.

Initiation of Clozaril treatment must be restricted to those patients with a WBC count
≥3500/mm^3 (3.5 x 10^9/L) and an ANC ≥2000/mm^3 (2.0 x 10^9/L), and within standardised normal limits.

Dose adjustment is indicated in patients who are also receiving medicinal products that have pharmacokinetic interactions with clozapine, such as benzodiazepines or selective serotonin re-uptake inhibitors (see section INTERACTIONS).

The following dosages are recommended for **oral administration**:

Treatment-resistant schizophrenia

Starting therapy

12.5 mg (half a 25 mg tablet) once or twice on the first day, followed by one or two 25 mg tablets on the second day. If well tolerated, the daily dose may then be increased slowly in increments of 25 mg to 50 mg in order to achieve a dose level of up to 300 mg/day within 2 to 3 weeks. Thereafter, if required, the daily dose may be further increased in increments of 50 mg to 100 mg at half-weekly or, preferably, weekly intervals.

Use in the elderly

It is recommended that treatment is initiated at a particularly low dose (12.5 mg given once on the first day) with subsequent dose increments restricted to 25 mg/day.

Use in children

The safety and efficacy of Clozaril in children have not been established.

Therapeutic dose range

In most patients, antipsychotic efficacy can be expected with 300 to 450 mg/day given in divided doses. Some patients may be treated with lower doses, and some patients may require doses up to 600 mg/day. The total daily dose may be divided unevenly, with the larger portion being taken at bedtime. For maintenance dose, see below.

Maximum dose

To obtain full therapeutic benefit, a few patients may require larger doses, in which case judicious increments (i.e. not exceeding 100 mg) are permissible up to 900 mg/day. The possibility of increased adverse reactions (in particular seizures) occurring at doses over 450 mg/day must be borne in mind.

Maintenance dose

After achieving maximum therapeutic benefit, many patients can be maintained effectively on lower doses. Careful downward titration is therefore recommended. Treatment should be maintained for at least 6 months. If the daily dose does not exceed 200 mg, once daily administration in the evening may be appropriate.

Ending therapy

In the event of planned termination of Clozaril therapy, a gradual reduction in dose over a 1-to 2-week period is recommended. If abrupt discontinuation is necessary (e.g. because of leucopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting and diarrhoea.

Re-starting therapy

In patients in whom the interval since the last dose of Clozaril exceeds 2 days, treatment should be re-initiated with 12.5 mg (half a 25-mg tablet) given once or twice on the first day. If this dose is well tolerated, it may be feasible to titrate the dose to the therapeutic level more quickly than is recommended for initial treatment. However, in any patient who has previously experienced respiratory or cardiac arrest with initial dosing (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE), but was then able to be successfully titrated to a therapeutic dose, re-titration should be done with extreme caution.

Switching from a previous antipsychotic therapy to Clozaril

It is generally recommended that Clozaril should not be used in combination with other antipsychotics. When Clozaril therapy is to be initiated in a patient undergoing oral antipsychotic therapy, it is recommended that the dosage of other antipsychotics be reduced or discontinued by gradually tapering it downwards. Based on the clinical circumstances, the prescribing physician should judge whether or not to discontinue the other antipsychotic therapy before initiating treatment with Clozaril.

Reducing the risk of suicidal behaviour in schizophrenia and schizoaffective disorder

The dosage and administration recommendations described in the preceding section DOSAGE AND ADMINISTRATION regarding the use of Clozaril in patients with treatment-resistant schizophrenia should also be followed when treating patients with schizophrenia or schizoaffective disorder at risk for recurrent suicidal behaviour.

A course of treatment with Clozaril of at least two years is recommended in order to maintain the reduction of risk for suicidal behaviour. It is recommended that the patient's risk of suicidal behaviour be reassessed after two years of treatment and that thereafter the decision to continue treatment with Clozaril be re-visited at regular intervals, based on thorough assessments of patient's risk for suicidal behaviour during treatment.

Psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed

The starting dose must not exceed 12.5 mg/day (half a 25 mg tablet), taken in the evening. Subsequent dose increases must be by 12.5 mg increments, with a maximum of two increments a week up to a maximum of 50 mg, a dose that cannot be reached until the end of the second week. The total daily amount should preferably be given as a single dose in the evening.

The mean effective dose is usually between 25 and 37.5 mg/day. In the event that treatment for at least one week with a dose of 50 mg fails to provide a satisfactory therapeutic response, dosage may be cautiously increased by increments of 12.5 mg/week.

The dose of 50 mg/day should only be exceeded in exceptional cases, and the maximum dose of 100 mg/day must never be exceeded.

Dose increases should be limited or deferred if orthostatic hypotension, excessive sedation or confusion occurs. Blood pressure should be monitored during the first weeks of treatment.

When there has been complete remission of psychotic symptoms for at least 2 weeks, an increase in anti-parkinsonian medication is possible if indicated on the basis of motor status. If this approach results in the recurrence of psychotic symptoms, Clozaril dosage may be increased by increments of 12.5 mg/week up to a maximum of 100 mg/day, taken in one or two divided doses (see above).

When ending therapy, a gradual reduction in dose by steps of 12.5 mg over a period of at least one week (preferably two) is recommended.

Treatment must be discontinued immediately in the event of neutropenia or agranulocytosis as indicated in section SPECIAL WARNINGS AND PRECAUTIONS FOR USE. In this situation, careful psychiatric monitoring of the patient is essential since symptoms may recur quickly.

Contraindications

- Known hypersensitivity to clozapine or to any of the excipients of Clozaril.
- Patients unable to undergo regular blood tests.
- History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy).
- Impaired bone marrow function.
- Uncontrolled epilepsy.

- Alcoholic and other toxic psychoses, drug intoxication, comatose conditions.
- Circulatory collapse and/or CNS depression of any cause.
- Severe renal or cardiac disorders (e.g. myocarditis).
- Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure.
- Paralytic ileus.

Special warnings and precautions for use

Special precautionary measure

Because of the association of Clozaril with agranulocytosis, the following precautionary measures are mandatory:

Drugs known to have a substantial potential to depress bone marrow function should not be used concurrently with Clozaril. In addition, the concomitant use of long-acting depot antipsychotics should be avoided because of the impossibility of removing these medications, which may be potentially myelosuppressive, from the body rapidly in situations where this may be required, e.g. granulocytopenia.

Patients with a history of primary bone marrow disorders may be treated only if the benefit outweighs the risk. They should be carefully reviewed by a haematologist prior to starting Clozaril.

Patients who have low WBC counts because of benign ethnic neutropenia should be given special consideration and may be started on Clozaril after agreement of a haematologist.

WBC counts and ANC monitoring

WBC and differential blood counts must be performed within 10 days prior to starting Clozaril treatment to ensure that only patients with normal leukocyte and absolute neutrophil counts (WBC $\geq$3500/mm^3 and ANC $\geq$2000/mm^3) will receive Clozaril. After the start of Clozaril treatment, the WBC count and ANC must be monitored weekly for 18 weeks and thereafter at least every four weeks throughout treatment and for 4 weeks after complete discontinuation of Clozaril.

At each consultation, the patient should be reminded to contact the treating physician immediately if any kind of infection, fever, sore throat or other flu-like symptoms develop. A differential blood count must be performed immediately if any symptoms or signs of an infection occur.

Low WBC count and/or ANC

If during the first 18 weeks of Clozaril therapy, the WBC count falls to between 3500/mm^3 and 3000/mm^3 and/or the ANC falls to between 2000/mm^3 and 1500/mm^3, haematological evaluations must be performed at least twice weekly.

After 18 weeks of Clozaril therapy, haematological evaluations should be performed at least twice weekly if the WBC count falls to between 3000/mm^3 and 2500/mm^3 and/or the ANC falls to between 1500/mm^3 and 1000/mm^3.

In addition, if, during Clozaril therapy, the WBC count is found to have dropped by a substantial amount from baseline, a repeat WBC count and a differential blood count should be performed. A substantial drop is defined as a single drop of 3000 mm^3 or more in the WBC count or a cumulative drop of 3000 mm^3 or more within three weeks.

Immediate discontinuation of Clozaril is mandatory if the WBC count is less than 3000/mm^3 or the ANC is less than 1500/mm^3 during the first 18 weeks of therapy, or if the WBC count is less than 2500/mm^3 or the ANC is less than 1000/mm^3 after the first 18 weeks of therapy. WBC counts and differential blood counts should then be performed daily and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. Following discontinuation of Clozaril, haematological evaluation is required until haematological recovery has occurred.

If Clozaril has been withdrawn and WBC count falls further to below 2000/mm^3 and/or the ANC falls below 1000/mm^3, the management of this condition must be guided by an experienced haematologist. If possible, the patient should be referred to a specialised haematological unit, where protective isolation and the administration of GM-CSF (granulocyte-macrophage colony stimulating factor) or G-CSF (granulocyte colony stimulating factor) may be indicated. It is recommended that the colony stimulating factor therapy be discontinued when the neutrophil count has returned to a level above 1000/mm^3.

Patients in whom Clozaril has been discontinued as a result of white blood cell deficiencies (see above) must not be re-exposed to Clozaril.

It is recommended that the haematological values be confirmed by performing two blood counts on two consecutive days; however, Clozaril should be discontinued after the first blood count.

Table 1: Blood monitoring during the first 18 weeks of Clozaril therapy

Blood cell count		Action required
WBC/mm^3 (/L)	ANC/mm^3 (/L)	
$\geq$3500 ($>3.5 \times 10^9$)	$\geq$2000 ($>2.0 \times 10^9$)	Continue Clozaril treatment.
3000-3500 (3.0×10^9-3.5×10^9)	1500-2000 (1.5×10^9-2.0×10^9)	Continue Clozaril treatment, sample blood twice weekly until counts stabilise or increase.
<3000 ($<3.0 \times 10^9$)	<1500 ($<1.5 \times 10^9$)	Immediately stop Clozaril treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

Table 2: Blood monitoring after 18 weeks of Clozaril therapy

Blood cell count		Action required
WBC/mm^3 (/L)	ANC/mm^3 (/L)	
$\geq$3000 ($>3.0 \times 10^9$)	$\geq$1500 ($>1.5 \times 10^9$)	Continue Clozaril treatment.
2500-3000 (2.5×10^9-3.0×10^9)	1000-1500 (1.0×10^9-1.5×10^9)	Continue Clozaril treatment, sample blood twice weekly until counts stabilise or increase.
<2500 ($<2.5 \times 10^9$)	<1000 ($<1.0 \times 10^9$)	Immediately stop Clozaril treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

In the event of interruption of therapy for non-haematological reasons

Patients who have been on Clozaril for more than 18 weeks and have had their treatment interrupted for more than 3 days but less than 4 weeks should have their WBC count and ANC monitored weekly for an additional 6 weeks. If no haematological abnormality occurs, monitoring at intervals not exceeding 4 weeks may be resumed. If Clozaril treatment has been interrupted for 4 weeks or longer, weekly monitoring is required for the next 18 weeks of treatment.

Other precautions

In the event of **eosinophilia**, discontinuation of Clozaril is recommended if the eosinophil count rises above 3000/mm^3. Therapy should be re-started only after the eosinophil count has fallen below 1000/mm^3.

In the event of **thrombocytopenia,** discontinuation of Clozaril is recommended if the platelet count falls below 50 000/mm^3.

Orthostatic hypotension, with or without syncope, can occur during Clozaril treatment. Rarely (about one case per 3000 Clozaril-treated patients), collapse can be profound and may be accompanied by cardiac and/or respiratory arrest. Such events are more likely to occur during initial titration in association with rapid dose escalation; on very rare occasions they occurred even after the first dose. Therefore, patients commencing Clozaril treatment require close medical supervision. Tachycardia that persists at rest, accompanied by arrhythmias, shortness of breath or signs and symptoms of heart failure, may rarely occur during the first month of treatment and very rarely thereafter. The occurrence of these signs and symptoms necessitates an urgent diagnostic evaluation for myocarditis, especially during the titration period. If the diagnosis of myocarditis is confirmed, Clozaril should be discontinued. Later in treatment, the same signs and symptoms may very rarely occur and may be linked to cardiomyopathy. Further investigation should be performed and if the diagnosis is confirmed, the treatment should be stopped unless the benefit clearly outweighs the risk to the patient.

Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson's disease.

In patients with a history of seizures, or suffering from renal or cardiovascular disorders (note: severe renal or cardiovascular disorders are contraindications) the initial dose should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments.

Patients with stable pre-existing liver disorders may receive Clozaril, but must undergo regular liver function tests. Such tests should be performed immediately in patients who develop symptoms of possible liver dysfunction such as nausea, vomiting and/or anorexia during Clozaril treatment. If the elevation of the values is clinically relevant or if symptoms of jaundice occur, treatment with Clozaril must be discontinued. It may be resumed (see section DOSAGE AND ADMINISTRATION - Re-starting therapy) only when the results of liver function tests are normal. In such cases, liver function should be closely monitored after re-introduction of Clozaril.

Clozapine exerts anticholinergic activity, which may produce undesirable effects throughout the body. Careful supervision is indicated in the presence of **prostatic enlargement** and **narrow-angle glaucoma**. Probably on account of its anticholinergic properties, Clozaril has been associated with varying degrees **of impairment of intestinal peristalsis**, ranging from **constipation** to **intestinal obstruction**, **faecal impaction** and **paralytic ileus** (see section UNDESIRABLE EFFECTS). On rare occasions these cases have proved fatal.

During Clozaril therapy, patients may experience transient **temperature elevations** above 38°C, with the peak incidence within the first 3 weeks of treatment. This fever is generally benign. Occasionally, it may be associated with an increase or decrease in the WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infection or the development of agranulocytosis. In the presence of high fever, the possibility of **neuroleptic malignant syndrome** (NMS) must be considered.

On rare occasions, severe hyperglycaemia, sometimes leading to ketoacidosis/hyperosmolar coma, has been reported during Clozaril treatment in patients with no prior history of hyperglycaemia. While a causal relationship to Clozaril use has not been definitely established, glucose levels returned to normal in most patients after discontinuation of Clozaril, and re-challenge produced a recurrence of hyperglycaemia in a few cases. The effect of Clozaril on glucose metabolism in patients with diabetes mellitus has not been studied. Impaired glucose tolerance, severe hyperglycaemia, ketoacidosis and hyperosmolar coma have been reported in patients with no prior history of hyperglycaemia. Exacerbation should be considered in patients receiving Clozaril who develop symptoms of hyperglycaemia, such as polydipsia, polyuria, polyphagia or weakness. In patients with significant treatment-emergent hyperglycaemia, discontinuation of Clozaril should be considered.

There is a risk of altering the metabolic balance resulting in slight impairment of glucose homeostasis and a possibility of unmasking a pre-diabetic condition or aggravating pre-existing diabetes.

Since Clozaril may cause sedation and weight gain, thereby increasing the risk of **thromboembolism**, immobilisation of patients should be avoided.

An increased risk of cerebrovascular adverse events has been seen in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Clozaril should be used with caution in patients with risk factors for stroke.

As with other antipsychotics, caution is advised in patients with known cardiovascular disease or family history of QT prolongation.

As with other antipsychotics, caution should be exercised when Clozaril is prescribed with medicines known to increase the QTc interval.

Use in the elderly

It is recommended that treatment be initiated at a particularly low dose (12.5 mg given once on the first day) and subsequent dose increments be restricted to 25 mg/day.

Clinical studies with Clozaril did not include sufficient numbers of subjects aged 65 years and over to determine whether or not they respond differently from younger subjects.

Orthostatic hypotension can occur with Clozaril treatment and there have been rare reports of tachycardia, which may be sustained, in patients taking Clozaril. Elderly patients, particularly those with compromised cardiovascular function, may be more susceptible to these effects.

Elderly patients may also be particularly susceptible to the anticholinergic effects of clozapine, such as urinary retention and constipation.

Elderly patients with Dementia-related Psychosis

In elderly patients with dementia-related psychosis, the efficacy and safety of clozapine has not been studied. Observational studies suggest that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. In the published literature, risk factors that may predispose this patient population to increased risk of death when treated with antipsychotics include sedation, the presence of cardiac conditions (e.g. cardiac arrhythmias) or pulmonary conditions (e.g. pneumonia, with or without aspiration). Clozaril should be used with caution in elderly patients with dementia.

Interactions

Pharmacodynamic-related interactions

Medicinal products known to have a substantial potential to depress bone marrow function should not be used concurrently with Clozaril (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Clozapine may enhance the central effects of alcohol, MAO inhibitors and CNS depressants such as narcotics, antihistamines, and benzodiazepines.

Particular caution is recommended when Clozaril therapy is initiated in patients who are receiving (or have recently received) a benzodiazepine or any other psychotropic agent, as these patients may have an increased risk of circulatory collapse, which, on rare occasions, can be profound and may lead to cardiac and/or respiratory arrest.

Because of the possibility of additive effects, caution is essential when substances possessing anticholinergic, hypotensive, or respiratory depressant effects are given concomitantly.

Concomitant use of lithium or other CNS-active agents may increase the risk of development of neuroleptic malignant syndrome (NMS).

Owing to its anti-alpha-adrenergic properties, clozapine may reduce the blood pressure-increasing effect of norepinephrine or other predominantly alpha-adrenergic agents and reverse the pressor effect of epinephrine.

Rare but serious reports of seizures, including onset of seizures in non-epileptic patients, and isolated cases of delirium where Clozaril was co-administered with valproic acid have been reported. These effects are possibly due to a pharmacodynamic interaction, the mechanism of which has not been determined.

As with other antipsychotics, caution should be exercised when Clozaril is prescribed with medicines known to increase the QTc interval, or causing electrolyte imbalance.

Pharmacokinetic-related interactions

Clozapine is a substrate for many CYP 450 isoenzymes, in particular 1A2 and 3A4. The risk of metabolic interactions caused by an effect on an individual isoform is therefore minimised. Nevertheless, caution is called for in patients receiving concomitant treatment with other substances that are either inhibitors or inducers of these enzymes.

No clinically relevant interactions have been observed thus far with tricyclic antidepressants, phenothiazines or type 1_C anti-arrhythmics, which are known to bind to cytochrome P450 2D6.

Concomitant administration of substances known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine.

- Substances known to induce the activity of 3A4 and with reported interactions with clozapine include, for instance, carbamazepine, phenytoin and rifampicin.
- Known inducers of 1A2 include, for instance, omeprazole and tobacco smoke. In cases of sudden cessation of tobacco smoking, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects.

Concomitant administration of substances known to inhibit the activity of cytochrome P450 isozymes may increase the plasma levels of clozapine.

- Substances known to inhibit the activity of the major isozymes involved in the metabolism of clozapine and with reported interactions include, for instance, cimetidine, erythromycin (3A4), fluvoxamine (1A2) and ciprofloxacin (1A2).
- Potent inhibitors of CYP3A, such as azole antimycotics and protease inhibitors, could potentially also increase clozapine plasma concentrations; no interactions have been reported to date, however.
- The plasma concentration of clozapine is increased by caffeine (1A2) intake and decreased by nearly 50% following a 5-day caffeine-free period.

Elevated clozapine plasma concentrations also have been reported in patients receiving the substances in combination with selective serotonin re-uptake inhibitors (SSRIs) such as paroxetine (1A2), sertraline, fluoxetine or citalopram.

Pregnancy and lactation

Pregnancy

Reproduction studies in animals have revealed no evidence of impaired fertility or harm to the fetus due to clozapine. However, the safe use of Clozaril in pregnant women has not been established. Therefore, Clozaril should be used in pregnancy only if the expected benefit clearly outweighs any potential risk.

Non-teratogenic effects

Neonates exposed to antipsychotic drugs, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Antipsychotic drugs, including Clozaril, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

Animal studies suggest that clozapine is excreted in breast milk; therefore, mothers receiving Clozaril should not breast-feed.

Women of childbearing potential

Some female patients treated with antipsychotics other than Clozaril may become amenorrheic. A return to normal menstruation may occur as a result of switching from other antipsychotics to Clozaril. Adequate contraceptive measures must therefore be ensured in women of childbearing potential.

Effects on ability to drive and use machines

Owing to the ability of Clozaril to cause sedation and lower the seizure threshold, activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment.

Undesirable effects

The adverse effects of clozapine are most often predictable based on its pharmacological properties with the exception of agranulocytosis (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Adverse reactions are ranked under headings of frequency, using the following convention: Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), including isolated reports is shown in table 3.

Table 3: Treatment-Emergent Adverse Experience Frequency estimate from Spontaneous and Clinical Trial Reports

Blood and lymphatic system disorders	
Common	Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis
Uncommon	Agranulocytosis
Rare	Anaemia
Very rare	Thrombocytopenia, thrombocythaemia
Metabolism and nutrition disorders	
Common	Weight gain
Rare	Impaired glucose tolerance, new onset diabetes, diabetes aggravated
Very rare	Ketoacidosis, hyperosmolar coma, severe hyperglycaemia, hypercholesterolaemia, hypertriglyceridaemia
Psychiatric disorders	
Common	Dysarthria
Uncommon	Dysphemia
Rare	Restlessness, agitation
Nervous system disorders	
Very common	Drowsiness/sedation, dizziness
Common	Blurred vision, headache, tremor, rigidity, akathisia, extrapyramidal symptoms, seizures/convulsions/myoclonic jerks
Rare	Confusion, delirium
Very rare	Tardive dyskinesia, obsessive compulsive symptoms
Cardiac disorders	
Very common	Tachycardia
Common	ECG changes
Rare	Circulatory collapse, arrhythmias, myocarditis, pericarditis
Very rare	Cardiomyopathy
Vascular system disorders	
Common	Hypertension, postural hypotension, syncope
Rare	Thromboembolism
Respiratory disorders	
Rare	Aspiration of ingested food, pneumonia and lower respiratory tract infection which may be fatal
Very rare	Respiratory depression/arrest
Gastrointestinal disorders	

Very common	Constipation, hypersalivation
Common	Nausea, vomiting, dry mouth
Rare	Dysphagia
Very rare	Parotid gland enlargement, intestinal obstruction/ileus/faecal impaction
Hepatobiliary disorders	
Common	Elevated liver enzymes
Rare	Hepatitis, cholestatic jaundice, pancreatitis
Very rare	Fulminant hepatic necrosis
Skin and subcutaneous tissue disorders	
Very rare	Skin reactions
Renal and urinary disorders	
Common	Urinary incontinence, urinary retention
Very rare	Interstitial nephritis
Reproductive system disorders	
Very rare	Priapism
General disorders	
Common	Fatigue, benign hyperthermia, disturbances in sweating/temperature regulation
Uncommon	Neuroleptic malignant syndrome
Very rare	Sudden unexplained death
Investigations	
Rare	Increased CPK

Very rare events of ventricular tachycardia, cardiac arrest and QT prolongation which may be associated with Torsades De Pointes have been observed although there is no conclusive causal relationship to the use of this medicine.

Overdose

In cases of acute intentional or accidental Clozaril overdosage, for which information on the outcome is available, to date the mortality is about 12%. Most of the fatalities were associated with cardiac failure or pneumonia caused by aspiration and occurred at doses above 2000 mg. There have been reports of patients recovering from an overdose in excess of 10,000 mg. However, in a few adult individuals, primarily those not previously exposed to Clozaril, the ingestion of doses as low as 400 mg led to life-threatening comatose conditions and, in one case, to death. In young children, the intake of 50 mg to 200 mg resulted in strong sedation or coma without being lethal.

Signs and symptoms

Drowsiness, lethargy, areflexia, coma, confusion, hallucinations, agitation, delirium, extrapyramidal symptoms, hyper-reflexia, convulsions; hypersalivation, mydriasis, blurred vision, thermolability; hypotension, collapse, tachycardia, cardiac arrhythmias; aspiration pneumonia, dyspnoea, respiratory depression or failure.

Treatment

Gastric lavage and/or the administration of activated charcoal within the first 6 hours after Clozaril ingestion. (Peritoneal dialysis and haemodialysis are unlikely to be effective.) Symptomatic treatment under continuous cardiac monitoring, surveillance of respiration, monitoring of electrolytes and acid-base balance. The use of epinephrine should be avoided in the treatment of hypotension because of the possibility of a 'reverse epinephrine' effect.

Close medical supervision is necessary for at least 5 days because of the possibility of delayed reactions.

Pharmacodynamics

Clozaril has been shown to be an antipsychotic agent that is different from classic antipsychotics.

In pharmacological experiments, the compound does not induce catalepsy or inhibit apomorphine- or amphetamine-induced stereotyped behaviour. It has only weak dopamine receptor-blocking activity at D_1, D_2, D_3 and D_5 receptors, but shows high potency for the D_4 receptor, in addition to potent anti-alpha-adrenergic, anticholinergic, antihistaminic, and arousal reaction-inhibiting effects. It has also been shown to possess antiserotoninergic properties.

Clinically Clozaril produces rapid and marked sedation, and exerts antipsychotic effects in patients with schizophrenia resistant to other antipsychotic agents. In such cases, Clozaril has proven effective in relieving both positive and negative schizophrenic symptoms in short- and long-term trials. In a double-blind clinical trial performed in 319 treatment-resistant patients, clinically relevant improvement was observed within 6 weeks in about 30% of the Clozaril-treated patients. Two open-label trials in which patients were treated for 12 months, showed clinically relevant improvement in 37% of patients within the first 6 weeks of treatment and in an additional 39%-44% of patients by the end of 12 months. The improvement was defined as a reduction of more than 20% from baseline in Brief Psychiatric Rating Scale Score. In addition, improvement in some aspects of cognitive dysfunction has been described.

Epidemiological studies showed an approximately sevenfold decrease in suicide attempts and a four to six fold decrease in mortality from suicide in clozapine-treated patients with schizophrenia or schizoaffective disorder compared to non-treated patients. In a randomised, multicentre clinical trial performed in 980 patients, Clozaril reduced the risk for suicidal behaviour (as measured by suicide attempts and hospitalisations to prevent suicide) by 26% over a 2-year period compared to olanzapine. This significant effect relative to olanzapine was achieved despite the fact that olanzapine-treated patients received significantly more concomitant antipsychotics, antidepressants, anxiolytics, sedatives and mood stabilisers than the Clozaril-treated patients.

Clozaril is unique in that it produces virtually no major extrapyramidal reactions such as acute dystonia and tardive dyskinesia. Furthermore, parkinsonian-like side effects and akathisia are rare. In contrast to classical antipsychotics, clozapine produces little or no prolactin elevation, thus avoiding adverse effects such as gynaecomastia, amenorrhoea, galactorrhoea, and impotence.

Potentially serious adverse reactions caused by Clozaril therapy are granulocytopenia and agranulocytosis occurring at an estimated incidence of 3% and 0.7% respectively (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Pharmacokinetics

The absorption of orally administered clozapine is 90% to 95%; neither the rate nor the extent of absorption is influenced by food.

Clozapine is subject to moderate first-pass metabolism, resulting in an absolute bioavailability of 50% to 60%. In steady-state conditions, when given twice daily, peak blood levels occur on an average at 2.1 hours (range: 0.4 to 4.2 hours), and the volume of distribution is 1.6 L/kg. Clozapine is approximately 95% bound to plasma proteins. Its elimination is biphasic, with a mean terminal half-life of 12 hours (range: 6 to 26 hours). After single doses of 75 mg the mean terminal half-life was 7.9 hours; it increased to 14.2 hours when steady-state conditions were reached by administering daily doses of 75 mg for at least 7 days. Dosage increases from 37.5 mg to 75 mg and 150 mg given twice daily were found to result during steady state in linearly dose-proportional increases in the area under the plasma concentration/time curve (AUC), and in the peak and minimum plasma concentrations.

Clozapine is almost completely metabolised before excretion. Of the main metabolites only the desmethyl metabolite was found to be active. Its pharmacological actions resemble those of clozapine, but are considerably weaker and of short duration. Only trace amounts of unchanged drug are detected in the urine and faeces, approximately 50% of the administered dose being excreted as metabolites in the urine and 30% in the faeces.

Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential (for reproductive toxicity, see section PREGNANCY AND LACTATION).

Acute toxicity

Acute toxicity studies in mice, rats and guinea pigs revealed oral LD_{50} values of 190 to 681 mg/kg body weight. In dogs, the oral LD_{50} was approximately 145 mg/kg; signs of overdosage consisted of muscular tremor, aggressive behaviour and vomiting.

Mutagenicity

Clozapine and/or its metabolites were devoid of genotoxic potential when investigated for induction of gene mutations, chromosome aberrations and primary DNA-damage in a spectrum of *in vitro* mutagenicity tests. No clastogenic activity was observed *in vivo* (bone marrow micronucleus test in mice).

Carcinogenicity

In Sprague-Dawley (CD) rats treated in the diet for 24 months, maximum tolerated doses of 35 mg/kg per day revealed no carcinogenic potential of clozapine. Likewise, no evidence of tumorigenic effects was obtained in two 78-week feeding studies in Charles River (CD) mice. In the first study, oral dose levels of up to 64 mg/kg were administered to males, and of up to 75 mg/kg to females respectively. In the second study, the drug intake achieved for both sexes was 61 mg/kg per day.

Reproductive toxicity

No embryotoxic or teratogenic potential of clozapine was revealed in rats or rabbits. In male rats treated for 70 days prior to mating, fertility was unaffected.

In female rats, fertility as well as pre- and postnatal development of the offspring was not adversely affected by oral clozapine treatment prior to mating. When rats were treated during the later part of pregnancy and during lactation, survival rates of the young from lactating dams, treated at dose levels up to 40 mg/kg body weight, were lowered and the young were hyperactive. However, there was no lasting effect on pup development after weaning.

Excipients

Clozaril tablets: magnesium stearate; silica, colloidal anhydrous; povidone; talc; maize starch; lactose monohydrate.

Pharmaceutical formulations may vary between countries.

Incompatibilities

Not applicable.

Storage

Clozaril should not be used after the date marked "EXP" on the pack.

Instructions for use and handling

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

Note: Clozaril must be kept out of the reach and sight of children.

Manufacturer:

See folding box.

International Package Leaflet

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