# 止敏吐® 膠囊
# EMEND® Capsules
# (aprepitant)

WPC-MK0869-C-062013
0869-TWN-2014-009131

本藥須由醫師處方使用
80 毫克 衛署藥輸字第 023985 號
125 毫克 衛署藥輸字第 023986 號

**治療分類**

EMEND® (aprepitant) 是一種 substance P neurokinin 1 ($NK_1$)之受體拮抗劑。

**組成**

每顆 EMEND 口服膠囊含 80 毫克或 125 毫克 aprepitant。

每顆 EMEND 膠囊含下列賦形劑：sucrose, microcrystalline cellulose, hydroxypropyl cellulose 和 sodium lauryl sulfate。膠囊殼的成分為 gelatin 和 titanium dioxide、另含 sodium lauryl sulfate 及 silicon dioxide，125 毫克的膠囊殼含有紅色及黃色氧化鐵(ferric oxide)之色素。

**臨床藥理學**

**作用機轉**

Aprepitant 具有獨特的作用模式；其對人類 substance P neurokinin 1($NK_1$)的接受體，具有選擇性與高度親合力的拮抗劑。經由相對篩選檢驗法(counter-screening assay)顯示與其他酵素、轉運物質(transporter)、離子通道(ion channel)以及現行化療引起的噁心和嘔吐(Chemotherapy Induced Nausea and Vomiting，CINV)療法之標的受體包括多巴胺(dopamine)與血清素(serotonin)的受體等比較之下，aprepitant 對 $NK_1$ 的選擇性至少高 3,000 倍以上。

臨床前研究顯示，$NK_1$-受體拮抗劑可以藉由中樞作用，抑制由細胞毒性類化療藥物(例如：cisplatin)所引起的嘔吐。臨床前研究與人體正子放射斷層掃瞄(Positron Emission Tomography, PET)的結果顯示，aprepitant 可以穿透進入腦部，並佔據腦部的 $NK_1$ 受體。臨床前研究顯示，aprepitant 對中樞系統的作用時間很長，可以抑制 cisplatin 引起的急性期與延遲期的嘔吐，並可增強具止吐作用的 $5\text{-}HT_3$-受體拮抗劑 ondansetron 與皮質類固醇 dexamethasone 等對 cisplatin 所引起的嘔吐的抑制作用。

**藥動學 (Pharmacokinetics)**

***吸收***

Aprepitant 的平均絕對口服生體可用率(mean absolute oral bioavailability)大約為 60 至 65%，而 aprepitant 的平均最高血中濃度($C_{max}$)大約出現在服藥 4 小時後($T_{max}$)。Aprepitant 膠囊與標準早餐一起服用時，對 aprepitant 口服生體可用率，在臨床上沒有明顯的影響。

在臨床劑量範圍內，aprepitant 的藥物動力學呈現非線性的關係。健康年輕成人在飲食後服用 aprepitant 單一劑量，在 80 mg 至 125 mg 劑量範圍，其 $AUC_{0-\infty}$ 的增加比用藥劑量增加比例高出 26%。

於第一天口服一次 125 mg 的 EMEND，並於第二、第三天各服用一次 80 mg 的情況下，第一天與第三天的 $AUC_{0\text{-}24hr}$ 分別約為 19.5 μg•hr/mL 與 20.1 μg•hr/mL。平均最高血中濃度($C_{max}$)大約會在服藥後 4 小時($T_{max}$)達到，第一天與第三天的 $C_{max}$ 分別為 1.5 μg/mL 與 1.4 μg/mL 。

***分佈***

Aprepitant 與血漿蛋白結合率大於 95%。穩定狀態下，人體的擬似分佈體積(apparent volume of distribution at steady state，$Vd_{ss}$)的幾何平均值約為 66 公升。

Aprepitant 可以通透過大鼠的胎盤，以及大鼠與白鼬的血腦障壁。正子放射斷層掃瞄(PET)研究顯示，aprepitant 可以通透過人體的血腦障壁(參見「臨床藥理及作用機轉」)。

***代謝***

Aprepitant 會受到廣泛的代謝作用。健康年輕的成人，口服單一劑量 [$^{14}$C]-aprepitant 300 mg 後 72 小時，血漿中的放射性大約有 24%是來自 aprepitant，顯示血漿中存在相當程度的代謝產物。人體血漿中曾找到七種弱活性的 aprepitant 代謝產物。Aprepitant 的代謝大部分是藉由 morpholine 環及其側鏈的氧化作用。使用人體肝臟微粒體(microsomes)的體外研究顯示，aprepitant 主要藉由 CYP3A4 酵素代謝，有少部份是由 CYP1A2 與 CYP2C19 代謝，並不經由 CYP2D6、CYP2C9 或 CYP2E1 代謝。

***排除***

Aprepitant 主要是經由代謝作用來排除，而不是經由腎臟排除。健康的受試者在使用單一劑量的 [$^{14}$C]-aprepitant 300 mg 後，只有 5% 的放射性出現在尿液中；在糞便中的則有 86%。

Aprepitant 的擬似血漿清除率(apparent plasma clearance)大約在 60 至 84 mL/min 的範圍內。擬似末端清除半衰期(apparent terminal half-life)大約在 9 到 13 個小時之間。

**病患特性**

***性別***

使用單一劑量的 EMEND 之後，女性的 aprepitant $AUC_{0\text{-}24hr}$ 和 $C_{max}$ 比男性的分別高出 9%和 17%。女性的 aprepitant 半衰期則比男性的低約 25%，而他們的 $T_{max}$ 則大致出現在相同時間。這些差異並不具臨床意義，所以不須依性別來調整 EMEND 的劑量。

***老年人***

第一天口服單一劑量的 EMEND 125 mg，並於第二天到第五天每天服用一次 80 mg 之後，與年輕成人相比，第一天時，老年人(≥ 65 歲)的 aprepitant 的 $AUC_{0\text{-}24hr}$ 高出 21%，第五天時則高出 36%。至於 $C_{max}$，第一天老年人比年輕成人高出 10%，第五天時則高出 24% 。這些差異不具臨床意義，所以對老年患者不須調整 EMEND 劑量。

***小兒科***

尚未對十八歲以下病患進行 EMEND 藥動學的研究。

***種族***

口服單一劑量的 EMEND 之後，西班牙裔受試者的 $AUC_{0\text{-}24hr}$ 分別比高加索裔與黑人高出約 27%及 31%，$C_{max}$ 則分別高出 19%及 29%。相較於高加索人，亞洲人口服單一劑量的 aprepitant，$AUC_{0\text{-}24hr}$ 和 $C_{max}$ 分別高出 74%和 47%。這些差異不具臨床意義，所以不須依種族來調整 EMEND 的劑量。

***身體質量指數 (Body Mass Index)***

身體質量指數(Body Mass Index; BMI)對於 aprepitant 藥動學的影響不具臨床意義。

***肝功能不全***

輕度至中度肝功能不全患者對 EMEND 的耐受性良好。第一天口服單一劑量的 EMEND 125 mg，並於第二天和第三天每天服用一次 80 mg 之後，輕度肝功能不全病患(Child-Pugh 分數從 5 到 6)，第一天和第三天的 aprepitant $AUC_{0\text{-}24hr}$，分別比接受同樣療程的健康受試者的低 11% 與 36%。而中度肝功能不全病患(Child-Pugh 分數從 7 到 9)，第一天和第三天的 aprepitant $AUC_{0\text{-}24hr}$，則分別比接受同樣療程的健康受試者高出 10% 與 18%。這些 $AUC_{0\text{-}24hr}$ 的差異不具臨床意義，所以對輕度與中度肝功能不全患者不須調整 EMEND 的劑量。沒有針對重度肝功能不全病患(Child-Pugh 分數大於 9)的臨床或藥物動力學資料。

***腎功能不全***

曾給嚴重腎功能不全的患者(肌酸酐廓清率 CrCl < 30 mL/min)以及需洗腎的末期腎病(End Stage Renal Disease，ESRD)患者服用單一劑量的 EMEND 240 mg 。

嚴重腎功能不全患者的 total aprepitant(含自由態及與蛋白質結合態)的 $AUC_{0-\infty}$ 比健康受試者低 21%、$C_{max}$ 則較低 32%。需洗腎的末期腎病患者的 total aprepitant 的 $AUC_{0-\infty}$降低 42%、$C_{max}$ 則降低 32%。由於腎病患者體內與蛋白質結合的 aprepitant 量的減少有限，與健康受試者相比，腎功能不全患者體內具有藥物活性的自由態藥物的 AUC ，並不會受到很大的影響。用藥後 4 或 48 小時進行洗腎，對 aprepitant 的藥物動力學並沒有顯著的影響；少於 0.2% 劑量會出現在透析液(dialysate)中。

對嚴重腎功能不全患者以及需洗腎的末期腎病(ESRD)患者均不須調整 EMEND 的劑量。

**藥效學 (Pharmacodynamics)**

Fosaprepitant (aprepitant 的前驅藥)在靜脈輸注後會快速轉化成 aprepitant。

***心電生理學***

在一項隨機分配、雙盲、陽性對照、thorough QTc 研究中，注射單一劑 200 mg 的 fosaprepitant 對於 QTc interval 沒有影響。

***以正子放射斷層掃瞄評估腦中 $NK_1$ 受體結合***

一項針對健康年輕男子口服單一劑 165 mg aprepitant 或以靜脈注射單一劑 150 mg fosaprepitant，以 PET 評估腦中 $NK_1$ 受體結合的研究。結果顯示相似的腦中 $NK_1$ 受體結合，即給藥後 $T_{max}$ (≥ 99 %)、第 24 小時(≥ 99 %)、於第 48 小時(≥ 97%)及第 120 小時(37 至 76 %)。Aprepitant 結合於腦中 $NK_1$ 受體與 aprepitant 血漿濃度具有良好的相關性。

**臨床研究**

***預防癌症化學療法所引起的噁心及嘔吐(CINV)***

控制良好的臨床研究顯示，口服投予 EMEND，並合併使用 ondansetron 及 dexamethasone，可預防高致吐性及中致吐性癌症化學療法(HEC 及 MEC)所引起的急性與延遲性噁心及嘔吐反應。

***高致吐性癌症化學療法 (HEC)***

在 2 項多中心、隨機、平行、雙盲的對照性臨床研究中，研究人員共針對 1094 位接受含有 cisplatin ≥ 70 mg/m$^2$ 之化學療法治療的患者比較 aprepitant 療程與標準療程的治療效果。其中有些患者也額外接受如 gemcitabine、etoposide、fluorouracil、vinorelbine tartrate、doxorubicin、cyclophosphamide、paclitaxel 或 docetaxel 等化學治療劑的治療。Aprepitant 療程包括於第 1 天服用 EMEND 125 mg，於第 2 與第 3 天每天服用 80 mg，並於第 1 天靜脈注射 ondansetron 32 mg 且服用 dexamethasone 12 mg，再於第 2 至 4 天每天服用一次 dexamethasone 8 mg。標準療程則包括使用安慰劑，並於第 1 天靜脈注射 ondansetron 32 mg 且服用 dexamethasone 20 mg，再於第 2 至 4 天每天服用兩次 dexamethasone 8 mg。雖然臨床試驗使用靜脈注射 ondansetron 32 mg，但這不再是一般建議劑量。參見所選用的 $5\text{-}HT_3$ 拮抗劑仿單中最適劑量資訊。

研究人員針對 EMEND 於第 1 化療週期之急性期(使用 cisplatin 治療後 0 至 24 小時)、延遲期(使用 cisplatin 治療後 25 至 120 小時)與整體治療期間(使用 cisplatin 治療後 0 至 120 小時)的止吐作用進行評估。療效的評估係依據下列標準的綜合評估結果：

- 完全反應(其定義為無任何嘔吐反應，且未使用任何救援療法)
- 完全保護(其定義為無任何嘔吐反應、未使用任何救援療法、且最大噁心反應視覺類比量表[VAS]分數 <25 mm)
- 噁心及嘔吐反應對日常生活的影響(功能生活指數－嘔吐[FLIE]總分 >108)

另外也依據下列個別療效評估標準來評估療效：

- 無任何嘔吐反應(其定義為無任何嘔吐反應，但不論是否使用救援療法)
- 無任何明顯噁心反應(最高 VAS <25 mm)

研究人員分別針對個別研究的結果以及兩項研究的綜合結果進行評估。

整合分析後所獲得的主要研究結果摘錄於表 1。

**表 1 接受高致吐性化學療法治療者中的病患比例，依治療組別與治療期別列表 — 第 1 化療週期**

| 綜合評估標準 | Aprepitant 療程* (N = 521)† % | 標準療程** (N = 524) † % | *P* 值 |
|---|---|---|---|
| **完全反應(無任何嘔吐反應，且未使用任何救援療法)** | | | |
| 整體治療期間‡ | 67.7 | 47.8 | <0.001 |
| 急性期§ | 86.0 | 73.2 | <0.001 |
| 延遲期" | 71.5 | 51.2 | <0.001 |
| **完全保護(無任何嘔吐反應、未使用任何救援療法、且最高噁心反應 VAS¶ <25 mm)** | | | |
| 整體治療期間 | 59.5 | 44.9 | <0.001 |
| 急性期 | 82.4 | 69.6 | <0.001 |
| 延遲期 | 63.7 | 47.8 | <0.001 |
| **對日常生活無任何影響(功能生活指數－嘔吐[FLIE]總分 >108)** | | | |
| 整體治療期間 | 74.4 | 63.9 | <0.001 |
| 個別評估標準 | | | |
| **無任何嘔吐反應(無任何嘔吐反應，但不論是否使用救援療法)** | | | |
| 整體治療期間 | 71.9 | 49.7 | <0.001 |
| 急性期 | 86.8 | 74.0 | <0.001 |
| 延遲期 | 76.2 | 53.5 | <0.001 |
| **無任何明顯噁心反應(最高 VAS <25 mm)** | | | |
| 整體治療期間 | 72.1 | 64.9 | 0.014 |
| 延遲期 | 74.0 | 66.9 | 0.013 |

*Aprepitant 療程：於第 1 天服用 EMEND 125 mg，於第 2 與第 3 天每天服用一次 80 mg，並於第 1 天靜脈注射 ondansetron 32 mg 且服用 dexamethasone 12 mg，再於第 2 至 4 天每天服用一次 dexamethasone 8 mg。

**標準療程：使用安慰劑，並於第 1 天靜脈注射 ondansetron 32 mg 且服用 dexamethasone 20 mg，再於第 2 至 4 天每天服用兩次 dexamethasone 8 mg。

†N：接受研究藥物 cisplatin 治療且至少完成一次治療後療效評估的患者數。

‡整體治療期間：使用 cisplatin 治療後 0 至 120 小時。

§急性期：使用 cisplatin 治療後 0 至 24 小時。

"延遲期：使用 cisplatin 治療後 25 至 120 小時。

¶視覺類比量表(VAS)分數範圍：0 = 無任何噁心反應；100 = 極度的噁心反應。

整合分析的結果顯示，在第 1 化療週期中，接受 aprepitant 療程治療之患者達到完全反應與完全保護之效果的比例在統計學上都明顯高於接受標準療程治療的患者。在第 1 化療週期的急性期與延遲期中，接受 aprepitant 療程治療的患者與接受標準療程治療的患者在達到完全反應和完全保護之效果的分析方面有統計學上明顯的差異。在這兩項研究的個別分析中也有相同的發現。

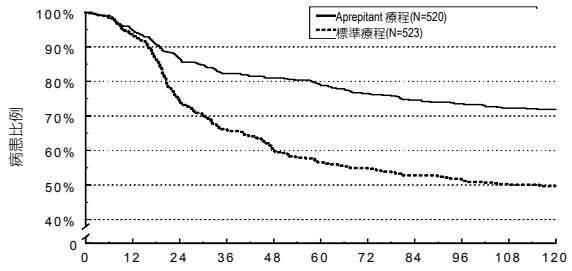
整合分析的結果顯示，在第 1 化療週期中，接受 aprepitant 療程治療之患者未發生任何嘔吐反應的比例在統計學上要明顯高於接受標準療程治療的患者。在第 1 化療週期的急性期與延遲期中，接受 aprepitant 療程治療的患者與接受標準療程治療的患者在無任何嘔吐反應的分析方面有統計學上明顯的差異。在這兩項研究的個別分析中也有相同的發現。

此外，整合分析的結果也顯示，在第 1 化療週期中，不論是否使用救援療法，接受 aprepitant 療程治療之患者在整體治療期間均無任何明顯噁心反應的比例，以及在延遲期無任何明顯噁心反應的比例，在統計學上都明顯高於接受標準療程治療的患者。

研究人員並利用功能生活指數－嘔吐(FLIE)來評估噁心及嘔吐反應對患者之日常生活的影響，這是一種已獲公認的病患報告式結果評估方法。整合分析的結果顯示，在第 1 化療週期中，和接受標準療程治療的患者相比較，接受 aprepitant 療程治療之患者表示噁心及嘔吐反應對其日常生活無任何影響(依據 FLIE 總分 >108 的評估標準)的比例在統計學上明顯較高。在這兩項研究的個別分析中也有相同的發現。

如圖 1 所示，依據整合分析的結果，aprepitant 療程組開始使用 cisplatin 後首次發生嘔吐反應的時間明顯(p<0.001)較標準療程組晚，發生率也有降低的現象。

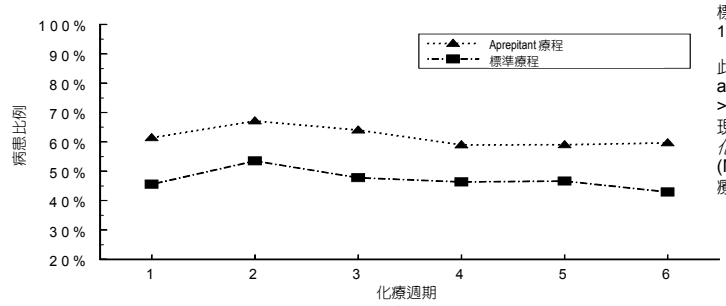
**圖 1：接受高致吐性化學療法治療者中一直未發生嘔吐反應的病患比例時間關係圖 — 第 1 化療週期**




Aprepitant 療程：於第 1 天服用 EMEND 125 mg，於第 2 與第 3 天每天服用一次 80 mg，並於第 1 天靜脈注射 ondansetron 32 mg 且服用 dexamethasone 12 mg，再於第 2 至 4 天每天服用一次 dexamethasone 8 mg。
標準療程：使用安慰劑，並於第 1 天靜脈注射 ondansetron 32 mg 且服用 dexamethasone 20 mg，再於第 2 至 4 天每天服用兩次 dexamethasone 8 mg。

*化療多週期延伸療程(Multiple-Cycle Extension)：*在同樣的這 2 項臨床研究中，共有 851 位患者繼續接受長達 6 個週期的化療多週期延伸療程。Aprepitant 療程在所有的化療週期中都能維持其療效。依據整合分析的結果，在開始使用 cisplatin 治療後的 6 個化療週期中，無任何嘔吐反應且無任何噁心反應之終點指標方面的療效反應率如圖 2 所示。在第 2 至第 6 週期中，無任何明顯噁心反應之終點指標的確認乃是依據直接向病患詢問的結果，而非採用第 1 化療週期中所使用的 VAS 量表。

**圖 2：接受高致吐性化學療法治療者中無任何嘔吐反應且無任何噁心反應的病患比例，依治療組別與化療週期列表**




| | N | N | N | N | N | N |
|---|---|---|---|---|---|---|
| Aprepitant 療程： | 516 | 290 | 216 | 140 | 86 | 60 |
| 標準療程： | 522 | 274 | 182 | 115 | 65 | 43 |

Aprepitant 療程：於第 1 天服用 EMEND 125 mg，於第 2 與第 3 天每天服用一次 80 mg，並於第 1 天靜脈注射 ondansetron 32 mg 且服用 dexamethasone 12 mg，再於第 2 至 4 天每天服用一次 dexamethasone 8 mg。
標準療程：使用安慰劑，並於第 1 天靜脈注射 ondansetron 32 mg 且服用 dexamethasone 20 mg，再於第 2 至 4 天每天服用兩次 dexamethasone 8 mg。

***中致吐性癌症化學療法 (MEC)***

在一項多中心、隨機、雙盲、平行的臨床研究中，研究人員共針對 866 位接受含有 cyclophosphamide 750-1500 mg/m$^2$ ；或 cyclophosphamide 500-1500 mg/m$^2$ 及 doxorubicin(60 mg/m$^2$)或 epirubicin(100 mg/m$^2$)之化學療法治療的患者比較 aprepitant 療程與標準療程的治療效果。其中有些患者也額外接受如 fluorouracil、methotrxate、docetaxel 或 paclitaxel 等化學治療劑的治療。Aprepitant 療程包括於第 1 天服用 EMEND 125 mg，於第 2 與第 3 天每天服用 80 mg，並於第 1 天口服 ondansetron 8 mg 及 dexamethasone 12 mg。標準療程則包括使用安慰劑與口服 ondansetron 8 mg(第一天，一天二次；第二與第三天，每 12 小時服用一次)，且於第 1 天口服 dexamethasone 20 mg。
研究人員針對 EMEND 於第 1 化療週期之急性期(使用 cisplatin 治療後 0 至 24 小時)、延遲期(使用 cisplatin 治療後 25 至 120 小時)與整體治療期間(使用 cisplatin 治療後 0 至 120 小時)的止吐作用進行評估。療效的評估係依據下列標準的綜合評估結果：

- 完全反應(其定義為無任何嘔吐反應，且未使用任何救援療法)
- 噁心及嘔吐反應對日常生活的影響(功能生活指數－嘔吐[FLIE]總分 >108)

另外也依據下列個別療效評估標準來評估療效：

- 無任何嘔吐反應(其定義為無任何嘔吐反應，但不論是否使用救援療法)
- 未使用任何救援療法

主要研究結果摘錄於表 2。

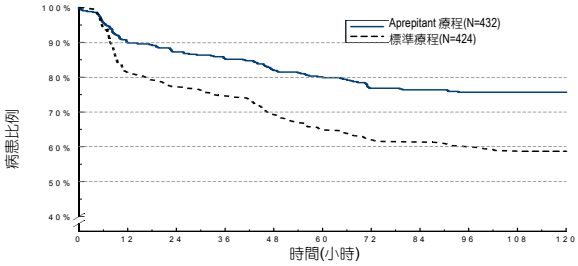
**表 2 接受中致吐性癌症化學療法治療者中的病患比例，依治療組別與治療期別列表 — 第 1 化療週期**

| 綜合評估標準 | Aprepitant 療程* (N = 433)† % | 標準療程** (N = 424)† % | *P* 值 |
|---|---|---|---|
| **完全反應(無任何嘔吐反應，且未使用任何救援療法)** | | | |
| 整體治療期間‡ | | | |
| 急性期§ | | | |
| 延遲期¶ | 51 | 42 | 0.015 |
| | 76 | 69 | 0.034 |
| | 55 | 49 | 0.064 |
| **對日常生活無任何影響(功能生活指數－嘔吐[FLIE]總分 >108)** | | | |
| 整體治療期間 | 64 | 56 | 0.019 |
| 個別評估標準 | | | |
| **無任何嘔吐反應** | | | |
| 整體治療期間 | 76 | 59 | <0.001 |
| 急性期 | 88 | 77 | <0.001 |
| 延遲期 | 81 | 69 | <0.001 |
| **未使用任何救援療法** | | | |
| 整體治療期間 | 59 | 56 | 0.480 |
| 急性期 | 83 | 80 | 0.366 |
| 延遲期 | 63 | 60 | 0.407 |

*Aprepitant 療程包括於第 1 天服用 EMEND 125 mg，於第 2 與第 3 天每天服用 80 mg，並於第 1 天口服 ondansetron 8 mg 及 dexamethasone 12 mg。
**標準療程則包括使用安慰劑與口服 ondansetron 8 mg(第一天，一天二次；第二與第三天，每 12 小時服用一次)，且於第 1 天口服 dexamethasone 20 mg。
†N: 包括完全反應之原始分析患者數。
‡整體治療期間：使用癌症化學療法治療後 0 至 120 小時。
§急性期：使用癌症化學療法治療後 0 至 24 小時。
¶延遲期：使用癌症化學療法治療後 25 至 120 小時。

此項臨床研究顯示，在第 1 化療週期的整體治療期間，接受 aprepitant 療程治療之患者(51%)達到完全反應(primary endpoint)之效果的比例在統計學上都明顯(p=0.015)高於接受標準療程治療的患者(42%)。其達到完全反應之未校正絕對偏差值(8.3%)顯示相對增加了 20%的完全反應 (aprepitant 療程組比標準療程組之相對風險值為 1.2)。在第 1 化療週期的急性期與延遲期中，接受 aprepitant 療程治療的患者達到完全反應之效果的比例高於接受標準療程治療的患者。
如圖 3 所示，依此項臨床研究結果，aprepitant 療程組開始使用癌症化學療法治療後首次發生嘔吐反應的時間明顯(p<0.001)較標準療程組晚，發生率也有降低的現象。

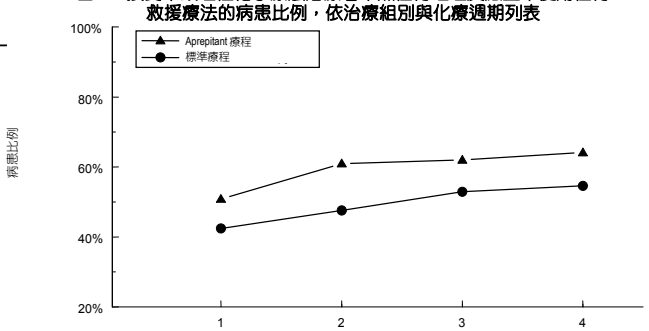
**圖 3：接受中致吐性化學療法治療者中一直未發生嘔吐反應的病患比例時間關係圖 — 第 1 化療週期**




Aprepitant 療程包括於第 1 天服用 EMEND 125 mg，於第 2 與第 3 天每天服用 80 mg，並於第 1 天口服 ondansetron 8 mg 及 dexamethasone 12 mg。
標準療程則包括使用安慰劑與口服 ondansetron 8 mg(第一天，一天二次；第二與第三天，每 12 小時服用一次)，且於第 1 天口服 dexamethasone 20 mg。

此項臨床研究顯示，在第 1 化療週期中，和接受標準療程治療的患者相比較，接受 aprepitant 療程治療之患者表示噁心及嘔吐反應對其日常生活無任何影響(依據 FLIE 總分 >108 的評估標準)的比例在統計學上明顯較高。在這兩項研究的個別分析中也有相同的發現。
*化療多週期延伸療程(Multiple-Cycle Extension)：*共有 744 位接受中致吐性化學療法(MEC)患者繼續接受長達 4 個週期的化療多週期延伸療程。Aprepitant 療程在所有的化療週期中都能維持其療效。其療效反應率如圖 4 所示。

**圖 4：接受中致吐性化學療法治療者中無任何嘔吐反應且未使用任何救援療法的病患比例，依治療組別與化療週期列表**




| | N | N | N | N |
|---|---|---|---|---|
| Aprepitant 療程 | 433 | 379 | 358 | 343 |
| 標準療程 | 424 | 355 | 325 | 304 |

Aprepitant 療程包括於第 1 天服用 EMEND 125 mg，於第 2 與第 3 天每天服用 80 mg，並於第 1 天口服 ondansetron 8 mg 及 dexamethasone 12 mg。
標準療程則包括使用安慰劑與口服 ondansetron 8 mg(第一天，一天二次；第二與第三天，每 12 小時服用一次)，且於第 1 天口服 dexamethasone 20 mg。

在第二項多中心、隨機、雙盲、平行的臨床研究中，研究人員共針對 848 位接受含有任何靜脈注射劑量的 oxaliplatin、carboplatin、epirubicin、idarubicin、ifosfamide、irinotecan、daunorubicin、doxorubicin、或 cyclophosphamide IV (<1500 mg/m$^2$)、或 cytarabine IV (>1 g/m$^2$)之化學療法治療的患者比較 aprepitant 療程與標準療程的治療效果。經隨機分配接受 aprepitant 療程的病患包括 76%女性及 24% 男性，同時接受化學治療各種腫瘤包括 52%乳癌、21%含直腸癌的腸胃道癌症、13%肺癌、及 6%婦癌。Aprepitant 療程包含於第 1 天服用 EMEND 125 mg 及於第 2 與第 3 天每天服用一次 80 mg，並於第 1 天口服 ondansetron 8 mg 兩次及服用 dexamethasone 12 mg。標準療程包含安慰劑併口服 ondansetron 8 mg (第一天兩次及第二和三天每 12 小時一次)，第一天併用口服 dexamethasone 20 mg。
研究人員針對 EMEND 於第 1 化療週期之整體治療期間(使用化學治療後 0 至 120 小時)的止吐作用進行評估。療效的評估係依據下列標準的綜合評估結果：
主要試驗指標：

- 在整體治療期間(使用化學治療後 0 至 120 小時)無任何嘔吐反應

其他預定的試驗指標：

- 完全反應(其定義為無任何嘔吐反應，且未使用任何救援療法)在整體治療期間(使用化學治療後 0 至 120 小時)
- 在整體治療期間(使用化學治療後 0 至 120 小時)首次發生嘔吐反應的時間
- 無任何嘔吐反應 – 急性期(輸注化學治療藥物後 0 至 24 小時)及延遲期(輸注化學治療藥物後 25 至 120 小時)
- 完全反應 - 急性期及延遲期，定義如上述
- 未使用任何救援療法 –整體治療期間、急性期及延遲期，定義如上述
- 對日常生活無任何影響(功能生活指數－嘔吐[FLIE]總分 >108) – 整體治療期間，定義如上述
- 無任何嘔吐反應且無任何明顯噁心反應(VAS <25 mm) – 整體治療期間，定義如上述

主要研究結果摘錄於表 3。

**表 3 第二項研究接受中致吐性癌症化學療法治療者中的病患比例，依治療組別與治療期別列表 — 第 1 化療週期**

| 試驗指標 | Aprepitant 療程* (N = 430)† % | 標準療程** (N = 418)† % | *P* 值‡ |
|---|---|---|---|
| 主要試驗指標 | | | |
| **無任何嘔吐反應** | | | |
| 整體治療期間§ | 76 | 62 | <0.0001 |

| 關鍵次要試驗指標 | | | |
|---|---|---|---|
| **完全反應**[¶] | | | |
| 整體治療期間[§] | 69 | 56 | 0.0003 |
| 其他次要試驗指標 | | | |
| **無任何嘔吐反應** | | | |
| 急性期[#] | 92 | 84 | 0.0002 |
| 延遲期[Þ] | 78 | 67 | 0.0005 |
| **對日常生活無任何影響(功能生活指數－嘔吐[FLIE]總分 >108)** | | | |
| 整體治療期間 | 73 | 66 | 0.035 |
| **完全反應** | | | |
| 急性期 | 89 | 80 | 0.0005 |
| 延遲期 | 71 | 61 | 0.0042 |
| **未使用任何救援療法** | | | |
| 整體治療期間 | 81 | 75 | 0.0427[ß] |
| 急性期 | | | 0.0179[ß] |
| 男性[a] | 97 | 100 | |
| 女性[a] | 95 | 88 | |
| 延遲期 | 84 | 79 | 0.0922[ß] |
| **無任何嘔吐且無明顯噁心反應 (VAS <25 mm)** | | | |
| 整體治療期間 | 65 | 53 | 0.0011 |

*Aprepitant 療程：於第 1 天服用 EMEND 125 mg，於第 2 與第 3 天每天服用一次 80 mg，並於第 1 天口服兩次 ondansetron 8 mg 及一次 dexamethasone 12 mg。

**標準療程：使用安慰劑，並於第 1 天口服兩次 ondansetron 8 mg 且服用一次 dexamethasone 20 mg，再於第 2 及第 3 天每 12 小時服用 ondansetron 8 mg。

[†]N：接受化療、研究藥物 cisplatin 治療且至少完成一次治療後療效評估的患者數。

[‡] 當檢定次級指標顯著性時，使用 Hochberg's procedure 作多重調整(multiplicity adjustment)。

[§]整體治療期間：化學治療後 0 至 120 小時。

[¶]完全反應 = 未接受救援治療且無任何嘔吐反應

[#]急性期：輸注化學治療藥物後 0 至 24 小時。

[Þ]延遲期：輸注化學治療藥物後 25 至 120 小時。

[ß]無統計顯著性

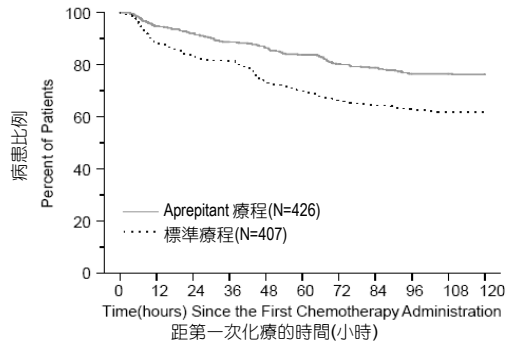
[a]數據依預定的分析計畫男女分開顯示。

[¶]視覺類比量表(VAS)分數範圍：0 = 無任何噁心反應；100 = 極度的噁心反應。

此項臨床研究顯示，在第 1 化療週期的整體治療期間，無任何嘔吐反應(主要試驗指標)的比例，接受 aprepitant 療程治療之患者(76%)高於接受標準療程治療的患者(62%)，且具統計意義(p<0.0001)。此外，在第 1 化療週期的整體治療期間(0-120 小時)，和接受標準療程治療的患者相比，接受 aprepitant 療程治療之患者有較高的完全反應比例。以無任何嘔吐反應及完全反應指標來看，不分年齡、性別、或腫瘤型態(乳房、腸胃道、肺或其他)，在數值上，aprepitant 都優於標準療程。

此項臨床研究顯示，aprepitant 療程組開始使用化學療法治療後首次發生嘔吐反應的時間較標準療程組晚，發生率也有降低的現象，以 Kaplan-Meier curves 分析圖表示如圖 5。

**圖 5: 在整體治療期間開始使用化學療法治療後首次發生嘔吐反應的時間之 Kaplan-Meier Curves 分析圖 –第 1 化療週期**
**(全部可分析之病人族群)**




此項臨床研究顯示，在第 1 化療週期中，和接受標準療程治療的患者相比較，接受 aprepitant 療程治療之患者表示噁心及嘔吐反應對其日常生活無任何影響(依據 FLIE 總分 >108 的評估標準)的比例在統計學上明顯較高。在這兩項研究的個別分析中也有相同的發現。

**適應症**

與其他止吐藥劑併用，可以防止由高致吐性及中致吐性癌症化療藥物在初次或重覆使用時所引起的急性或延遲性噁心與嘔吐。

**用法用量**

EMEND (aprepitant)為口服的膠囊劑。

EMEND 得採用三天給藥的方式，併入包括一種皮質類固醇和一種 5-HT$_3$ 拮抗劑的治療療程一起使用。在開始併用 EMEND IV 150 mg 進行治療前，必須參閱所選用的 5-HT$_3$ 拮抗劑仿單。EMEND 的建議劑量為第一天在化學治療進行前一小時口服 125 mg ，在第二天和第三天早晨每天服用一次 80 mg。

用於預防高致吐性癌症化療藥物所引起的噁心嘔吐之療程的建議劑量如下：

| | 第一天 | 第二天 | 第三天 | 第四天 |
|---|---|---|---|---|
| EMEND* | 125 mg 口服 | 80 mg 口服 | 80 mg 口服 | 無 |
| Dexamethasone** | 12 mg 口服 | 8 mg 口服 | 8 mg 口服 | 8 mg 口服 |
| 5-HT$_3$ 拮抗劑 | 參見選用的 5-HT$_3$ 拮抗劑仿單中最適劑量資訊 | 無 | 無 | 無 |

**Dexamethasone 須在第一天化學治療進行前 30 分鐘以及第二天到第四天的早晨服用。Dexamethasone 的劑量是考慮藥物交互作用而決定。

用於預防中致吐性癌症化療藥物所引起的噁心嘔吐之療程的建議劑量如下：

| | 第一天 | 第二天 | 第三天 |
|---|---|---|---|
| EMEND* | 125 mg 口服 | 80 mg 口服 | 80 mg 口服 |
| Dexamethasone** | 12 mg 口服 | 無 | 無 |
| 5-HT$_3$ 拮抗劑 | 參見選用的 5-HT$_3$ 拮抗劑仿單中最適劑量資訊 | 無 | 無 |

**Dexamethasone 須在第一天化學治療進行前 30 分鐘給藥。Dexamethasone 的劑量是考慮藥物交互作用而決定。

EMEND IV 150 mg (fosaprepitant)為 aprepitant 的前驅藥物，以靜脈輸注。EMEND IV 150 mg 僅須於第一天單劑給予。

***一般資訊***

EMEND 與皮質類固醇併用的其他相關資訊，請參見「藥物交互作用」一節。

並請參考各併用止吐劑的完整處方資訊。

EMEND 可以與食物或不與食物一起服用。

不同年齡、性別、種族或不同 BMI 使用 EMEND 時，劑量無須調整。

對嚴重腎功能不全患者(肌酸酐廓清率 <30 mL/min)或需洗腎的末期腎病(ESRD)患者不須調整 EMEND 劑量。

對輕度至中度肝功能不全患者(Child-Pugh 分數從 5 到 9)不須調整 EMEND 的劑量。沒有針對重度肝功能不全患者(Child-Pugh 分數大於 9)的臨床資料。

**禁忌**

EMEND 不可用於對此產品的任何成份過敏的病人。

EMEND 不可與 pimozide、terfenadine、astemizole 或 cisapride 同時使用。Aprepitant 對 cytochrome P450 isoenzyme 3A4 (CYP3A4)具與劑量相關性的抑制作用，會導致這些藥物的血中濃度升高，可能會引發嚴重或危及生命的反應(參見「藥物交互作用」)。

**注意事項**

EMEND 為與劑量相關的 CYP3A4 抑制劑，與主要經由 CYP3A4 酵素代謝的口服藥物併用治療患者時必須謹慎；有些化療藥物是藉由 CYP3A4 酵素代謝(參見「藥物交互作用」)。Aprepitant 對 CYP3A4 的中度抑制作用，125 mg/80 mg 的使用劑量，會導致這些併用藥物的血中濃度升高(參見「藥物交互作用」)。EMEND 對經由 CYP3A4 酵素代謝的口服藥物的動力學影響大於對經由 CYP3A4 酵素代謝的靜脈注射藥物的動力學影響。(參見「藥物交互作用」)

EMEND 與 warfarin 一起使用，可能會導致臨床上有意義地降低前凝血酶原時間(prothrombin time)之國際標準比值(International Normalized Ratio, INR)。長期接受 warfarin 治療的病患，於每次化療週期伴隨 EMEND 三天療程開始 2 週內，應密切監控國際標準比值(INR)，尤其是第 7 到 10 天(參見「藥物交互作用」)。

服用 EMEND 期間及之後 28 天，荷爾蒙避孕藥的功效可能會降低，於 EMEND 治療期間，應使用其他替代或輔助性避孕法並於服用 EMEND 最後一次劑量後持續一個月(參見「藥物交互作用」)。

**懷孕**

尚未針對懷孕婦女作適當且控制良好的臨床研究。懷孕期間，只有當使用 EMEND 的潛在效益大於對母親與胎兒可能造成的危險時，才可使用 EMEND。

**哺乳母親**

Aprepitant 會從泌乳大鼠的乳汁中排出。目前尚不知本藥品是否會由人乳中排出。因為許多藥品會由人乳中排出，而且 EMEND 可能會對喝母乳的嬰兒產生不良反應，所以必須考慮本藥品對母親的重要性，而在停止哺乳或停止用藥之間做一選擇。

**小兒科的使用**

EMEND 用於小兒患者的安全性與有效性尚未建立。

**老年人的使用**

臨床研究發現，EMEND 用於老年病患(≥65 歲)的安全性與有效性與用於較年輕病患(<65 歲)相當，故對老年病患不需調整劑量。

**藥物交互作用**

Aprepitant 是 CYP3A4 酵素的受質、是其弱至中度(與劑量相關)抑制劑、也是其誘發劑。Aprepitant 也是 CYP2C9 的誘發劑。

**Aprepitant 對其他藥物的藥動學的影響**

由於 aprepitant 是 CYP3A4 酵素的弱至中度(125 mg/80 mg)抑制劑，aprepitant 能增加同樣經由 CYP3A4 代謝的口服併用藥物的血中濃度。Aprepitant (125 mg/80 mg)增加經由 CYP3A4 代謝的靜脈注射併用藥物的血中濃度之程度較小。不能與 EMEND 同時使用的藥物包括：pimozide、terfenadine、astemizole 或 cisapride。由於 aprepitant 會視劑量而不同程度地抑制 CYP3A4，而引起前述藥物血中濃度上升，導致嚴重甚至危及生命的反應發生(參見「禁忌」)。

已有研究顯示，aprepitant 會促進 S(-) warfarin 和 tolbutamide 經由 CYP2C9 的代謝作用。因此，這些藥物或其他已知由 CYP2C9 代謝的藥物，例如：phenytoin，如果與 EMEND 併用時，這些藥物的血中濃度可能降低。

屬於 P-醣原蛋白傳導物質(P-glycoprotein transporter)受質的藥物應該不會與 EMEND 產生交互作用，因為在藥物交互作用的臨床研究中，EMEND 並未與 digoxin 產生交互作用。

***5-HT$_3$ 拮抗劑：*** 在一些藥物交互作用的臨床研究中，在療程第一天給予 EMEND 125 mg，第二天和第三天給予 EMEND 80 mg，其對於 ondansetron、granisetron 或 hydrodolasetron(dolasetron 的活性代謝物)的藥物動力學並未造成具有臨床意義的影響。

***皮質類固醇 (Corticosteroids)：***

*Dexamethasone：* 在療程當中，第一天口服 EMEND 125 mg 和 dexamethasone 20 mg，第 2 到第 5 天則每天口服 EMEND 80 mg 和 dexamethasone 8 mg，由於 dexamethasone 是 CYP3A4 的受質，dexamethasone 在第 1 與第 5 天的 AUC 增加了 2.2 倍。當與 EMEND (125 mg/80 mg)併用時，須將 dexamethasone 的常用口服劑量減少約 50%，以達到未與 EMEND 併用時同樣的 dexamethasone 曝藥量。癌症化學療法引起 心及嘔吐的臨床研究顯示與 EMEND 併用的 dexamethasone 每日劑量，約為 dexamethasone 一般劑量的 50%(請參見「用法用量」)。

*Methylprednisolone：* 在療程當中，第一天口服給予 EMEND 125 mg 和靜脈注射 methylprednisolone 125 mg，第 2 和第 3 天則每天口服 EMEND 80 mg 和口服 methylprednisolone 40 mg 時，由於 methylprednisolone 是 CYP3A4 的受質，其 AUC 第 1 天增加了 1.3 倍，第 3 天則增加了 2.5 倍。故與 EMEND (125 mg/80 mg)併用時，須將 methylprednisolone 的常用靜脈注射劑量減少約 25%及常用口服劑量減少約 50%，以達到未與 EMEND 併用時同樣的 methylprednisolone 曝藥量。

***化療藥物：*** 在臨床研究上，EMEND (125 mg/80 mg)會與主要或是部份經由 CYP3A4 酵素代謝的化療藥物一起使用，這些藥物包括 etoposide、vinorelbine、docetaxel、ifosfamide、cyclophosphamide、irinotecan 以及 paclitaxel。這些化療藥物的使用劑量並未因可能有潛在的藥物交互作用而調整。使用這些藥物或其他主要經由 CYP3A4 代謝的化療藥物的患者應謹慎併留意監視。Apprepitant 上市後，曾有併用 ifosfamide 而發生的神經毒性案例的通報，一種與使用 ifosfamide 相關的不良反應(參見「注意事項」)。

*Docetaxel：* 在另一項藥物動力學研究中得知，EMEND (125 mg/80 mg)對於 docetaxel 的藥物動力學沒有影響。

Vinorelbine:在另一項動力學研究中，併用 EMEND (125 mg/80 mg)對 vinorelbine 的動力學參數沒有影響。

***Warfarin：***曾針對健康受試者穩定地給予抗凝血藥物 warfarin 長期治療法，於第一天給予單一劑量 EMEND 125 mg，第 2 和第 3 天則每天給予 EMEND 80 mg。雖然第 3 天時 R(+)或 S(-) warfarin 的血漿 AUC 不受 EMEND 影響，但於 EMEND 結束投藥 5 天後，S(-) warfarin(是 CYP2C9 的受質)的最低血中濃度(trough concentration)降低了 34%，伴隨「前凝血酶原時間」(prothrombin time)，以國際標準比值(International Normalized Ratio，INR)表示，降低 14%。長期接受 warfarin 治療的病患，於每次化療週期伴隨 EMEND 三天療程開始 2 週內，應密切監控國際標準比值(INR)，尤其是第 7 到 10 天。

***Tolbutamide：***第一天口服 EMEND 125 mg，第 2 和第 3 天則每天口服 EMEND 80 mg，同時在前述 EMEND 療程每次服藥前以及第 4，8 和 15 天口服單劑 tolbutamide 500 mg 後，tolbutamide(是 CYP2C9 的受質)的 AUC 在 第 4 天降低 23%，第 8 天降低 28%，第 15 天則降低 15%。

***口服避孕藥：***連續 14 天每天服用一顆 aprepitant 100 mg 膠囊以及含有 ethinyl estradiol 35 mcg 和 norethindrone 1 mg 的口服避孕藥之後，ethinyl estradiol 的 AUC 減少 43%，norethindrone 的 AUC 亦減少 8%。於另一項試驗中，連續 21 天口服單一劑量避孕藥含 ethinyl estradiol 及 norethindrone 且於第 8 天併用 EMEND 125 mg，第 9 及第 10 天服用 80 mg/day 並於第 8 天靜脈注射 ondansetron 32 mg 且於第 8 天口服 dexamethasone 12 mg，第 9 至 11 天，口服 dexamethasone 8 mg/day。此試驗顯示，於第 10 天時 ethinyl estradiol 的 AUC 減少 19 %，第 9 至 21 天 ethinyl estradiol 的最低血中濃度降低 64 %。然而，於第 10 天時 EMEND 對 norethindrone 的 AUC 並無影響，於第 9 至 21 天 norethindrone 的最低血中濃度降低 60%。服用 EMEND 期間及之後的 28 天，荷爾蒙避孕藥的功效可能會降低，於 EMEND 治療期間，應使用其他替代或輔助性避孕法並於服用 EMEND 最後一次劑量後持續一個月。

***Midazolam：***因 midazolam 是敏感的 CYP3A4 受質，以第一天和第五天分別口服給予單一劑量的 midazolam 2 mg，併用在第一天給予 EMEND 125 mg，第 2 到第 5 天每天給予 80 mg 的療程顯示，EMEND 使 midazolam 的 AUC 在第 1 天增加 2.3 倍，而在第 5 天增加 3.3 倍。當與 EMEND (125 mg/80 mg)併用時，須考量這些經由 CYP3A4 代謝的 midazolam 或其他 benzodiazepines 類的藥物(alprazolam, triazolam)血中濃度增加時可能造成的影響。

另一項與 midazolam 靜脈注射併用的研究中，第一天口服 EMEND 125 mg，第 2 和第 3 天則每天口服 EMEND 80 mg，同時在前述 EMEND 療程每次服藥前以及在第 4，8 和 15 天各靜脈注射 midazolam 2 mg。EMEND 的三天療程使 midazolam 的 AUC 在 第 4 天增加 25%，而在第 8 天則降低 19%。這些影響並不具臨床意義。Midazolam 的 AUC 在 第 15 天時與基礎值近似。

另一項 EMEND 併用 midazolam 靜脈注射的研究中，在口服一劑 EMEND 125 mg 之後一小時，再靜脈注射 midazolam 2 mg，midazolam 的血漿 AUC 增加了 1.5 倍。這些影響並不具臨床意義。

**其他藥物對 Aprepitant 藥動學的影響**

Aprepitant 是 CYP3A4 的受質; 因此，EMEND 與會抑制 CYP3A4 酵素活性的藥物併用時，可能使 aprepitant 血中濃度增加。故，EMEND 與強力的 CYP3A4 抑制劑(例如：ketoconazole)併用時，必須審慎進行；但是 EMEND 與中度的 CYP3A4 抑制劑(例如：diltiazem)併用時， 對 aprepitant 血中濃度，並未引起具有臨床意義的變化。

Aprepitant 是 CYP3A4 的受質; 因此，EMEND 與會強烈誘發 CYP3A4 活性的藥物(例如： rifampin) 併用時，可能使 aprepitant 血中濃度降低，因而降低 EMEND 的藥效。

***Ketoconazole：***在每天服用 400 mg ketoconazole(一種 CYP3A4 的強力抑制劑)為期十天療程中的第五天給予單一劑量的 125 mg EMEND，曾使 aprepitant 的 AUC 增加五倍左右，而 aprepitant 的平均終端排除半衰期(terminal half-life)則增加約三倍。EMEND 與 CYP3A4 的強力抑制劑併用時，必須審慎。

***Rifampin：***在每天服用 600 mg rifampin(一種 CYP3A4 的強力誘導劑)為期十四天療程中的第九天給予單一劑量的 375 mg EMEND，曾使 aprepitant 的 AUC 降低 11 倍左右，而平均終端排除半衰期，則降低約三倍。EMEND 與可誘發 CYP3A4 活性的藥物併用時，可能使 EMEND 的血中濃度降低，因而降低其藥效。

**其他的藥物交互作用**

***Diltiazem：***患有輕度至中度高血壓的病人，每天服用一次相當於 230 mg 膠囊的 aprepitant 錠劑，並且每天服用三次 120 mg 的 diltiazem，連續五天之後，會使 aprepitant 的 AUC 增加兩倍左右，同時 diltiazem 的 AUC 也增加約 1.7 倍。這些藥物動力學上的改變，除了 diltiazem 單獨作用引起的變化之外，對心電圖 (ECG)、心跳速度或血壓並沒有造成 具臨床意義的影響。

***Paroxetine：***每天服用一次相當於 85 mg 或 170 mg 膠囊的 aprepitant 錠劑，並且每天服用一次 20 mg 的 paroxetine，會使 aprepitant 與 paroxetine 的 AUC 都降低 25% 左右，$C_{max}$ 也都降低 20% 左右。

**不良反應**

Aprepitant 的整體安全性已在大約 6500 位受試者作過評估。

***預防癌症化學療法所引起的噁心及嘔吐(CINV)***

***高致吐性癌症化學療法(HEC)***

在兩項控制良好的臨床試驗中，病患接受高致吐性癌症化學治療，544 位病患是在 Cycle 1(第 1 化療週期)接受 aprepitant 3 天療程治療，其中 413 位病患繼續 Multiple-Cycle extension(化療多週期延伸療程)，最多達六個化療週期。口服 EMEND 3 天療程併用 ondansetron 和 dexamethasone 時，病患的耐受性大致良好。這些臨床研究所報告大多數不良事件的程度介於輕微到中度之間。

在第 1 化療週期中，與藥物有關的臨床不良反應發生率，標準療程大約是 14%，而口服 aprepitant 3 天療程則在 19%左右。因為與藥物有關的臨床不良反應而停用治療的比例，在口服 aprepitant 3 天療程是約 0.6%，相較於標準療程是 0.4%左右。

口服 aprepitant 3 天療程較標準療程發生率高之最常見與藥物相關的不良反應包括：打嗝(4.6%)、肝指數 ALT 升高(2.8%)、消化不良(2.6%)、便秘(2.4%)、頭痛(2.0%)和食慾減退(2.0%)。

在另一項以活性藥物對照的研究中，1169 位接受口服 aprepitant 3 天療程和 HEC 的病患所發生的不良事件與其他口服 aprepitant 3 天療程的 HEC 研究所見的大致相同。

***中致吐性癌症化學療法(MEC)***

在兩項控制良好的臨床試驗中，病患接受中致吐性癌症化學療法治療，868 位病患是在 Cycle 1(第 1 化療週期)接受口服 aprepitant 3 天療程，其中 686 位病患繼續延伸療程，最多達四個化療週期。在該兩項研究中，口服 EMEND 3 天療程併用 ondansetron 和 dexamethasone 時，病患的耐受性大致良好。這些臨床研究所報告大多數不良事件的程度介於輕微到中度之間。

綜合分析這兩項研究結果，在第 1 化療週期中，與藥物有關的不良反應發生率，標準療程大約是 15%，而口服 aprepitant 3 天療程則在 14%左右。因為與藥物有關的臨床不良反應而停用治療的比例，在口服 aprepitant 3 天療程是約 0.7%，相較於標準療程是 0.2%左右。

口服 aprepitant 3 天療程較標準療程發生率高之最常見與藥物相關的不良反應為倦怠(1.4%)。

***高致吐性癌症化學療法及中致吐性癌症化學療法***

以下是綜合分析在高致吐性癌症化學療法及中致吐性癌症化學療法研究中，曾通報於使用口服 aprepitant 3 天療程、發生率高於標準療程且與藥物有關的不良反應：

*[常見(≥1/100，<1/10)，不常見(≥1/1000，<1/100)，罕見(≥1/10,000, <1/1,000)]*

***感染及侵染：***

*罕見：*念珠菌、葡萄球菌感染

***血液與淋巴系統異常：***

*不常見：*貧血 、發熱性嗜中性白血球減少症

***代謝與營養方面異常：***

*常見：*食慾減退

*罕見：*多飲症(polydipsia)

***精神方面異常：***

*不常見：*焦慮(anxiety)

*罕見：*失去方向感(disorientation)、欣快感(euphoria mood)

***神經系統異常：***

*不常見：*頭暈、困倦

*罕見：*認知異常、昏睡、味覺改變(dysgeusia)

***眼部異常：***

*罕見：*結膜炎

***耳部與內耳迷路(labyrinth)異常：***

*罕見：*耳鳴

***心臟方面異常：***

*不常見：*心悸

*罕見：*心搏徐緩(bradycardia)、心血管異常

***血管方面異常：***

*不常見：*熱潮紅(hot flush)

***呼吸、胸部、和縱膈腔方面異常：***

*常見：*打嗝

*罕見：*口咽疼痛、噴嚏、咳嗽、鼻涕逆流(postnasal drip)、喉嚨刺激

***胃腸道方面異常：***

*常見：*消化不良

*不常見：*噯氣(eructation)、噁心、胃酸食道逆流疾病(gastroesophageal reflux disease)、嘔吐、腹痛、口乾、胃腸脹氣

*罕見：*大便堅硬、穿孔性十二指腸潰瘍(perforating duodenal ulcer)、嗜中性白血球缺乏性結腸炎、口腔炎、腹脹

***皮膚和皮下組織異常：***

*不常見：*皮疹、粉刺

*罕見：*光敏感反應、多汗(hyperhidosis)、脂漏(seborrhoea)、皮膚病變(skin lesion) 、搔癢性皮疹(rash pruritic)

***骨骼肌肉及結　組織方面異常：***

*罕見：*肌肉痙攣、肌無力(muscular weakness)

***腎臟和泌尿方面異常：***

*不常見：*排尿困難

*罕見：*頻尿

***一般性異常以及用藥部位的情況：***

*常見：*倦怠

*不常見：*虛弱無力(asthenia)不舒服(malaise)

*罕見：*水腫、胸部不適、步態不穩

***研究 (Investigations)：***

*常見：*肝指數 ALT 升高。

*不常見：*肝指數 AST 升高、血鹼性磷酸酶(blood alkaline phosphatase)升高

*罕見：*尿量增多、陽性尿液潛血反應、血鈉降低、體重減輕、呈現尿糖、嗜中性白血球數減少

在高致吐性癌症化學療法及中致吐性癌症化學療法研究中，病患接受 Multiple-Cycle extension(化療多週期延伸療程)，最多達六個化療週期，所觀察到的整體不良反應與 Cycle 1 所觀察到的結果大致類似。

在另一個針對化療引起的 心和嘔吐的臨床研究(Chemotherapy Induced Nausea and Vomiting，CINV study) 裏，有位病患進行癌症化療時接受 aprepitant，通報出現史帝芬強生氏症候群(Stevens-Johnson Syndrome)的嚴重不良反應。

其他研究

曾經研究服用單一劑 EMEND® 40 mg 用於非化療病人，預防接受一般平衡麻醉之手術後發生的噁心及嘔吐。在這些研究中，觀察到發生率比活性對照藥物(ondansetron)高的其他不良反應有: : ALT 升高、上腹部疼痛、腸音異常、口齒不清(dysarthria)、呼吸困難、感覺麻痺、失眠、瞳孔縮小、噁心、感覺障礙、胃不適、視力減退、喘鳴。

此外，在 PONV 臨床研究中，服用較高劑量之 aprepitant 的病患中，通報有兩項嚴重不良經驗：一例便秘及一例腸阻塞(sub-ileus)。

而在一個非 CINV/非 PONV 的研究裏，有位接受 aprepitant 的患者通報發生血管水腫(angioedema) 和蕁麻疹的嚴重不良事件。

上市後經驗:

下列不良反應為 aprepitant 上市後使用期間確認的，因這些不良經驗為自動通報的，不確知通報者所在使用者族群的大小，所以無法據以計算發生頻率或建立該不良經驗的發生是否因使用 aprepitant 的關係。

皮膚及皮下組織異常: 搔癢、疹子、蕁麻疹、罕見的史帝夫-強生症候群/毒性表皮壞死溶解症(toxic epidermal necrolysis)

免疫系統失調：包含全身性過敏的過敏反應

**用藥過量**

目前尚無治療 EMEND 用藥過量的確切資訊。健康人對高達 600 mg 單一劑量 aprepitant 的耐受性良好。在一些非 CINV 的研究中，使用每天單劑 375 mg aprepitant 最長達 42 天，患者的耐受性大致都良好。有 33 位癌症病患，第一天使用單劑 375 mg aprepitant ，第 2 到第 5 天每天服用 250 mg，病患的耐受性亦大致良好。

有位服用 1440 mg aprepitant 的病患發生胭倦和頭痛的症狀。

發生用藥過量時，EMEND 必須立即停藥，並須給與支持性治療和追蹤觀察。由於 aprepitant 具有止吐作用，催吐藥物可能無效。

Aprepitant 無法以血液透析法(hemodialysis)去除。

**貯存**

貯存於 30°C (86°F)以下

**包裝**

止敏吐 膠囊 125 毫克(EMEND Capsules 125 mg): 鋁箔盒裝，每盒 1 顆

止敏吐 膠囊 80 毫克(EMEND Capsules 80 mg): 鋁箔盒裝，每盒 1 顆

製造廠：Alkermes Pharma Ireland Limited

廠　址：Monksland Athlone Co. Westmeath, Ireland

委託分包裝廠：聯亞生技開發股份有限公司新竹二廠

廠　址：新竹縣湖口鄉光復北路 45 號

藥　商：美商默沙東藥廠股份有限公司台灣分公司

地　址：台北市信義路五段 106 號 12 樓

# EMEND™ Capsules
# (aprepitant)

**THERAPEUTIC CLASS**

EMEND® (aprepitant), is a substance P neurokinin 1 ($NK_1$) receptor antagonist.

**COMPOSITION**

Each capsule of EMEND for oral administration contains either 80 mg, or 125 mg of aprepitant. Each capsule of EMEND contains the following inactive ingredients: sucrose, microcrystalline cellulose, hydroxypropyl cellulose and sodium lauryl sulfate. The capsule shell excipients are gelatin and titanium dioxide, and may contain sodium lauryl sulfate and silicon dioxide. The 125-mg capsule shell also contains red ferric oxide and yellow ferric oxide.

**CLINICAL PHARMACOLOGY**

***Mechanism of Action***

Aprepitant has a unique mode of action; it is a selective high affinity antagonist at human substance P neurokinin 1 ($NK_1$) receptors. Counter-screening assays showed that aprepitant was at least 3,000-fold selective for the $NK_1$ receptor over other enzyme, transporter, ion channel and receptor sites including the dopamine and serotonin receptors that are targets for existing chemotherapy induced nausea and vomiting (CINV) therapies.

$NK_1$-receptor antagonists have been shown pre-clinically to inhibit emesis induced by cytotoxic chemotherapeutic agents, such as cisplatin, via central actions. Preclinical and human Positron Emission Tomography (PET) studies with aprepitant have shown that it is brain penetrant and occupies brain $NK_1$ receptors. Preclinical studies show that aprepitant has a long duration of central activity, inhibits both the acute and delayed phases of cisplatin-induced emesis, and augments the antiemetic activity of the 5-$HT_3$-receptor antagonist ondansetron and the corticosteroid dexamethasone against cisplatin-induced emesis.

***Pharmacokinetics***

***Absorption***

The mean absolute oral bioavailability of aprepitant is approximately 60 to 65% and the mean peak plasma concentration ($C_{max}$) of aprepitant occurred at approximately 4 hours ($T_{max}$). Oral administration of the capsule with a standard breakfast had no clinically meaningful effect on the bioavailability of aprepitant.

The pharmacokinetics of aprepitant are non-linear across the clinical dose range. In healthy young adults, the increase in $AUC_{0-\infty}$ was 26% greater than dose proportional between 80-mg and 125-mg single doses administered in the fed state.

Following oral administration of a single 125-mg dose of EMEND on Day 1 and 80 mg once daily on Days 2 and 3, the $AUC_{0\text{-}24hr}$ was approximately 19.5 µg•hr/mL and 20.1 µg•hr/mL on Day 1 and Day 3, respectively. The $C_{max}$ of 1.5 µg/mL and 1.4 µg/mL were reached in approximately 4 hours ($T_{max}$) on Day 1 and Day 3, respectively.

***Distribution***

Aprepitant is greater than 95% bound to plasma proteins. The geometric mean apparent volume of distribution at steady state ($Vd_{ss}$) is approximately 66 L in humans.

Aprepitant crosses the placenta in rats, and crosses the blood brain barrier in rats and ferrets. PET studies in humans indicate that aprepitant crosses the blood brain barrier (see CLINICAL PHARMACOLOGY, *Mechanism of Action*).

***Metabolism***

Aprepitant undergoes extensive metabolism. In healthy young adults, aprepitant accounts for approximately 24% of the radioactivity in plasma over 72 hours following a single oral 300-mg dose of [$^{14}$C]-aprepitant, indicating a substantial presence of metabolites in the plasma. Seven metabolites of aprepitant, which are only weakly active, have been identified in human plasma. The metabolism of aprepitant occurs largely via oxidation at the morpholine ring and its side chains. *In vitro* studies using human liver microsomes indicate that aprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19, and no metabolism by CYP2D6, CYP2C9, or CYP2E1.

***Elimination***

Aprepitant is eliminated primarily by metabolism; aprepitant is not renally excreted. Following administration of a single oral 300-mg dose of [$^{14}$C]-aprepitant to healthy subjects, 5% of the radioactivity was recovered in urine and 86% in feces.

The apparent plasma clearance of aprepitant ranged from approximately 60 to 84 mL/min. The apparent terminal half-life ranged from approximately 9 to 13 hours.

***Characteristics in Patients***

***Gender***

Following oral administration of a single dose of EMEND, the $AUC_{0\text{-}24hr}$ and $C_{max}$ for aprepitant are 9% and 17% higher, respectively, in females as compared with males. The half-life of aprepitant is approximately 25% lower in females as compared with males and its $T_{max}$ occurs at approximately the same time. These differences are not considered clinically meaningful. No dosage adjustment for EMEND is necessary based on gender.

***Elderly***

Following oral administration of a single 125-mg dose of EMEND on Day 1 and 80 mg once daily on Days 2 through 5, the $AUC_{0\text{-}24hr}$ of aprepitant was 21% higher on Day 1 and 36% higher on Day 5 in elderly (≥65 years) relative to younger adults. The $C_{max}$ was 10% higher on Day 1 and 24% higher on Day 5 in elderly relative to younger adults. These differences are not considered clinically meaningful. No dosage adjustment for EMEND is necessary in elderly patients.

***Pediatric***

The pharmacokinetics of EMEND have not been evaluated in patients below 18 years of age.

***Race***

Following oral administration of a single dose of EMEND, the $AUC_{0\text{-}24hr}$ is approximately 27% and 31% higher in Hispanics as compared with Caucasians and Blacks, respectively. The $C_{max}$ is 19% and 29% higher in Hispanics as compared with Caucasians and Blacks, respectively. Single dose administration of oral aprepitant in Asians resulted in a 74% and 47% increase in $AUC_{0\text{-}24hr}$ and $C_{max}$, respectively, as compared to Caucasians. These differences are not considered clinically meaningful. No dosage adjustment for EMEND is necessary based on race.

***Body Mass Index (BMI)***

Body Mass Index (BMI) had no clinically meaningful effect on the pharmacokinetics of aprepitant.

***Hepatic Insufficiency***

EMEND was well tolerated in patients with mild to moderate hepatic insufficiency. Following administration of a single 125-mg dose of EMEND on Day 1 and 80 mg once daily on Days 2 and 3 to patients with mild hepatic insufficiency (Child-Pugh score 5 to 6), the $AUC_{0\text{-}24hr}$ of aprepitant was 11% lower on Day 1 and 36% lower on Day 3, as compared with healthy subjects given the same regimen. In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), the $AUC_{0\text{-}24hr}$ of aprepitant was 10% higher on Day 1 and 18% higher on Day 3, as compared with healthy subjects given the same regimen. These differences in $AUC_{0\text{-}24hr}$ are not considered clinically meaningful; therefore, no dosage adjustment for EMEND is necessary in patients with mild to moderate hepatic insufficiency.

There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9).

***Renal Insufficiency***

A single 240-mg dose of EMEND was administered to patients with severe renal insufficiency (CrCl<30 mL/min) and to patients with end stage renal disease (ESRD) requiring hemodialysis.

In patients with severe renal insufficiency, the $AUC_{0-\infty}$ of total aprepitant (unbound and protein bound) decreased by 21% and $C_{max}$ decreased by 32%, relative to healthy subjects. In patients with ESRD undergoing hemodialysis, the $AUC_{0-\infty}$ of total aprepitant decreased by 42% and $C_{max}$ decreased by 32%. Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound drug was not significantly affected in patients with renal insufficiency compared with healthy subjects. Hemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; less than 0.2% of the dose was recovered in the dialysate.

No dosage adjustment for EMEND is necessary for patients with severe renal insufficiency or for patients with ESRD undergoing hemodialysis.

***Pharmacodynamics***

Fosaprepitant, a prodrug of aprepitant, when administered intravenously is rapidly converted to aprepitant.

***Cardiac Electrophysiology***

In a randomized, double-blind, positive controlled, thorough QTc study, a single 200-mg dose of fosaprepitant had no effect on the QTc interval."

***Brain NK1 Receptor Occupancy Assessed by Positron Emission Tomography***

A positron emission tomography study in healthy young men administered a single oral dose of 165 mg aprepitant or a single intravenous dose of 150 mg fosaprepitant demonstrated similar brain NK1 receptor occupancy at Tmax, (≥ 99 %), 24 hours (≥ 99 %), 48 hours (≥ 97 %), and 120 hours (37 to 76 %) following dosing. Occupancy of brain NK1 receptors by aprepitant correlate well with aprepitant plasma concentrations.

***Clinical Studies***

***PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING(CINV)***

Oral administration of EMEND in combination with ondansetron and dexamethasone has been shown to prevent acute and delayed nausea and vomiting associated with highly and moderately emetogenic chemotherapy (HEC and MEC) in well-controlled clinical studies.

***Highly Emetogenic Chemotherapy (HEC)***

In 2 multicenter, randomized, parallel, double-blind, controlled clinical studies, the aprepitant regimen was compared with standard therapy in 1094 patients receiving a chemotherapy regimen that included cisplatin ≥70 mg/m$^2$. Some patients also received additional chemotherapeutic agents such as gemcitabine, etoposide, fluorouracil, vinorelbine tartrate, doxorubicin, cyclophosphamide, paclitaxel, or docetaxel. The aprepitant regimen consisted of EMEND 125 mg on Day 1 and 80 mg/day on Days 2 and 3 in combination with ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg on Day 1 and 8 mg once daily on Days 2 through 4. Standard therapy consisted of placebo in combination with ondansetron 32 mg IV on Day 1 and dexamethasone 20 mg on Day 1 and 8 mg twice daily on Days 2 through 4. Although a 32 mg IV dose of ondansetron was used in clinical trials, this may no longer be the currently recommended dose. See the package insert for the selected 5-$HT_3$ antagonist for appropriate dosing information.

The antiemetic activity of EMEND was evaluated during the acute phase (0 to 24 hours post-cisplatin treatment), the delayed phase (25 to 120 hours post-cisplatin treatment) and overall (0 to 120 hours post-cisplatin treatment) in Cycle 1. Efficacy was based on evaluation of the following composite measures:

- complete response (defined as no emetic episodes and no use of rescue therapy)
- complete protection (defined as no emetic episodes, no use of rescue therapy, and a maximum nausea visual analogue scale [VAS] score <25 mm)
- impact of nausea and vomiting on daily life (Functional Living Index-Emesis [FLIE] total score >108).

Efficacy was also based on the following individual efficacy measures:

- no emesis (defined as no emetic episodes regardless of use of rescue therapy)
- no significant nausea (maximum VAS <25 mm).

The results were evaluated for each individual study and for the 2 studies combined.

A summary of the key study results from the combined analysis is shown in Table 1.

**Table 1 Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase — Cycle 1**

| COMPOSITE MEASURES | Aprepitant Regimen* (N = 521)† % | Standard Therapy** (N = 524)† % | p-Value |
|---|---|---|---|
| **Complete Response (no emesis and no rescue therapy)** | | | |
| Overall‡ | 67.7 | 47.8 | <0.001 |
| Acute phase§ | 86.0 | 73.2 | <0.001 |
| Delayed phase‖ | 71.5 | 51.2 | <0.001 |
| **Complete Protection (no emesis, no rescue therapy and maximum nausea VAS¶ <25 mm)** | | | |
| Overall | 59.5 | 44.9 | <0.001 |
| Acute phase | 82.4 | 69.6 | <0.001 |
| Delayed phase | 63.7 | 47.8 | <0.001 |
| **No Impact on Daily Life (Functional Living Index-Emesis [FLIE] total score >108)** | | | |
| Overall | 74.4 | 63.9 | <0.001 |
| INDIVIDUAL MEASURES | | | |
| **No Emesis (no emetic episodes regardless of use of rescue therapy)** | | | |
| Overall | 71.9 | 49.7 | <0.001 |
| Acute phase | 86.8 | 74.0 | <0.001 |
| Delayed phase | 76.2 | 53.5 | <0.001 |
| **No Significant Nausea (maximum VAS <25 mm)** | | | |
| Overall | 72.1 | 64.9 | 0.014 |
| Delayed phase | 74.0 | 66.9 | 0.013 |

*Aprepitant Regimen: EMEND 125 mg orally on Day 1 and 80 mg orally once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg orally on Day 1 and 8 mg orally once daily on Days 2 to 4.

**Standard therapy: Placebo plus ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg orally on Day 1 and 8 mg orally twice daily on Days 2 to 4.

†N: Number of patients who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.

‡Overall: 0 to 120 hours post-cisplatin treatment.

§Acute phase: 0 to 24 hours post-cisplatin treatment.

‖Delayed phase: 25 to 120 hours post-cisplatin treatment.

¶Visual analogue scale (VAS) score range: 0 = no nausea; 100 = nausea as bad as it can be.

In the combined analysis, a statistically significantly higher proportion of patients receiving the aprepitant regimen in Cycle 1 had a complete response and had complete protection, compared with patients receiving standard therapy. A statistically significant difference in complete response and complete protection was observed in patients receiving the aprepitant regimen during the acute phase and the delayed phase in Cycle 1, compared with patients receiving standard therapy. These findings were also observed in each of the 2 individual studies.

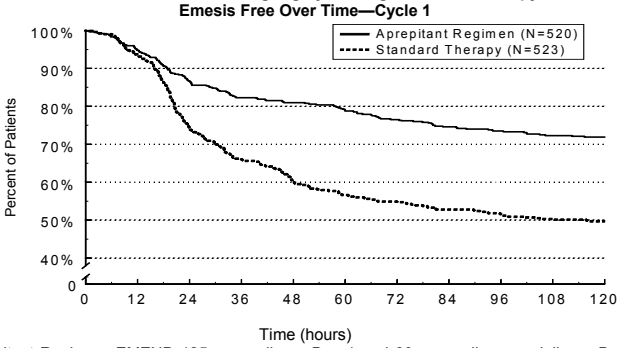
In the combined analysis, a statistically significantly higher proportion of patients receiving the aprepitant regimen in Cycle 1 had no emesis, compared with patients receiving standard therapy. A statistically significant difference in no emesis was observed in patients receiving the aprepitant regimen during the acute and delayed phases in Cycle 1, compared with patients receiving standard therapy. These findings were also observed in each of the 2 individual studies.

Furthermore, in the combined analysis, regardless of use of rescue therapy, a statistically significantly higher proportion of patients receiving the aprepitant regimen in Cycle 1 had no significant nausea overall and no significant nausea during the delayed phase, compared with patients receiving standard therapy.

The impact of nausea and vomiting on patients' daily lives was assessed using the Functional Living Index-Emesis (FLIE), a validated patient-reported outcome measure. In the combined analysis, a statistically significantly higher proportion of patients receiving the aprepitant regimen in Cycle 1 reported no impact of nausea and vomiting on daily life, as measured by a

FLIE total score >108, compared with patients receiving standard therapy. These findings were also observed in each of the 2 individual studies.
In the combined analysis, the estimated time to first emesis after initiation of cisplatin treatment was significantly (p<0.001) longer with the aprepitant regimen, and the incidence of first emesis was reduced in the aprepitant regimen group compared with standard therapy group as depicted in Figure 1.

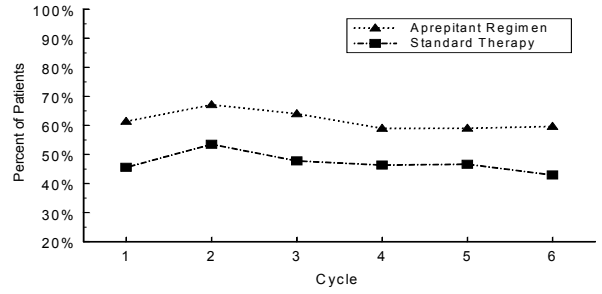
**Figure 1: Percent of Patients Receiving Highly Emetogenic Chemotherapy Who Remain Emesis Free Over Time—Cycle 1**




Aprepitant Regimen: EMEND 125 mg orally on Day 1 and 80 mg orally once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg orally on Day 1 and 8 mg orally once daily on Days 2 to 4.
Standard Therapy: Placebo plus ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg orally on Day 1 and 8 mg orally twice daily on Days 2 to 4.

*Multiple-Cycle Extension:* In the same 2 clinical studies, 851 patients continued into the Multiple-Cycle extension for up to 6 cycles of chemotherapy. The efficacy of the aprepitant regimen was maintained during all cycles. The response rates for the endpoint of no emesis and no significant nausea over the 6 cycles of chemotherapy following initiation of cisplatin therapy from the combined analysis are depicted in Figure 2. During Cycles 2 to 6, the endpoint of no significant nausea was determined by response to a direct question rather than by use of the VAS employed in Cycle 1.

**Figure 2: Percent of Patients Receiving Highly Emetogenic Chemotherapy with No Emesis and No Significant Nausea by Treatment Group and Cycle**




| | N | N | N | N | N | N |
|---|---|---|---|---|---|---|
| Aprepitant Regimen: | 516 | 290 | 216 | 140 | 86 | 60 |
| Standard Therapy: | 522 | 274 | 182 | 115 | 65 | 43 |

Aprepitant Regimen: EMEND 125 mg orally on Day 1 and 80 mg orally once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg orally on Day 1 and 8 mg orally once daily on Days 2 to 4.
Standard Therapy: Placebo plus ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg orally on Day 1 and 8 mg orally twice daily on Days 2 to 4.

***Moderately Emetogenic Chemotherapy (MEC)***
In a multicenter, randomized, double-blind, parallel-group, clinical study, the aprepitant regimen was compared with standard therapy in 866 breast cancer patients receiving a chemotherapy regimen that included cyclophosphamide 750-1500 mg/m$^2$; or cyclophosphamide 500-1500 mg/m$^2$ and doxorubicin (≤60 mg/m$^2$) or epirubicin (≤100 mg/m$^2$). Some patients also received other chemotherapeutic agents such as fluorouracil, methotrexate, docetaxel or paclitaxel. The aprepitant regimen consisted of EMEND 125 mg on Day 1 and 80 mg/day on Days 2 and 3 in combination with ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1. Standard therapy consisted of placebo in combination with ondansetron 8 mg orally (twice on Day 1, and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1.
The antiemetic activity of EMEND was evaluated during the acute phase (0 to 24 hours post-chemotherapy treatment), the delayed phase (25 to 120 hours post-chemotherapy treatment) and overall (0 to 120 hours post-chemotherapy treatment) in Cycle 1. Efficacy was based on evaluation of the following composite measures:

- complete response (defined as no emetic episodes and no use of rescue therapy)
- impact of nausea and vomiting on daily life (Functional Living Index-Emesis [FLIE] total score >108).

Efficacy was also based on the following individual efficacy measures:

- no emesis (defined as no emetic episodes regardless of use of rescue therapy)
- no rescue therapy.

A summary of the key study results is shown in Table 2.

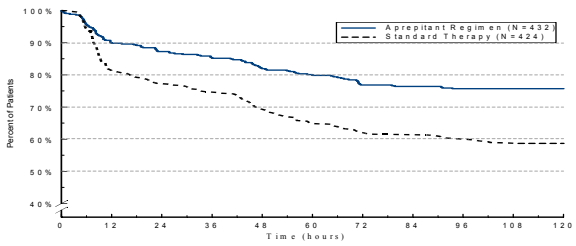
**Table 2 Percent of Patients Receiving Moderately Emetogenic Chemotherapy Responding by Treatment Group and Phase — Cycle 1**

| COMPOSITE MEASURES | Aprepitant Regimen* (N = 433)† % | Standard Therapy** (N = 424)† % | p-Value |
|---|---|---|---|
| **Complete Response (no emesis and no rescue therapy)** | | | |
| Overall‡ | 51 | 42 | 0.015 |
| Acute phase§ | 76 | 69 | 0.034 |
| Delayed phase‖ | 55 | 49 | 0.064 |
| **No Impact on Daily Life (Functional Living Index-Emesis [FLIE] total score >108)** | | | |
| Overall | 64 | 56 | 0.019 |
| INDIVIDUAL MEASURES | | | |
| **No Emesis** | | | |
| Overall | 76 | 59 | <0.001 |
| Acute phase | 88 | 77 | <0.001 |
| Delayed phase | 81 | 69 | <0.001 |
| **No Rescue Therapy** | | | |
| Overall | 59 | 56 | 0.480 |
| Acute phase | 83 | 80 | 0.366 |
| Delayed phase | 63 | 60 | 0.407 |

*Aprepitant Regimen: EMEND 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3 plus ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1.
**Standard Therapy: Placebo plus ondansetron 8 mg orally (twice on Day 1 and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1.
†N: Number of patients included in the primary analysis of complete response.
‡Overall: 0 to 120 hours post-chemotherapy treatment.
§Acute phase: 0 to 24 hours post-chemotherapy treatment.
‖Delayed phase: 25 to 120 hours post-chemotherapy treatment.

In this study, a statistically significantly (p=0.015) higher proportion of patients receiving the aprepitant regimen (51%) in Cycle 1 had a complete response (primary endpoint) during the overall phase compared with patients receiving standard therapy (42%). The unadjusted absolute difference in complete response (8.3%) represents a 20% relative improvement (relative risk ratio = 1.2, aprepitant regimen over standard therapy). A higher proportion of patients receiving the aprepitant regimen in Cycle 1 had a complete response during the acute and delayed phases compared with patients receiving standard therapy.
In this study, the estimated time to first emesis after initiation of chemotherapy treatment was significantly (p<0.001) longer with the aprepitant regimen, and the incidence of first emesis was reduced in the aprepitant regimen group compared with the standard therapy group as depicted in Figure 3.

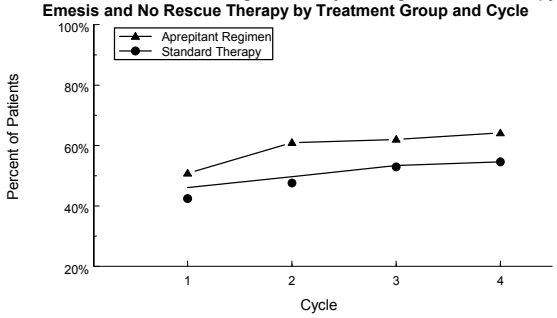
**Figure 3: Percent of Patients Receiving Moderately Emetogenic Chemotherapy Who Remain Emesis Free Over Time—Cycle 1**




Aprepitant Regimen: EMEND 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3 plus ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1.
Standard Therapy: Placebo plus ondansetron 8 mg orally (twice on Day 1 and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1.

In this study, a statistically significantly higher proportion of patients receiving the aprepitant regimen in Cycle 1 reported no impact of nausea and vomiting on daily life, as measured by a FLIE total score >108, compared with patients receiving standard therapy.
*Multiple-Cycle Extension:* A total of 744 patients receiving MEC continued into the Multiple-Cycle extension for up to 4 cycles of chemotherapy. The efficacy of the aprepitant regimen was maintained during all cycles. The response rates are depicted in Figure 4.

**Figure 4: Percent of Patients Receiving Moderately Emetogenic Chemotherapy with No Emesis and No Rescue Therapy by Treatment Group and Cycle**




| | N | N | N | N |
|---|---|---|---|---|
| Aprepitant Regimen | 433 | 379 | 358 | 343 |
| Standard Therapy | 424 | 355 | 325 | 304 |

Aprepitant Regimen: EMEND 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3 plus ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1.
Standard Therapy: Placebo plus ondansetron 8 mg orally (twice on Day 1 and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1.

In a second multicenter, randomized, double-blind, parallel-group, clinical study, the aprepitant regimen was compared with standard therapy in 848 patients receiving a chemotherapy regimen that included any IV dose of oxaliplatin, carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin, doxorubicin; cyclophosphamide IV (<1500 mg/m$^2$); or cytarabine IV (>1 g/m$^2$). Patients who were randomized to receive the aprepitant regimen consisted of 76% women and 24% men. Patients receiving the aprepitant regimen were receiving chemotherapy for a variety of tumor types including 52% with breast cancer, 21% with gastrointestinal cancers including colorectal cancer, 13% with lung cancer and 6% with gynecological cancers. The aprepitant regimen consisted of EMEND 125 mg on Day 1 and 80 mg/day on Days 2 and 3 in combination with ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1. Standard therapy consisted of placebo in combination with ondansetron 8 mg orally (twice on Day 1, and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1.
The antiemetic activity of EMEND was evaluated during the overall phase (0 to 120 hours post-chemotherapy treatment) in Cycle 1. Efficacy was based on the evaluation of the following endpoints:
Primary endpoint:

- no vomiting in the overall period (0 to 120 hours post-chemotherapy)

Other prespecified endpoints:

- complete response (defined as no vomiting and no use of rescue therapy) in the overall period (0 to 120 hours post-chemotherapy)
- time to first vomiting episode overall (0 to 120 hours post-chemotherapy)
- no vomiting – Acute (0 to 24 hours following initiation of chemotherapy infusion) and Delayed (25 to 120 hours following initiation of chemotherapy infusion)
- complete response - Acute and Delayed, as defined above
- no use of rescue therapy – Overall, Acute, and Delayed, as defined above
- no Impact on Daily Life (Functional Living Index-Emesis [FLIE] total score >108) – Overall, as defined above
- no vomiting and no significant nausea (VAS <25 mm) – Overall, as defined above

A summary of the key study results is shown in Table 3.

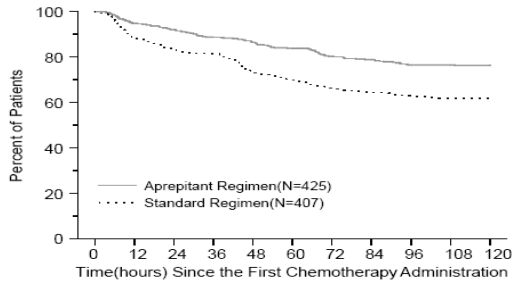
**Table 3 Percent of Patients Receiving Moderately Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 2 – Cycle 1**

| ENDPOINTS | Aprepitant Regimen* (N = 430)† % | Standard Therapy** (N = 418)† % | p-Value‡ |
|---|---|---|---|
| PRIMARY ENDPOINT | | | |
| **No Vomiting** | | | |
| Overall§ | 76 | 62 | <0.0001 |
| KEY SECONDARY ENDPOINT | | | |
| **Complete Response¶** | | | |
| Overall§ | 69 | 56 | 0.0003 |
| OTHER SECONDARY ENDPOINTS | | | |
| **No Vomiting** | | | |
| Acute phase# | 92 | 84 | 0.0002 |
| Delayed phaseÞ | 78 | 67 | 0.0005 |
| **No Impact on Daily Life (FLIE total score >108)** | | | |
| Overall | 73 | 66 | 0.035 |
| **Complete Response** | | | |
| Acute phase | 89 | 80 | 0.0005 |
| Delayed phase | 71 | 61 | 0.0042 |
| **No Use of Rescue Therapy** | | | |
| Overall | 81 | 75 | 0.0427ß |
| Acute phase | | | 0.0179ß |
| Maleª | 97 | 100 | |
| Femaleª | 95 | 88 | |
| Delayed phase | 84 | 79 | 0.0922ß |
| **No Vomiting and No Significant Nausea (VAS <25 mm)** | | | |
| Overall | 65 | 53 | 0.0011 |

*Aprepitant Regimen: EMEND 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3 plus ondansetron 8 mg orally twice on Day 1 plus dexamethasone 12 mg orally on Day 1.
**Standard Therapy: Placebo plus ondansetron 8 mg orally (twice on Day 1 and every 12 hours on Days 2 and 3) plus dexamethasone 20 mg orally on Day 1.
†N = Number of patients who received chemotherapy treatment, study drug, and had at least one post-treatment efficacy evaluation.
‡Hochberg's procedure was used as a multiplicity adjustment when testing secondary endpoints for significance.
§Overall: 0 to 120 hours post chemotherapy treatment.
¶Complete Response = No Vomiting with no rescue therapy
# Acute phase: 0 to 24 hours following initiation of chemotherapy infusion.
Þ Delayed phase: 25 to 120 hours following initiation of chemotherapy infusion.
ßNot statistically significant.
ªData are shown separately for males and females per prespecified analytic plan
Visual analogue scale (VAS) score range: 0 mm = no nausea; 100 mm = nausea as bad as it could be.

In this study, a statistically significantly (p<0.0001) higher proportion of patients receiving the aprepitant regimen (76%) in Cycle 1 had no vomiting (primary endpoint) during the overall phase compared with patients receiving standard therapy (62%). In addition, a higher proportion of patients receiving the aprepitant regimen in Cycle 1 had a complete response in the overall phase (0-120 hours) compared with patients receiving standard therapy. Aprepitant was numerically superior versus standard therapy regardless of age, gender, or tumor type (breast, gastrointestinal, lung or other) as assessed by the No Vomiting and Complete Response endpoints.
In this study, the estimated time to first vomiting after initiation of chemotherapy treatment was longer with the aprepitant regimen, and the incidence was reduced in the aprepitant regimen group compared with standard therapy group as depicted in the Kaplan-Meier curves in Figure 5.

**Figure 5: Kaplan-Meier Curves for Time to First Vomiting Episode From Start of Chemotherapy Administration in the Overall Phase – Cycle 1 (Full Analysis Set Patient Population)**




In this study, a statistically significantly higher proportion of patients receiving the aprepitant regimen in Cycle 1 reported no impact of nausea and vomiting on daily life, as measured by a FLIE total score >108, compared with patients receiving standard therapy.

## INDICATIONS

EMEND, in combination with other antiemetic agents, is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of:

- highly emetogenic cancer chemotherapy (see DOSAGE AND ADMINISTRATION)
- moderately emetogenic cancer chemotherapy (see DOSAGE AND ADMINISTRATION).

## DOSAGE AND ADMINISTRATION

EMEND (aprepitant) is available as capsules for oral administration.
EMEND is given for 3 days as part of a regimen that includes a corticosteroid and a 5-$HT_3$ antagonist. The package insert for the co-administered 5-$HT_3$ antagonist must be consulted prior to initiation of treatment with EMEND. The recommended dose of EMEND is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg orally once daily in the morning on Days 2 and 3.
Recommended dosing for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy:

| | Day 1 | Day 2 | Day 3 | Day 4 |
|---|---|---|---|---|
| EMEND | 125 mg orally | 80 mg orally | 80 mg orally | none |
| Dexamethasone** | 12 mg orally | 8 mg orally | 8 mg orally | 8 mg orally |
| 5-$HT_3$ antagonist | See the package insert for the selected 5-$HT_3$ antagonist for appropriate dosing information. | none | none | none |

**Dexamethasone should be administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. The dose of dexamethasone accounts for drug interactions.
Recommended dosing for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy:

| | Day 1 | Day 2 | Day 3 |
|---|---|---|---|
| EMEND* | 125 mg orally | 80 mg orally | 80 mg orally |
| Dexamethasone** | 12 mg orally | none | none |
| 5-$HT_3$ antagonist | See the package insert for the selected 5-$HT_3$ antagonist for appropriate dosing information. | none | none |

**Dexamethasone should be administered 30 minutes prior to chemotherapy treatment on Day 1. The dose of dexamethasone accounts for drug interactions.
EMEND IV 150 mg (fosaprepitant), a lyophilized prodrug of aprepitant for intravenous administration, is also available. EMEND IV 150 mg is available as a single dose and is administered on Day 1 only.

***GENERAL INFORMATION***

See DRUG INTERACTIONS for additional information on the administration of EMEND with corticosteroids.
Refer to the full prescribing information for coadministered antiemetic agents.
EMEND may be taken with or without food.
No dosage adjustment is necessary based on age, gender, race or Body Mass Index (BMI).
No dosage adjustment is necessary for patients with severe renal insufficiency (creatinine clearance <30 mL/min) or for patients with end stage renal disease undergoing hemodialysis.
No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency (Child-Pugh score 5 to 9). There are no clinical data in patients with severe hepatic insufficiency (Child-Pugh score >9).

## CONTRAINDICATIONS

EMEND is contraindicated in patients who are hypersensitive to any component of the product.
EMEND should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Dose-dependent inhibition of cytochrome P450 isoenzyme 3A4 (CYP3A4) by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions (see DRUG INTERACTIONS).

## PRECAUTIONS

EMEND, a dose-dependent inhibitor of CYP3A4, should be used with caution in patients receiving concomitant orally administered medicinal products that are primarily metabolized through CYP3A4; some chemotherapy agents are metabolized by CYP3A4 (see DRUG INTERACTIONS). Moderate inhibition of CYP3A4 by aprepitant, 125 mg/80 mg regimen, could result in elevated plasma concentrations of these concomitant medicinal products administered orally (see DRUG INTERACTIONS). The effect of EMEND on the pharmacokinetics of orally administered CYP3A4 substrates is greater than the effect of EMEND on the pharmacokinetics of intravenously administered CYP3A4 substrates (see DRUG INTERACTIONS).
Coadministration of EMEND with warfarin may result in a clinically significant decrease in International Normalized Ratio (INR) of prothrombin time. In patients on chronic warfarin therapy, the INR should be closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of the 3-day regimen of EMEND with each chemotherapy cycle (see DRUG INTERACTIONS).
The efficacy of hormonal contraceptives during and for 28 days after administration of EMEND may be reduced. Alternative or back-up methods of contraception should be used during treatment with EMEND and for 1 month following the last dose of EMEND (see DRUG INTERACTIONS).

## PREGNANCY

There are no adequate and well-controlled studies in pregnant women. EMEND should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and the fetus.

## NURSING MOTHERS

Aprepitant is excreted in the milk of lactating 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 possible adverse effects of EMEND on nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

## PEDIATRIC USE

Safety and effectiveness of EMEND in pediatric patients have not been established.

## USE IN THE ELDERLY

In clinical studies, the efficacy and safety of EMEND in the elderly (≥65 years) were comparable to those seen in younger patients (<65 years). No dosage adjustment is necessary in elderly patients.

## DRUG INTERACTIONS

Aprepitant is a substrate, a moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9.

**Effect of aprepitant on the pharmacokinetics of other agents**

As a moderate (125 mg/80 mg) inhibitor of CYP3A4, aprepitant can increase plasma concentrations of orally coadministered medicinal products that are metabolized through CYP3A4. Aprepitant (125 mg/80 mg) can increase plasma concentrations of intravenously coadministered medicinal products metabolized through CYP3A4 to a lesser extent.
EMEND should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Dose-dependent inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions (see CONTRAINDICATIONS).
Aprepitant has been shown to induce the metabolism of S(-) warfarin and tolbutamide, which are metabolized through CYP2C9. Coadministration of EMEND with these drugs or other drugs that are known to be metabolized by CYP2C9, such as phenytoin, may result in lower plasma concentrations of these drugs.
EMEND is unlikely to interact with drugs that are substrates for the P-glycoprotein transporter, as demonstrated by the lack of interaction of EMEND with digoxin in a clinical drug interaction study.
***5-$HT_3$ antagonists:*** In clinical drug interaction studies, EMEND, when given as a regimen of 125 mg on Day 1 and 80 mg on Days 2 and 3, did not have clinically important effects on the pharmacokinetics of ondansetron, granisetron, or hydrodolasetron (the active metabolite of dolasetron).
***Corticosteroids:***
*Dexamethasone:* EMEND, when given as a regimen of 125 mg with dexamethasone coadministered orally as 20 mg on Day 1, and EMEND when given as 80 mg/day with dexamethasone coadministered orally as 8 mg on Days 2 through 5, increased the AUC of dexamethasone, a CYP3A4 substrate by 2.2-fold, on Days 1 and 5. The usual oral dexamethasone doses should be reduced by approximately 50% when coadministered with EMEND (125 mg/80 mg regimen), to achieve exposures of dexamethasone similar to those obtained when it is given without EMEND. The daily dose of dexamethasone administered in clinical chemotherapy induced nausea and vomiting studies with EMEND reflects an approximate 50% reduction of the dose of dexamethasone (see DOSAGE AND ADMINISTRATION).
*Methylprednisolone:* EMEND, when given as a regimen of 125 mg on Day 1 and 80 mg/day on Days 2 and 3, increased the AUC of methylprednisolone, a CYP3A4 substrate, by 1.3-fold on Day 1 and by 2.5-fold on Day 3, when methylprednisolone was coadministered intravenously as 125 mg on Day 1 and orally as 40 mg on Days 2 and 3. The usual IV methylprednisolone dose should be reduced by approximately 25%, and the usual oral methylprednisolone dose should be reduced by approximately 50% when coadministered with EMEND (125 mg/80 mg regimen), to achieve exposures of methylprednisolone similar to those obtained when it is given without EMEND.
***Chemotherapeutic agents:*** In clinical studies, EMEND (125 mg/80 mg regimen) was administered with the following chemotherapeutic agents metabolized primarily or in part by CYP3A4: etoposide, vinorelbine, docetaxel, ifosfamide, cyclophosphamide, irinotecan, and paclitaxel. The doses of these agents were not adjusted to account for potential drug interactions. Caution and careful monitoring are advised in patients receiving these agents or other chemotherapy agents metabolized primarily by CYP3A4. Post-marketing events of neurotoxicity, a potential adverse reaction of ifosfamide, have been reported after aprepitant and ifosfamide coadministration (see PRECAUTIONS).

*Docetaxel:* In a separate pharmacokinetic study, EMEND (125 mg/80 mg regimen) did not influence the pharmacokinetics of docetaxel.
*Vinorelbine*: In a separate pharmacokinetic study, EMEND (125 mg/80 mg regimen) did not influence the pharmacokinetics of vinorelbine.
***Warfarin:*** A single 125-mg dose of EMEND was administered on Day 1 and 80 mg/day on Days 2 and 3 to healthy subjects who were stabilized on chronic warfarin therapy. Although there was no effect of EMEND on the plasma AUC of R(+) or S(-) warfarin determined on Day 3, there was a 34% decrease in S(-) warfarin (a CYP2C9 substrate) trough concentration accompanied by a 14% decrease in the prothrombin time (reported as International Normalized Ratio or INR) 5 days after completion of dosing with EMEND. In patients on chronic warfarin therapy, the prothrombin time (INR) should be closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of the 3-day regimen of EMEND with each chemotherapy cycle.
***Tolbutamide:*** EMEND, when given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, decreased the AUC of tolbutamide (a CYP2C9 substrate) by 23% on Day 4, 28% on Day 8, and 15% on Day 15, when a single dose of tolbutamide 500 mg was administered orally prior to the administration of the 3-day regimen of EMEND and on Days 4, 8, and 15.
***Oral contraceptives:*** Aprepitant, when given once daily for 14 days as a 100-mg capsule with an oral contraceptive containing 35 µg of ethinyl estradiol and 1 mg of norethindrone, decreased the AUC of ethinyl estradiol by 43%, and decreased the AUC of norethindrone by 8%.
In another study, a single dose of an oral contraceptive containing ethinyl estradiol and norethindrone was administered on Days 1 through 21 with EMEND, given as a regimen of 125 mg on Day 8 and 80 mg/day on Days 9 and 10 with ondansetron 32 mg IV on Day 8 and oral dexamethasone given as 12 mg on Day 8 and 8 mg/day on Days 9, 10, and 11. In the study, the AUC of ethinyl estradiol decreased by 19% on Day 10 and there was as much as a 64% decrease in ethinyl estradiol trough concentrations during Days 9 through 21. While there was no effect of EMEND on the AUC of norethindrone on Day 10, there was as much as a 60% decrease in norethindrone trough concentrations during Days 9 through 21.
The efficacy of hormonal contraceptives during and for 28 days after administration of EMEND may be reduced. Alternative or back-up methods of contraception should be used during treatment with EMEND and for 1 month following the last dose of EMEND.
***Midazolam:*** EMEND increased the AUC of midazolam, a sensitive CYP3A4 substrate, by 2.3-fold on Day 1 and 3.3-fold on Day 5, when a single oral dose of midazolam 2 mg was coadministered on Day 1 and Day 5 of a regimen of EMEND 125 mg on Day 1 and 80 mg/day on Days 2 through 5. The potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) should be considered when coadministering these agents with EMEND (125 mg/80 mg).
In another study with intravenous administration of midazolam, EMEND was given as 125 mg on Day 1 and 80 mg/day on Days 2 and 3, and midazolam 2 mg IV was given prior to the administration of the 3-day regimen of EMEND and on Days 4, 8, and 15. EMEND increased the AUC of midazolam by 25% on Day 4 and decreased the AUC of midazolam by 19% on Day 8 relative to the dosing of EMEND on Days 1 through 3. These effects were not considered clinically important. The AUC of midazolam on Day 15 was similar to that observed at baseline.
An additional study was completed with intravenous administration of midazolam and EMEND. Intravenous midazolam 2 mg was given 1 hour after oral administration of a single dose of EMEND 125 mg. The plasma AUC of midazolam was increased by 1.5-fold. This effect was not considered clinically important.
**Effect of other agents on the pharmacokinetics of aprepitant**
Aprepitant is a substrate for CYP3A4; therefore, coadministration of EMEND with drugs that inhibit CYP3A4 activity may result in increased plasma concentrations of aprepitant. Consequently, concomitant administration of EMEND with strong CYP3A4 inhibitors (e.g., ketoconazole) should be approached cautiously; but concomitant administration of EMEND with moderate CYP3A4 inhibitors (e.g., diltiazem) does not result in clinically meaningful changes in plasma concentrations of aprepitant.
Aprepitant is a substrate for CYP3A4; therefore, coadministration of EMEND with drugs that strongly induce CYP3A4 activity (e.g., rifampin) may result in reduced plasma concentrations of aprepitant that may result in decreased efficacy of EMEND.
***Ketoconazole:*** When a single 125-mg dose of EMEND was administered on Day 5 of a 10-day regimen of 400 mg/day of ketoconazole, a strong CYP3A4 inhibitor, the AUC of aprepitant increased approximately 5-fold and the mean terminal half-life of aprepitant increased approximately 3-fold. Concomitant administration of EMEND with strong CYP3A4 inhibitors should be approached cautiously.
***Rifampin:*** When a single 375-mg dose of EMEND was administered on Day 9 of a 14-day regimen of 600 mg/day of rifampin, a strong CYP3A4 inducer, the AUC of aprepitant decreased approximately 11-fold and the mean terminal half-life decreased approximately 3-fold. Coadministration of EMEND with drugs that induce CYP3A4 activity may result in reduced plasma concentrations and decreased efficacy of EMEND.
**Additional interactions**
***Diltiazem:*** In patients with mild to moderate hypertension, administration of aprepitant once daily, as a tablet formulation comparable to 230 mg of the capsule formulation, with diltiazem 120 mg 3 times daily for 5 days, resulted in a 2-fold increase of aprepitant AUC and a simultaneous 1.7-fold increase of diltiazem AUC. These pharmacokinetic effects did not result in clinically meaningful changes in ECG, heart rate, or blood pressure beyond those changes induced by diltiazem alone.
***Paroxetine:*** Coadministration of once daily doses of aprepitant, as a tablet formulation comparable to 85 mg or 170 mg of the capsule formulation, with paroxetine 20 mg once daily, resulted in a decrease in AUC by approximately 25% and $C_{max}$ by approximately 20% of both aprepitant and paroxetine.

## SIDE EFFECTS

The overall safety of aprepitant was evaluated in approximately 6500 individuals.
***PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CINV)***
***Highly Emetogenic Chemotherapy (HEC)***
In 2 well-controlled clinical trials in patients receiving highly emetogenic cancer chemotherapy (HEC), 544 patients were treated with the 3-day aprepitant regimen during Cycle 1 of chemotherapy and 413 of these patients continued into the Multiple-Cycle extension for up to 6 cycles of chemotherapy. The 3-day oral EMEND regimen was given in combination with ondansetron and dexamethasone and was generally well tolerated. Most adverse experiences reported in these clinical studies were described as mild to moderate in intensity.
In Cycle 1, drug-related clinical adverse experiences were reported in approximately 19% of patients treated with the 3-day oral aprepitant regimen compared with approximately 14% of patients treated with standard therapy. Treatment was discontinued due to drug-related clinical adverse experiences in 0.6% of patients treated with the 3-day oral aprepitant regimen compared with 0.4% of patients treated with standard therapy.
The most common drug-related adverse experiences reported in patients treated with the 3-day oral aprepitant regimen and greater than standard therapy were: hiccups (4.6%), ALT increased (2.8%), dyspepsia (2.6%), constipation (2.4%), headache (2.0%), and decreased appetite (2.0%).
In an additional active-controlled clinical study in 1169 patients receiving the 3-day oral aprepitant regimen and HEC, the adverse experience profile was generally similar to that seen in the other HEC studies with the 3-day oral aprepitant regimen.
***Moderately Emetogenic Chemotherapy (MEC)***
In 2 well-controlled clinical trials in patients receiving moderately emetogenic cancer chemotherapy (MEC), 868 patients were treated with the 3-day oral aprepitant regimen during Cycle 1 of chemotherapy and 686 of these patients continued into extensions for up to 4 cycles of chemotherapy. In both studies, the 3-day oral EMEND regimen was given in combination with ondansetron and dexamethasone and was generally well tolerated. Most adverse experiences reported in these clinical studies were described as mild to moderate in intensity.
In the combined analysis of Cycle 1 data for these 2 studies, drug-relatedadverse experiences were reported in approximately 14% of patients treated with the 3-day oral aprepitant regimen compared with approximately 15% of patients treated with standard therapy. Treatment was discontinued due to drug-related adverse experiences in 0.7% of patients treated with the 3-day oral aprepitant regimen compared with 0.2% of patients treated with standard therapy.
The most common drug-related adverse experience reported at a greater incidence in patients treated with the 3-day oral aprepitant regimen than with standard therapy was fatigue (1.4%).
***Highly and Moderately Emetogenic Chemotherapy***
In a pooled analysis of the HEC and MEC studies the following drug-related adverse experiences were reported in patients treated with the 3-day oral aprepitant regimen and at a greater incidence than standard therapy:
*[Common (≥1/100, <1/10), Uncommon (≥1/1,000, <1/100), Rare (≥1/10,000, <1/1,000)]*
***Infection and infestations:***
*Rare:* candidiasis, staphylococcal infection.
***Blood and the lymphatic system disorders:***
*Uncommon:* anemia, febrile neutropenia.
***Metabolism and nutrition disorders:***
*Common:* decreased appetite
*Rare:* polydipsia.
***Psychiatric disorders:***
*Uncommon:* anxiety
*Rare:* disorientation, euphoric mood.
***Nervous system disorders:***
*Uncommon:* dizziness, somnolence
*Rare:* cognitive disorder, lethargy, dysgeusia.
***Eye disorders:***
*Rare:* conjunctivitis.
***Ear and labyrinth disorders:***
*Rare:* tinnitus.
***Cardiac disorders:***
*Uncommon* palpitations
*Rare:* bradycardia, cardiovascular disorder.
***Vascular disorders:***
*Uncommon:* hot flush.
***Respiratory, thoracic and mediastinal disorders:***
*Common:* hiccups
*Rare:* oropharyngeal pain, sneezing, cough, postnasal drip, throat irritation.
***Gastrointestinal disorders:***
*Common:* dyspepsia
*Uncommon:* eructation, nausea, gastroesophageal reflux disease, vomiting, abdominal pain, dry mouth, flatulence
*Rare:* feces hard, duodenal ulcer perforation, neutropenic colitis, stomatitis, abdominal distension.
***Skin and subcutaneous tissue disorders:***
*Uncommon:* rash, acne
*Rare:* photosensitivity reaction, hyperhidrosis, seborrhoea, skin lesion, rash pruritic.
***Musculoskeletal and connective tissue disorders:***
*Rare:* muscle spasms, muscular weakness.
***Renal and urinary disorders:***
*Uncommon:* dysuria
*Rare:* pollakiuria.
***General disorders and administration site conditions:***
*Common:* fatigue
*Uncommon:* asthenia, malaise
*Rare:* edema, chest discomfort, gait disturbance.
***Investigations:***
*Common*: ALT increased
*Uncommon:* AST increased, blood alkaline phosphatase increased
*Rare:* urine output increased, red blood cells urine positive, blood sodium decreased, weight decreased, glucose urine present, neutrophil count decreased.
The adverse experience profiles in the Multiple-Cycle extensions of HEC and MEC studies for up to 6 cycles of chemotherapy were generally similar to those observed in Cycle 1.
In another CINV study, Stevens-Johnson syndrome was reported as a serious adverse experience in a patient receiving aprepitant with cancer chemotherapy.
Other Studies
Single 40-mg doses of EMEND have also been studied for the prevention of post-operative nausea and vomiting (PONV) in non-chemotherapy patients receiving general balanced anesthesia. In these studies, additional adverse reactions that were observed at a greater incidence than with the active comparator (ondansetron) included: ALT increased, abdominal pain upper, bowel sounds abnormal, dysarthria, dyspnoea, hypoaesthesia, insomnia, miosis, nausea, sensory disturbance, stomach discomfort, visual acuity reduced, wheezing.
In addition, two serious adverse experiences were reported in PONV clinical studies in patients taking a higher dose of aprepitant: one case of constipation, and one case of sub-ileus.
One case of angioedema and urticaria was reported as a serious adverse event in a patient receiving aprepitant in a non-CINV/non-PONV study.
***Post-Marketing Experience:***
The following adverse reactions have been identified during post-marketing use of aprepitant. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to the drug.
***Skin and subcutaneous tissue disorders:*** pruritus, rash, urticaria, rarely Stevens-Johnson syndrome/toxic epidermal necrolysis
***Immune system disorders:*** hypersensitivity reactions including anaphylactic reactions

## OVERDOSAGE

No specific information is available on the treatment of overdosage with EMEND. Single doses up to 600 mg of aprepitant were generally well tolerated in healthy subjects. Aprepitant was generally well tolerated when administered as 375 mg once daily for up to 42 days to patients in non-CINV studies. In 33 cancer patients, administration of a single 375-mg dose of aprepitant on Day 1 and 250 mg once daily on Days 2 to 5 was generally well tolerated.
Drowsiness and headache were reported in one patient who ingested 1440 mg of aprepitant.
In the event of overdose, EMEND should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of aprepitant, drug-induced emesis may not be effective.
Aprepitant cannot be removed by hemodialysis.

## STORAGE

**Store at or below 30°C.**

## AVAILABILITY

One capsule per pack.

Manufacturer: Alkermes Pharma Ireland Limited
Address: Monksland Athlone Co. Westmeath, Ireland