吉興藥品股份有限公司　函

機關地址：台南市中華東路三段 200 號
聯絡人：陳頡陞 0973-371-099
電話：(06) 267-3303
傳真：(06) 290-1920

受文者：天主教中華聖母修女會醫療財團法人

發文日期：中華民國 110 年 11 月 09 日
發文字號：吉(管)字第 110110911 號
速別：
密等及解密條件或保密期限：
附件：藥證、衛福部核備函、新包裝照片、新仿單

裝

主旨：本公司經銷藥品「Aloxi Solution for Injection (嘔立舒注射劑)，衛署藥輸字第 024785 號」變更製造廠名稱及仿單，詳如說明，敬請查照。

說明：

訂

一、本公司經銷藥品「Aloxi Solution for Injection (嘔立舒注射劑)，衛署藥輸字第 024785 號」製造廠名稱由 Pierre Fabre Medicament 變更為「FAREVA PAU 1」，仿單記載的製造廠名稱也隨之變動；另製造廠地址及國際條碼皆不變。

二、本公司待舊包裝售罄，預計 11 月中旬自批號 41002153 起，將提供新包裝藥品並隨貨附上新版仿單。

線

三、因上述事宜造成　貴院不便，敬請見諒，並請繼續惠予本公司支持為禱。

正本：天主教中華聖母修女會醫療財團法人
副本：

行政院衛生署藥品許可證

衛署藥輸 字第 024785 號

簽審文件號碼：DHA00202478509

中文名稱： 嘔立舒注射劑

英文名稱： Aloxi Solution for Injection

類　　別： 本藥限由醫師使用

藥商名稱： 和聯藥業股份有限公司

劑　　型： 注射劑

製造廠名稱： 詳如後

包裝種類： 100ml 以下玻璃瓶裝

製造廠地址： 詳如後

處　　方：

Each ml contains：

Palonosetron (as Hydrochloride)……0.05 mg

適 應 症：

預防化學療法引起之噁心和嘔吐。

- 中度致嘔性癌症化學療法--預防起始及反覆療程引起之急性及延遲性噁心和嘔吐。
- 高度致嘔性癌症化學療法--預防起始及反覆療程引起之急性噁心和嘔吐。

前項藥品經本署審核與藥事法之規定相符應發給許可證以資證明

行政院衛生署署長

侯勝茂

發證日期 玖拾柒 年 壹 月 參拾 日

有效日期 壹佰零貳 年 壹 月 參拾 日

核准展延至	107年01月30日	112年1月30日	年 月 日	年 月 日
文號		1066041937		

E 003644

	變更事項	核准文號	核准日期	變更事項	核准文號	核准日期
其他	**藥商名稱變更：** 和聯生技藥業股份有限公司	1015034021				
	適應症變更		101.10.23			
	成人 預防化學療法引起之噁心和嘔吐。 • 中度致嘔性癌症化學療法-- 預防起始及反覆療程引起之急性及延遲性噁心和嘔吐。 • 高度致嘔性癌症化學療法-- 預防起始及反覆療程引起之急性噁心和嘔吐。 兒童與青少年(1 個月大至 17 歲) • 預防高度致嘔性癌症化學療法引起之急性噁心和嘔吐。 • 預防中度致嘔性癌症化學療法引起之噁心和嘔吐。	1046039893	104.10.19			
	核准變更項目：「PIERRE FABRE MEDICAMENT PRODUCTION, AQUITAINE PHARM INTERNATIONAL」製造廠廠名，變更為「FAREVA PAU 1」。	1101492110	110.5.06			

本品係依本署89、12、12衛署藥字第0890035812號公告
「經本署認定得免除銜接性試驗，且經本署核定之新藥」

DMF Number：DMF(43)2595
成分名：PALONOSETRON HCL
廠名(址)：「HELSINN ADVANCED SYNTHESIS S.A.」【VIA INDUSTRIA, 24 6710 BIASCA, SWITZERLAND】
本案係依 102 年年 2 月 21 日署授食字第 1021401257 號公告審查通過；並依 1050041363 號函併入本製劑許可證管理。

110.3.24
1096038163

BULK MANUFACTURE AND PRIMARY PACKAGING :
廠名：PIERRE FABRE MEDICAMENT PRODUCTION, AQUITAINE PHARM INTERNATIONAL
廠址：AVENUE DE BEARN 64320 IDRON FRANCE
SECONDARY PACKAGING AND RELEASE :
廠名：HELSINN BIREX PHARMACEUTICALS LTD
廠址：DAMASTOWN, MULHUDDART, DUBLIN 15, IRELAND

正本

檔　　號：
保存年限：

衛生福利部　函

機關地址：11558 台北市南港區忠孝東路六段488號
傳　　真：(02)2653-2071
聯絡人及電話：紀厚邑(02)2787-7682
電子郵件信箱：joechi@fda.gov.tw

105
台北市松山區敦化北路311號5樓

受文者：和聯生技藥業股份有限公司

發文日期：中華民國110年5月6日
發文字號：衛授食字第1101492110號
速別：普通件
密等及解密條件或保密期限：
附件：

主旨：貴公司申請許可證「嘔立舒注射劑」(衛署藥輸字第024785號)製造廠廠名變更一案(案號:1101492110)，本部同意，請查照。

說明：

一、復貴公司110年3月23日未列字號藥品變更登記申請書。

二、核准變更項目：「PIERRE FABRE MEDICAMENT PRODUCTION, AQUITAINE PHARM INTERNATIONAL」製造廠廠名，變更為「FAREVA PAU 1」。

正本：和聯生技藥業股份有限公司
副本：

部長陳時中

Letter from
Ministry of Health and Welfare, Taiwan, R.O.C

Tung Hua North Road, Taipei, Taiwan, R.O.C.
Receiver: HOLLING BIO-PHARMA CORPORATION
Issue date: May 06th ,2021
Document number: FDA1101492110
Importance:
Confidential or Disclosure date:
Attached:

Subject : The application (case no.: 1101492110) for name change of manufacturer for Aloxi injection (MA No.: 024785) has been approved.

Explanation :
1.This is response to your application on March 23,2021.
2.The approved items: Name change of manufacturer from “PIERRE FABRE MEDICAMENT PRODUCTION, AQUITAINE PHARM INTERNATIONAL” to “FAREVA PAU 1”.

“嘔立舒”注射劑

Aloxi Solution for Injection

衛署藥輸字第 024785 號

本藥限由醫師使用

1.【適應症】：

成人

預防化學療法引起之噁心和嘔吐。

- 中度致嘔性癌症化學療法--預防起始及反覆療程引起之急性及延遲性噁心和嘔吐。
- 高度致嘔性癌症化學療法--預防起始及反覆療程引起之急性噁心和嘔吐。

兒童與青少年(1 個月大至 17 歲)

- 預防高度致嘔性癌症化學療法引起之急性噁心和嘔吐。
- 預防中度致嘔性癌症化學療法引起之噁心和嘔吐。

2.【用法用量】

建議劑量：

成人

在開始化學治療約 30 分鐘前，靜脈注射超過 30 秒，投予單一劑量 0.25 毫克。

兒童與青少年(1 個月大至 17 歲)

在開始化學治療約 30 分鐘前投於單一劑量 palonosetron 20 微公克/公斤(最大劑量不可超過 1500 微公克)，靜脈輸注時間須超過 15 分鐘。

用法：

ALOXI供靜脈注射用，ALOXI不應與其他藥物混合。投與ALOXI之前與之後均需用生理食鹽水沖洗輸注管線（infusion line）。

非經腸胃道投予之藥物，只要溶液和容器容許情況下，給藥前應檢視藥物產品是否有微粒狀物質或褪色的情形。

3.【劑型/單位含量】

ALOXI為單次使用之無菌、清澈、無色溶液，玻璃瓶裝，每5毫升內含0.25毫克（free base）。

4.【禁忌症】

ALOXI忌用於已知對此藥物或其任何成分過敏之病患。『請參閱副作用』。

5.【警告與注意事項】

過敏反應（Hypersensitivity）：

無論是否已知對其他 5-HT3 受體拮抗劑過敏，都曾有病患發生過敏反應（含過敏性休克）的通報。

血清素症候群

5-HT3受體拮抗劑曾有發生血清素症候群的案例報告，大多數報告與併用血清素作用藥物相關 (例如：選擇性血清素回收抑制劑 「selective serotonin reuptake inhibitors (SSRIs)」、血清素與正腎上腺素回收抑制劑「serotonin and norepinephrine reuptake inhibitors (SNRIs)」、單胺氧化酶抑制劑「monoamine oxidase inhibitors」、mirtazapine、fentanyl、lithium、tramadol及靜脈注射甲基藍「methylene blue」)。其中包含死亡案例。單獨使用5-HT3受體拮抗劑過量亦曾有發生血清素症候群的案例報告。與使用5-HT3受體拮抗劑相關之血清素症候群案例報告多數發生於麻醉過後之恢復室或輸液中心。血清素症候群相關症狀可能包括下列徵兆及症狀之組合：精神狀態改變 (如：情緒激動、幻覺、譫妄及昏迷)、自律神經失調 (如：心搏過速、血壓不穩、頭暈、發汗、潮紅、體溫過高)、神經肌肉症狀 (如：顫抖、僵直、肌陣攣、反射亢進、不協調)、癲癇發作，可能伴隨胃腸道症狀 (如：噁心、嘔吐、腹瀉)。病患應被監測是否發生血清素症候群，特別是併用本品及其他血清素作用藥物時。若發生血清素症候群之症狀，應立即停藥並給予支持性治療。**病患應被告知血清素症候群之風險，特別是當本品與其他血清素作用藥物併用時**。

6.【副作用】

臨床試驗經驗：

由於臨床試驗在差異很大的情況執行，藥物於臨床試驗中所發現的不良反應比率，不能與臨床試驗中的其他藥品直接比較，並且在實際上可能無法反映出報告比率。

化學療法引起之噁心和嘔吐

1374位成人病患投予Palonosetron，預防中度或高度致嘔性化學療法誘發之噁心及嘔吐的臨床試驗中。Aloxi造成副作用的發生頻率及嚴重程度和Ondansetron或Dolasetron相似。下表（表1）列出這些試驗中，超過2%的病患曾發生的不良反應。

表 1：化學療法所誘發的噁心及嘔吐之試驗中，任何治療組發生 ≥ 2%之不良反應

症狀	0.25 毫克 ALOXI （個數＝633）	Ondansetron 32 毫克靜脈注射 （個數＝410）	Dolasetron 100 毫克靜脈注射 （個數＝194）
頭痛	60（9%）	34（8%）	32（16%）
便秘	29（5%）	8（2%）	12（6%）
腹瀉	8（1%）	7（2%）	4（2%）
暈眩	8（1%）	9（2%）	4（2%）
疲勞	3（＜1%）	4（1%）	4（2%）
腹痛	1（＜1%）	2（＜1%）	3（2%）
失眠	1（＜1%）	3（1%）	3（2%）

在其他研究中，2 名受試者在投予將近 0.75 毫克單一劑量的 palonosetron 後產生嚴重的便秘，該劑量為建議劑量的三倍。其中一位是在一項術後噁心嘔吐的研究中，口服劑量為 10 微克/公斤的病患；另一位則是在一項藥物動力學研究中以靜脈投予 0.75 毫克的健康受試者。

在臨床實驗中，下列是由研究者評估為與治療相關或緣由不明，且不常被報告的副作用，這些反應是在接受癌症化學療法的成人病患投與 ALOXI 之後產生的：

心臟血管：1%：非持續性心跳過速（non-sustained tachycardia）、心跳徐緩（bradycardia）、低血壓；＜1%：高血壓、心肌缺血（myocardial ischemia）、期外收縮（extrasystoles）、竇性心跳過速（sinus tachycardia）、竇性心律不整（sinus arrhythmia）、心室上部期外收縮（supraventricular extrasystoles）和 QT 延長。在許多個案中，與 ALOXI 的關聯性不明確。
皮膚：＜1%：過敏性皮膚炎（allergic dermatitis）、紅疹。
聽覺與視力：＜1%：動暈症（motion sickness）、耳鳴、眼刺激性（eye irritation）和弱視（amblyopia）。
腸胃道系統：1%：腹瀉，＜1%：消化不良、腹痛、口乾、打嗝和氣脹（flatulence）。
一般性：1%：虛弱，＜1%：疲倦、發燒、熱潮紅、類似感冒的症狀。
肝臟：＜1%：AST 和/或 ALT 及膽紅素短暫而無症狀的增高。這些變化主要發現於接受高度致嘔性化學療法的病患中。
代謝：1%：高鉀血症，＜1%：電解質波動（electrolyte fluctuations）、高血糖症、代謝性酸中毒、糖尿症（glycosuria）、胃口降低、厭食症。
肌肉骨骼：＜1%：關節痛。
神經系統：1%：暈眩，＜1%：嗜睡、失眠、睡眠過度、感覺異常。
精神：1%：焦慮，＜1%：欣快的心情（euphoric mood）。
泌尿系統：＜1%：尿滯留（urinary retention）。
血管：＜1%：靜脈褪色（vein discoloration）、靜脈曲張（vein distension）。

兒童與青少年

在一個 163 位兒童與青少年癌症病患，於第 1 化療週期開始治療約 30 分鐘前，靜脈輸注投於單一劑量 palonosetron 20 微公克/公斤(最大劑量不可超過 1.5 毫克)以預防化學療法誘發之噁心及嘔吐的臨床試驗，病患平均年齡 8.4 歲(2 個月大至 16.9 歲之間)，男性 46%，93%為白種人。
下列有關 palonosetron 的不良反應包括:
神經系統：<1%：頭痛、暈眩、運動障礙
一般性：＜1%：輸注部位疼痛
皮膚：＜1%：過敏性皮膚炎（allergic dermatitis）、皮膚疾病。
在此試驗的第四個化療療程，評估兒童與青少年病患的不良反應。
上市後使用經驗：
在 ALOXI 核准後使用已發現下列不良反應，因為這些反應是未知大小總數中所自動通報的，不能確實的估計其頻率或確定與藥物暴露量之關係。
上市後使用經驗（post-marketing experience），非常少數（＜1/10,000）有過敏性反應（含過敏性休克）和注射部位反應（灼熱、硬結 induration，不舒服和疼痛）的案例。

7【藥物交互作用】

Palonosetron 經由腎臟排泄和由數個細胞色素 P450（CYP）酵素調控的代謝途徑排出體外。進一步活體外實驗顯示 Palonosetron 並非 CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1 和 CYP3A4/5 的抑制劑（CYP2C19 未被探討），也不會誘發 CYP1A2, CYP2D6, 或 CYP3A4/5 的活性。所以，Palonosetron 產生臨床上重要之藥物交互作用的可能性很低。
併用 5-HT3 受體拮抗劑及其他血清素作用劑時，曾通報血清素症候群(包括精神狀態的變化、自律神經失調、神經肌肉的症狀)，包括選擇性血清素再吸收抑制劑(SSRIs), 正腎上腺素再回收抑制劑(SNRIs)(請參考警告與注意事項 5.2 節)
在健康受試者靜脈注射 0.25 毫克 palonosetron 及 20 毫克 dexamethasone，顯示 palonosetron 及 dexamethasone 併用時並無藥物動力學之交互作用。
在一個於健康受試者在第一天投與 0.25 毫克 palonosetron(靜脈輸注)及在第三天口服投與 aprepitant(125 毫克/80 毫克/80 毫克)，palonosetron 的藥物動力學沒有顯著改變(AUC: 沒變, Cmax: 增加 15%).
在一個健康受試者單一劑量靜脈投予 Palonosetron（0.75 毫克），並穩定口服 metoclopramide（10 毫克，一天四次）的研究中，證明無明顯的藥物動力的交互作用。
在對照的臨床實驗中，ALOXI 注射劑已安全地與腎上腺皮質類固醇，止痛劑，止吐劑/止噁心劑，抗痙攣藥劑和抗副交感神經藥劑合併使用。
在鼠科動物癌症模型（murine tumor models）中，Palonosetron 並未抑制五種測試之化學療法藥劑（cisplatin, cyclophosphamide, cytarabine, doxorubicin 和 mitomycin C）的抗癌活性。

8.【特殊族群使用】

懷孕

致畸性作用：B 類

風險摘要

在懷孕婦女身上 ALOXI 並沒有進行適當及良好控制的研究。在大白鼠及兔子的器官形成期以口服投予 Palonosetron 的動物生殖試驗，劑量高達人類建議靜脈投予的 1894 倍及 3789 倍，觀察到對胚胎-胎兒發育無影響。因為動物生殖試驗無法完全用以預測人類的反應，所以，在懷孕期間，ALOXI 只有確認需要時才可使用。
動物實驗數據

在動物實驗，在懷孕大白鼠的器官形成期以口服投予高達 60 毫克/公斤/天的 Palonosetron（約為根據體表面積所計算之人類建議靜脈投予劑量的 1894 倍）或在懷孕兔子的器官形成期以口服投予高達 60 毫克/公斤/天的 Palonosetron（約為根據體表面積所計算之人類建議靜脈投予劑量的 3789 倍），觀察到對胚胎-胎兒發育無影響。

哺乳的母親

目前仍未知 ALOXI 是否會存在乳汁中。由於許多藥物會分泌於乳汁中，可能對受乳的嬰兒產生嚴重不良的反應，以及 Palonosetron 在大白鼠致癌性試驗（參見第 13 節-非臨床毒理學）顯示可能導致產生腫瘤，因此，當考慮到藥物對母親的重要性時，須決定停止哺乳或停止服藥。

兒童與青少年使用

在一項有 165 位 2 個月大至 17 歲以下兒童與青少年癌症病患的臨床試驗，於開始致嘔性化學療法治療約 30 分鐘前，隨機靜脈輸注投予單一劑量 palonosetron 20 微公克/公斤(最大劑量不可超過 1.5 毫克)（參見第 14.2 節臨床試驗），這個試驗證明兒童與青少年癌症病患較成人病患需要較高劑量來預防化學療法誘發之噁心及嘔吐，其安全性與已確立之成人安全性一致（參見第 6.1 節副作用）。

在新生兒(小於 1 個月)之安全性與有效性並未確立。

老年人使用

65 歲以上與較年輕者（18 到 64 歲之間）的癌症病患在群體藥物動力學分析的數據並未顯示在 Palonosetron 藥物動力學兩者間有任何差異。在 Palonosetron 臨床試驗的 1374 位成人癌症病患中，316 位（23%）大於或等於 65 歲，71 位（5%）大於或等於 75 歲。在這些年長受試者和較年輕受試者之間沒有發現安全性或有效性上的差異，但是，不能排除在某些年長者有較高的敏感性。對年老的患者不須調整劑量或特別的監控。

腎功能不全

輕度到中度的腎功能不全不會明顯地影響 Palonosetron 的藥物動力學參數。嚴重腎功能不全的全身總暴露量（Total systemic exposure）與健康受試者相比，約增加 28%。任何程度的腎功能不全使用 Palonosetron 時，不須調整劑量。

肝功能不全

肝功能不全對於 Palonosetron 的全身廓清率，與健康受試者相較下並無顯著的影響。任何程度的肝功能不全使用 Palonosetron 時，不需調整劑量。

種族

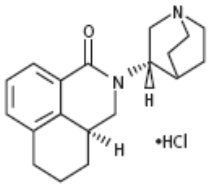
以 24 名健康的日本受試者投予劑量範圍 3~90 微克/公斤的 Palonosetron，來描述藥物動力學特性。日本人的全身廓清率雖然較白人高出 25%，但是，不需要調整劑量。黑人的藥物動力學分析數據則尚未完成。

10【過量】

目前沒有 ALOXI 的解毒劑。過量應以支持性照護加以處置。50 位成人癌症病患在一項劑量範圍研究中，投與 90 微克/公斤（相當於 6 毫克固定劑量）的 palonosetron。此一劑量約為建議劑量 0.25 毫克的 25 倍。這一劑量群組和其他劑量群組產生副作用的發生率相類似，而且沒有觀察到劑量-反應效力（dose response effects）。然而，因為分佈體積大，並未進行透析實驗。透析不是有效處理 palonosetron 過量的方法。靜脈投予單一劑量為 30 毫克/公斤的 palonosetron（根據體表面積，對於大白鼠和小白鼠而言，分別為人類劑量的 947 倍和 474 倍）對大白鼠和小白鼠是致命性的。主要的毒性症狀是痙攣、喘氣（gasping）、蒼白、發紺和虛脫。

11【簡述】

Aloxi（Palonosetron HCl）為一止吐劑與止噁心劑。它是一種高親合性的血清素亞型 3 受體（5-HT_3）拮抗劑。Palonosetron HCl 之化學式為（3a<u>S</u>)-2-[(<u>S</u>)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*benz[*de*]isoquinoline hydrochloride。分子式為 $C_{19}H_{24}N_2O \cdot HCl$，分子量為 332.87。Palonosetron HCl 為(s、s)型異構物，其結構式如下：



Palonosetron HCl 是一種白色或灰白色的晶體粉末。它能完全溶於水，能溶於丙二醇，微溶於乙醇與 2-丙醇。Aloxi 注射劑是一種供靜脈投予的無菌、清澈、無色、非熱原性的等張緩衝溶液。每一瓶 5 毫升的 ALOXI 注射劑含有 0.25 毫克 Palonosetron 鹼基，賦形劑: 207.5 毫克甘露醇（Mannitol），依地酸二鈉（Disodium Edetate）和【檸檬酸鈉緩衝劑（Citrate buffer）含檸檬酸鈉 sodium citrate 單水檸檬酸（citric acid monohydrate）】及水供靜脈投予。溶液 pH 值為 4.5 到 5.5。

12【臨床藥理學】

作用機轉

Palonosetron 是一種具高度親合性的 5-HT_3 受體拮抗劑，對其他受體幾乎沒有親合性。癌症的化學療法可能容易產生噁心和嘔吐的現象，尤其是使用 Cisplatin 之類的藥物。5-HT_3 受體分佈在腦極後區（area postrema）之化學接受感應區（CTZ）中心及迷走神經末梢上。一般認為化學療法藥物會促使小腸的腸嗜鉻性細胞釋放血清素，釋放出來的血清素接著活化位在迷走神經傳入神經（vagal afferents）的 5-HT_3 受體，啟動嘔吐反射，而造成噁心與嘔吐。

藥效學

在臨床實驗中，Palonosetron 對於血壓、心跳速率、和包括 QT_c 在內的心電圖參數的影響與 Ondansetron 及 Dolasetron

相似。在非臨床研究中，Palonosetron 擁有阻斷參與心室的去極化和再極化之離子通道的能力，進而延長動作電位時相。

在一個雙盲、隨機分配、平行、安慰劑及活性藥物(moxifloxacin)對照試驗，在成年男性與女性評估 Palonosetron 對 QTc 間隔的作用，該試驗目的是在 221 名健康受試者，單一劑量靜脈注射投予 0.25，0.75 或 2.25 毫克 palonosetron，以評估對心電圖的影響。此試驗證明，在劑量高達 2.25 毫克時，對任何心電圖間隔，包括 QTc 間隔（心臟再極化 cardiac repolarization）無顯著影響。

藥物動力學

健康的受試者和癌症病患靜脈投予 Palonosetron 後，血漿濃度隨著從體內緩慢地排泄掉而開始下降。在健康的受試者和癌症病患，投予劑量範圍在 0.3~90 微公克/公斤時，其平均最大血漿濃度（C_{max}）和濃度－時間曲線下的面積（$AUC_{0-\infty}$）與劑量成正比。追蹤以靜脈投予單一劑量為 3 微公克/公斤（或 0.21 毫克/70 公斤）Palonosetron 的六名癌症病患，其平均（±標準偏差 SD）最高血漿濃度約為 5630±5480ng 納克/升(ng/L)，而平均 AUC 為 35.8±20.9 小時 • 微克/升(h • mcg/L。

追蹤以一天一次，每隔一天靜脈投予 0.25 毫克 Palonosetron，共計 3 劑量在 11 位癌症病患， 從第一天到第五天，Palonosetron 之血漿濃度，平均增加 42±34%。

追蹤以靜脈投予 0.25 毫克 Palonosetron 一天一次共計三天，在 12 位健康的受試者，從第一天到第三天，Palonosetron 之血漿濃度，平均（±標準偏差 SD）增加 110±45%。

分佈

Palonosetron 的分佈體積約為 8.3±2.5 公升/公斤。將近 62%的 Palonosetron 是與血漿蛋白相結合的。

代謝

Palonosetron 可以透過不同的途徑排出體外，其中將近 50%代謝成為兩種主要的代謝產物：N-oxide-palonosetron 和 6-S-hydroxy-palonosetron。這些產物對於 5-HT_3 受體拮抗劑活性均低於 Palonosetron 的 1%。活體外代謝實驗顯示 Palonosetron 的代謝與 CYP2D6、及涉入程度較小的 CYP3A 和 CYP1A2 有關。然而在 CYP2D6 受酶質的弱代謝者（poor metabolizer）和強代謝者（extensive metabolizer）之間，臨床藥物動力學參數未有顯著差異。

排泄

以靜脈投予單一劑量為 10 微公克/公斤的[^{14}C]－palonosetron 後，將近 80%的劑量在 144 小時內會出現在尿液中，而接近 40%的投予劑量仍為 palonosetron。在健康受試者的全身廓清率為 0.160±0.035 升/小時/公斤，而腎臟廓清率為 0.067±0.018 升/小時/公斤。平均末端排泄半衰期約為 40 小時。

特殊族群-兒童與青少年

在兒童與青少年癌症患者，投與單一劑量靜脈注射 ALOXI 10 微克/公斤或 20 微克/公斤的藥物動力學數據顯示，當劑量從 10 微克/ kg 增加至 20 微克/公斤，平均 AUC 與劑量成比例增加。

單一劑量靜脈輸注 ALOXI，所有年齡組在 15 分鐘輸注結束時，其最高血漿濃度（CT）是高變異性的，<6 歲病患較老年患者低的傾向。

投與 20 微克/ kg 後，在整體年齡組平均半衰期為 29.5 小時，在各年齡組約介於 20 至 30 小時。12 歲到 17 歲患者其總清除率 clearance(L/h/kg)，與健康的成年人相似。在分佈體積(以 L/kg 表示)無明顯的差異。

表 2 在兒童與青少年癌症患者，靜脈投與 ALOXI 20 微克/公斤輸注超過 15 分鐘的藥物動力學參數

藥物動力學參數[a]	兒童與青少年族群			
	<2 y	2 to <6 y	6 to <12 y	12 to <17 y
	N=12	N=42	N=38	N=44
CT[b], ng/L	9025 (197)	9414 (252)	16275 (203)	11831 (176)
		N=5	N=7	N=10
$AUC_{0-\infty}$, h·mcg/L		103.5 (40.4)	98.7 (47.7)	124.5 (19.1)
	N=6	N=14	N=13	N=19
Clearance[c], L/h/kg	0.31 (34.7)	0.23 (51.3)	0.19 (46.8)	0.16 (27.8)
Vss[c], L/kg	6.08 (36.5)	5.29 (57.8)	6.26 (40.0)	6.20 (29.0)

[a] 幾何平均值（CV）

[b] 為 15 分鐘輸注結束時 palonosetron 的血漿濃度

[c] 廓清率和 Vss 計算是從 10 微公克/公斤及 20 微克/公斤以體重調整

13【非臨床毒理學】

以 CD-1 小白鼠進行的一項為期 104 週的致癌性試驗中，受試動物分別口服劑量為 10，30 和 60 毫克/公斤/天的 Palonosetron。投與 Palonosetron 並未導致產生腫瘤。實驗所用之最高劑量產生對 Palonosetron 的全身性曝露值（systemic exposure）（血漿 AUC）約為人類投與 0.25 毫克之建議靜脈注射劑量產生的曝露值（AUC＝29.8 h•mcg/L）的 150 到 289 倍。以 Sprague-Dawley rats 進行的一項為期 104 週的致癌性研究中，雄性與雌性大白鼠以口服方式分別投與劑量為 15，30 和 60 毫克/公斤/天和 15，45 和 90 毫克/公斤/天的 Palonosetron。最高劑量產生對 Palonosetron 的全身性曝露值（血漿 AUC）約為人類投與建議靜脈注射劑量產生的曝露值的 137 和 308 倍。雄性大白鼠投與 Palonosetron，會增加腎上腺良性嗜鉻細胞瘤與合併良性及惡性嗜鉻細胞瘤的發生率，提高胰島細胞腺瘤與合併腺瘤及癌瘤和腦下垂體腺瘤的發生率。在雌性大白鼠身上，則會產生肝細胞腺瘤與癌瘤，並增加甲狀腺 C 細胞腺瘤及合併腺

瘤與癌瘤的發生率。
Palonosetron 在安姆氏試驗(Ames test)試驗，中國倉鼠卵巢細胞（CHO/HGPRT）正向突變試驗，體外（*ex vivo*）肝細胞非程式 DNA 合成（UDS）試驗或小白鼠微核試驗，都顯示沒有基因毒性。然而，在中國倉鼠卵巢細胞（CHO）之細胞染色體異常試驗中，卻呈現陽性反應斷裂作用（clastogenic effects）。
口服投與高達 60 毫克/公斤/天的 Palonosetron（約為根據體表面積所計算之人類建議靜脈投予劑量的 1894 倍）對於雄性與雌性大白鼠的生育繁殖能力沒有影響。

14【臨床試驗】

成人化學療法所引發之的噁心與嘔吐

三個第三期臨床試驗和一個第二期臨床試驗，曾研究以靜脈投予單一劑量的 Palonosetron 預防中度及高度致嘔性化學療法所引發之急性與延遲的噁心與嘔吐的效力。在這些雙盲性實驗中，評估完整的反應速率（無嘔吐現象與救援治療）和其他效力參數在投予化學療法藥劑後，至少追蹤 120 小時。Palonosetron 在化學療法之反覆療程中的安全性和效力也被研究。

中度致嘔性化學療法

以 1132 位病患所進行的兩個第三期雙盲性臨床實驗，比較在投與包括 carboplatin, cisplatin≦50 毫克/m^2，cyclophosphamide＜1500 毫克/m^2， doxorubicin＞25 毫克/m^2, epirubicin，irinotecan 和 methotrexate＞250 毫克/m^2 等中度致嘔性化學療法藥劑之前 30 分鐘，以單一劑量靜脈注射 ALOXI 和 ondansetron（研究一）或 dolasetron（研究二）的效力。研究一中並未預防性地同時投予腎上腺皮質類固醇，而研究二中只有 4%到 6%的病人使用。這些研究中多數病患為女性（77%），白人（65%）以及先前未接受過化學治療（54%）。其平均年齡為 55 歲。

高度致嘔性化學療法

一項以 161 名未曾接受化學療法之成人癌症患者為對象的第二期雙盲性/劑量-範圍研究之臨床實驗，評估以靜脈注射單一劑量從 0.3 到 90 微克/公斤（相當於小於 0.1 毫克到 6 毫克固定劑量）之間的 Palonosetron，對於接受高度致嘔性化學療法藥物（cisplatin≧70 毫克/m^2 或 cyclophosphamide＞1100 毫克/m^2）治療之患者的效力。腎上腺皮質類固醇並未預防性地同時投予。這項實驗的數據分析顯示：避免由高度致嘔性化學療法所引起的急性噁心與嘔吐的最低有效劑量為 0.25 毫克。
一項以 667 位病患進行的第三期雙盲性臨床實驗，比較在使用包含 cisplatin≧60 毫克/m^2，cyclophosphamide＞1500 毫克/m^2 和 dacarbazine 等高度致嘔性化學療法前 30 分鐘以靜脈注射單一劑量之 ALOXI 和 ondansetron 的結果（研究 3）。67%的病患在化學治療前，曾預防性地同時投予腎上腺皮質類固醇。在 667 位病患中，51%是女性，60%是白人，59%未曾接受過化學療法。其平均年齡為 52 歲。

療效結果

在第三期臨床試驗中，ALOXI 的止吐活性，在投與化學治療藥物後的急性期（0 至 24 小時）〔表 3〕、延遲期（24 至 120 小時）〔表 4〕和全程期（0 至 120 小時）〔表 5〕被評估。

表 3：預防急性的噁心與嘔吐（0 至 24 小時）：完整的反應速率

化學療法	研究	治療組	個數 [a]	相對於完整反應之%	p-值 [b]	97.5%信賴區間 ALOXI 減比較組 [c]
中度致嘔性	1	ALOXI 0.25 毫克	189	81	0.009	〔2%,23%〕
		Ondansetron 32 毫克 靜脈注射	185	69		
	2	ALOXI 0.25 毫克	189	63	NS	〔-2%,22%〕
		Dolasetron 100 毫克 靜脈注射	191	53		
高度致嘔性	3	ALOXI 0.25 毫克	223	59	NS	〔-9%,13%〕
		Ondansetron 32 毫克 靜脈注射	221	57		

[a] 計畫接受治療者（intent-to-treat cohort）。
[b] 2-sided Fisher's exact test。顯著水準（significance level）為 α＝0.025。
[c] 這些實驗以證明非次等性（non-inferiority）來設計。比-15%大的下限值證明 ALOXI 與比較組之間的非次等性。

這些研究顯示 ALOXI 能有效預防中度和高度致嘔性癌症化學療法之起始及反覆療程所產生之急性噁心與嘔吐。研究 3 中，當併用預防性腎上腺皮質類固醇時更為有效。在急性期並未充分顯示比其他 5-HT_3 受體拮抗劑更好的臨床療效。

表 4：預防延遲的噁心與嘔吐（24 至 120 小時）：完整的反應速率

化學療法	研究	治療組	個數 [a]	相對於完整反應之%	p-值 [b]	97.5%信賴區間 ALOXI 減比較組 [c]
中度致	1	ALOXI 0.25 毫克	189	74	＜0.001	〔8%,30%〕
		Ondansetron 32 毫克 靜脈注射	185	55		

嘔性	2	ALOXI 0.25 毫克	189	54	0.004	〔3%,27%〕
		Dolasetron 100 毫克 靜脈注射	191	39		

a 計畫接受治療者（intent-to-treat cohort）。
b 2-sided Fisher's exact test。顯著水準（significance level）為 α＝0.025。
c 這些實驗以證明非次等性（non-inferiority）來設計。比-15%大的下限值證明 ALOXI 與比較組之間的非次等性。

這些研究顯示 ALOXI 能有效預防中度致嘔性癌症化學療法之起始及反覆療程所產生之延遲性噁心與嘔吐。

表 5：預防全程的噁心與嘔吐（0 至 120 小時）：完整的反應速率

化學療法	研究	治療組	個數 [a]	相對於完整反應之%	p-值 [b]	97.5%信賴區間 ALOXI 減比較組 [c]
中度致嘔性	1	ALOXI 0.25 毫克	189	69	＜0.001	〔7%,31%〕
		Ondansetron 32 毫克 靜脈注射	185	50		
	2	ALOXI 0.25 毫克	189	46	0.021	〔0%,24%〕
		Dolasetron 靜脈注射 100 毫克	191	34		

[a] 計畫接受治療者（intent-to-treat cohort）。
[b] 2-sided Fisher's exact test。顯著水準（significance level）為 α＝0.025。
[c] 這些實驗以證明非次等性（non-inferiority）來設計。比-15%大的下限值證明 ALOXI 與比較組之間的非次等性。

這些研究顯示：中度致嘔性癌症化學療法之起始及反覆療程後 120 小時（5 天）中，ALOXI 能有效預防噁心與嘔吐。

兒童與青少年化學療法所引發之噁心與嘔吐

在一項雙盲、使用活性藥物對照、於兒童與青少年癌症患者的臨床試驗，收納病人(N = 327)的平均年齡為8.3歲（範圍為2個月至16.9歲），53%為男性和96%的白人。
在開始投與致嘔性化療藥物30分鐘前，病患隨機靜脈輸注投於palonosetron 20微克/公斤(最大劑量不可超過1.5毫克)(在投與palonosetron後4及8小時接著輸注安慰劑)或在開始投與致嘔性化療藥物30分鐘前，靜脈注射投於0.15毫克/公斤ondansetron(在第一劑ondansetron4至8小時之後，接著輸注0.15毫克/公斤ondansetron，最大劑量不可超過32毫克)
投與的致嘔性化療藥物包括doxorubicin, cyclophosphamide (<1500 mg/m^2), ifosfamide, cisplatin, dactinomycin, carboplatin, 及daunorubicin。55%病患在化療時，有投與輔助性藥物corticosteroids,包括 dexamethasone。
在化療的第一個週期急性期之完全反應的定義為，開始化療後的最初24小時無嘔吐，無乾嘔，且無使用救援或救助藥物。
以靜脈投於palonosetron相較於靜脈注射ondansetron為非次等性（non-inferiority）來證明療效。
非次等性（non-inferiority）的符合要件是，靜脈注射palonosetron減去靜脈ondansetron的完全反應率差異的97.5%的信賴區間之下限需大於-15%。非次等性（non-inferiority）的界限為15%。

療效結果

如表 6 中所示，靜脈投與 ALOXI20 微克/公斤(最大劑量不可超過 1.5 毫克)，證明在 0 至 24 小時之間相較對照之活性藥物為非次等性（non-inferiority）的。

表 6 預防急性的噁心與嘔吐（0 至 24 小時）：完整的反應速率

靜脈投與ALOXI 20微克/公斤 (N=165)	靜脈投與 Ondansetron 0.15毫克/公斤x3 (N=162)	97.5%信賴區間 ALOXI 減比較組 Ondansetron 的差異
59.4%	58.6%	0.36% [-11.7%, 12.4%]

為調整治療組的多樣性，非次等性（non-inferiority）的界限為負值，常以-15%作為97.5%的信賴區間比較範圍的下限。
當病患投於ALOXI低於建議劑量20 mcg/kg 時，並未符合非次等性（non-inferiority）的要件。

16【包裝/儲存/運輸】

0.25 毫克/5 毫升（free base），單次使用玻璃瓶紙盒包裝
儲存
儲存於溫度 25°C 以下
允許短期儲存於 15~30°C（59~86°F）。
避免冷凍
避免光照。

Bulk manufacture and primary packaging:

廠名：FAREVA PAU 1
廠址：Avenue de Bearn 64320 Idron France
Secondary packaging and release：
廠名：Helsinn Birex Pharmaceutical Ltd
廠址：Damastown, Mulhuddart, Dublin 15, Ireland
藥 商：和聯生技藥業股份有限公司
地 址：台北市敦化北路311號

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Chemotherapy-Induced Nausea and Vomiting in Adults

ALOXI is indicated for:

- Moderately emetogenic cancer chemotherapy -- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses
- Highly emetogenic cancer chemotherapy -- prevention of acute nausea and vomiting associated with initial and repeat courses

1.2 Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients Aged 1 month to Less than 17 Years

ALOXI is indicated for prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy.

1.3 Postoperative Nausea and Vomiting in Adults

ALOXI is indicated for prevention of postoperative nausea and vomiting (PONV) for up to 24 hours following surgery. Efficacy beyond 24 hours has not been demonstrated.

As with other antiemetics, routine prophylaxis is not recommended in patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and vomiting must be avoided during the postoperative period, ALOXI is recommended even where the incidence of postoperative nausea and/or vomiting is low.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

Chemotherapy-Induced Nausea and Vomiting

Age	Dose*	Infusion Time
Adults	**0.25 mg** x 1	Infuse over **30 seconds** beginning approx. 30 min before the start of chemo
Pediatrics (1 month to less than 17 years)	**20 micrograms per kilogram** (max 1.5 mg) x 1	Infuse over **15 minutes** beginning approx. 30 min before the start of chemo

*Note different dosing units in pediatrics

Postoperative Nausea and Vomiting

Dosage for Adults - a single 0.075 mg intravenous dose administered over 10 seconds immediately before the induction of anesthesia.

2.2 Instructions for Intravenous Administration

ALOXI is supplied ready for intravenous administration at a concentration of 0.05 mg/mL (50 mcg/ mL). ALOXI should not be mixed with other drugs. The infusion line should be flushed with normal saline before and after administration of ALOXI. Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

3 DOSAGE FORM AND STRENGTHS

ALOXI is supplied as a single-use sterile, clear, colorless solution in glass vials that provide:

- 0.25 mg (free base) per 5 mL (concentration: 0.05 mg/mL, 50 mcg/mL)
- 0.075 mg (free base) per 1.5 mL (concentration: 0.05 mg/mL, 50 mcg/mL)

4 CONTRAINDICATIONS

ALOXI is contraindicated in patients known to have hypersensitivity to the drug or any of its components. [*see Adverse Reactions (6.2)*]

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions, including anaphylaxis, have been reported with or without known hypersensitivity to other 5-HT_3 receptor antagonists.

5.2 Serotonin Syndrome

The development of serotonin syndrome has been reported with 5-HT3 receptor antagonists. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of another 5-HT3 receptor antagonist alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT3 receptor antagonist use occurred in a post-anesthesia care unit or an infusion center.

Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g. agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of Aloxi and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue Aloxi and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if Aloxi is used concomitantly with other serotonergic drugs [*see Drug Interactions (7), Patient Counseling Information (17)*].

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Chemotherapy-Induced Nausea and Vomiting

Adults

In clinical trials for the prevention of nausea and vomiting induced by moderately or highly emetogenic chemotherapy, 1374 adult patients received palonosetron. Adverse reactions were similar in frequency and severity with ALOXI and ondansetron or dolasetron. Following is a listing of all adverse reactions reported by ≥ 2% of patients in these trials (Table 1).

Table 1: Adverse Reactions from Chemotherapy-Induced Nausea and Vomiting Studies ≥ 2% in any Treatment Group

Event	Aloxi 0.25 mg (N=633)	Ondansetron 32 mg I.V. (N=410)	Dolasetron 100 mg I.V. (N=194)
Headache	60 (9%)	34 (8%)	32 (16%)
Constipation	29 (5%)	8 (2%)	12 (6%)
Diarrhea	8 (1%)	7 (2%)	4 (2%)
Dizziness	8 (1%)	9 (2%)	4 (2%)
Fatigue	3 (< 1%)	4 (1%)	4 (2%)
Abdominal Pain	1 (< 1%)	2 (< 1%)	3 (2%)
Insomnia	1 (< 1%)	3 (1%)	3 (2%)

In other studies, 2 subjects experienced severe constipation following a single palonosetron dose of approximately 0.75 mg, three times the recommended dose. One patient received a 10 mcg/kg oral dose in a post-operative nausea and vomiting study and one healthy subject received a 0.75 mg I.V. dose in a pharmacokinetic study.

In clinical trials, the following infrequently reported adverse reactions, assessed by investigators as treatment-related or causality unknown, occurred following administration of ALOXI to adult patients receiving concomitant cancer chemotherapy:

Cardiovascular**:** 1%: non-sustained tachycardia, bradycardia, hypotension, < 1%: hypertension, myocardial ischemia, extrasystoles, sinus tachycardia, sinus arrhythmia, supraventricular extrasystoles and QT prolongation. In many cases, the relationship to ALOXI was unclear.

Dermatological: < 1%: allergic dermatitis, rash.

Hearing and Vision: < 1%: motion sickness, tinnitus, eye irritation and amblyopia.

Gastrointestinal System: 1%: diarrhea, < 1%: dyspepsia, abdominal pain, dry mouth, hiccups and flatulence.

General: 1%: weakness, < 1%: fatigue, fever, hot flash, flu-like syndrome.

Liver: < 1%: transient, asymptomatic increases in AST and/or ALT and bilirubin. These changes occurred predominantly in patients receiving highly emetogenic chemotherapy.

Metabolic: 1%: hyperkalemia, < 1%: electrolyte fluctuations, hyperglycemia, metabolic acidosis, glycosuria, appetite decrease, anorexia.

Musculoskeletal: < 1%: arthralgia.

Nervous System: 1%: dizziness, < 1%: somnolence, insomnia, hypersomnia, paresthesia.

Psychiatric: 1%: anxiety, < 1%: euphoric mood.

Urinary System: < 1%: urinary retention.

Vascular: < 1%: vein discoloration, vein distention.

Pediatrics

In a pediatric clinical trial for the prevention of chemotherapy-induced nausea and vomiting 163 cancer patients received a single 20 mcg/kg (maximum 1.5 mg) intravenous infusion of palonosetron 30 minutes before beginning the first cycle of emetogenic chemotherapy. Patients had a mean age of 8.4 years (range 2 months to 16.9 years) and were 46% male; and 93% white.

The following adverse reactions were reported for palonosetron:

Nervous System: <1%: headache, dizziness, dyskinesia.

General: <1%: infusion site pain.

Dermatological: <1%: allergic dermatitis, skin disorder.

In the trial, adverse reactions were evaluated in pediatric patients receiving palonosetron for up to 4 chemotherapy cycles.

6.2 Postoperative Nausea and Vomiting

The adverse reactions cited in Table 2 were reported in ≥ 2% of adults receiving I.V. Aloxi 0.075 mg immediately before induction of anesthesia in one phase 2 and two phase 3 randomized placebo-controlled trials. Rates of events between palonosetron and placebo groups were similar. Some events are known to be associated with, or may be exacerbated by concomitant perioperative and intraoperative medications administered in this surgical population. Please refer to Section 12.2, thorough QT/QTc study results, for data demonstrating the lack of palonosetron effect on QT/QTc.

Table 2: Adverse Reactions from Postoperative Nausea and Vomiting Studies ≥ 2% in any Treatment Group

Event	Aloxi 0.075 mg (N=336)	Placebo (N=369)
Electrocardiogram QT prolongation	16 (5%)	11 (3%)
Bradycardia	13 (4%)	16 (4%)
Headache	11 (3%)	14 (4%)
Constipation	8 (2%)	11(3%)

In these clinical trials, the following infrequently reported adverse reactions, assessed by investigators as treatment-related or causality unknown, occurred following administration of ALOXI to adult patients receiving concomitant perioperative and intraoperative medications including those associated with anesthesia:

Cardiovascular: 1%: electrocardiogram QTc prolongation, sinus bradycardia, tachycardia, < 1%: blood pressure decreased, hypotension, hypertension, arrhythmia, ventricular extrasystoles, generalized edema, ECG T wave amplitude decreased, platelet count decreased. The frequency of these adverse effects did not appear to be different from placebo.

Dermatological: 1%: pruritus.

Gastrointestinal System: 1%: flatulence, < 1%: dry mouth, upper abdominal pain, salivary hypersecretion, dyspepsia, diarrhea, intestinal hypomotility, anorexia.

General: < 1%: chills.

Liver: 1%: increases in AST and/or ALT, < 1%: hepatic enzyme increased.

Metabolic: < 1%: hypokalemia, anorexia.

Nervous System: < 1%: dizziness.

Respiratory: < 1%: hypoventilation, laryngospasm.

Urinary System: 1%: urinary retention.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of ALOXI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Very rare cases (<1/10,000) of hypersensitivity reactions including anaphylaxis and anaphylactic shock and injection site reactions (burning, induration, discomfort and pain) were reported from postmarketing experience of ALOXI 0.25 mg in the prevention of chemotherapy-induced nausea and vomiting.

7 DRUG INTERACTIONS

Palonosetron is eliminated from the body through both renal excretion and metabolic pathways with the latter mediated via multiple CYP enzymes. Further *in vitro* studies indicated that palonosetron is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4/5 (CYP2C19 was not investigated) nor does it induce the activity of CYP1A2, CYP2D6, or CYP3A4/5. Therefore, the potential for clinically significant drug interactions with palonosetron appears to be low.

Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT3 receptor antagonists and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) [*see Warnings and Precautions (5.2)*].

Coadministration of 0.25 mg I.V. palonosetron and 20 mg I.V. dexamethasone in healthy subjects revealed no pharmacokinetic drug-interactions between palonosetron and dexamethasone.

In an interaction study in healthy subjects where palonosetron 0.25 mg (I.V. bolus) was administered on day 1 and oral aprepitant for 3 days (125 mg/80 mg/80 mg), the pharmacokinetics of palonosetron were not significantly altered (AUC: no change, Cmax: 15% increase).

A study in healthy volunteers involving single-dose I.V. palonosetron (0.75 mg) and steady state oral metoclopramide (10 mg four times daily) demonstrated no significant pharmacokinetic interaction.

In controlled clinical trials, ALOXI injection has been safely administered with corticosteroids, analgesics, antiemetics/antinauseants, antispasmodics and anticholinergic agents.

Palonosetron did not inhibit the antitumor activity of the five chemotherapeutic agents tested (cisplatin, cyclophosphamide, cytarabine, doxorubicin and mitomycin C) in murine tumor models.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

Adequate and well controlled studies with ALOXI have not been conducted in pregnant women. In animal reproduction studies, no effects on embryo-fetal development were observed with the administration of oral palonosetron during the period of organogenesis at doses up to 1894 and 3789 times the recommended human intravenous dose in rats and rabbits, respectively. Because animal reproduction studies are not always predictive of human response, ALOXI should be used during pregnancy only if clearly needed.

Animal Data

In animal studies, no effects on embryo-fetal development were observed in pregnant rats given oral palonosetron at doses up to 60 mg/kg/day (1894 times the recommended human intravenous dose based on body surface area) or pregnant rabbits given oral doses up to 60 mg/kg/day (3789 times the recommended human intravenous dose based on body surface area) during the period of organogenesis.

8.3 Nursing Mothers

It is not known whether ALOXI is present in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants and the potential for tumorigenicity shown for palonosetron in the rat carcinogenicity study *[*see *Nonclinical Toxicology (13.1)]*, 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.

8.4 Pediatric Use

Chemotherapy-Induced Nausea and Vomiting

Safety and effectiveness of ALOXI have been established in pediatric patients aged 1 month to less than 17 years for the prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy. Use is supported by a clinical trial where 165 pediatric patients aged 2 months to <17 years were randomized to receive a single dose of palonosetron 20 mcg/kg (maximum 1.5 mg) administered as an intravenous infusion 30 minutes prior to the start of emetogenic chemotherapy [*see Clinical Studies (14.2)]*. While this study demonstrated that pediatric patients require a higher palonosetron dose than adults to prevent chemotherapy-induced nausea and vomiting, the safety profile is consistent with the established profile in adults [*see Adverse Reactions (6.1)]*.

Safety and effectiveness of ALOXI in neonates (less than 1 month of age) have not been established.

Postoperative Nausea and Vomiting Studies

Safety and efficacy have not been established in pediatric patients for prevention of postoperative nausea and vomiting. Two pediatric trials were performed.

Pediatric Study 1, a dose finding study was conducted to compare two doses of palonosetron, 1 mcg/kg (max 0.075 mg) versus 3 mcg/kg (max 0.25 mg). A total of 150 pediatric surgical patients participated, age range 1 month to <17 years. No dose response was observed.

Pediatric Study 2, a multicenter, double-blind, double-dummy, randomized, parallel group, active control, single-dose non-inferiority study, compared I.V. palonosetron (1 mcg/kg, max 0.075 mg) versus I.V. ondansetron. A total of 670 pediatric surgical patients participated, age 30 days to <17 years. The primary efficacy endpoint, Complete Response (CR: no vomiting, no retching, and no antiemetic rescue medication) during the first 24 hours postoperatively was achieved in 78.2% of patients in the palonosetron group and 82.7% in the ondansetron group. Given the pre-specified non-inferiority margin of -10%, the stratum adjusted Mantel-Haenszel statistical non-inferiority confidence interval for the difference in the primary endpoint, complete response (CR), was [-10.5, 1.7%], therefore non-inferiority was not demonstrated. Adverse reactions to palonosetron were similar to those reported in adults (see Table 2).

8.5 Geriatric Use

Population pharmacokinetics analysis did not reveal any differences in palonosetron pharmacokinetics between cancer patients ≥ 65 years of age and younger patients (18 to 64 years). Of the 1374 adult cancer patients in clinical studies of palonosetron, 316 (23%) were ≥ 65 years old, while 71 (5%) were ≥ 75 years old. No overall differences in safety or effectiveness were observed between these subjects and the younger subjects, but greater sensitivity in some older individuals cannot be ruled out. No dose adjustment or special monitoring are required for geriatric patients.

Of the 1520 adult patients in Aloxi PONV clinical studies, 73 (5%) were ≥65 years old. No overall differences in safety were observed between older and younger subjects in these studies, though the possibility of heightened sensitivity in some older individuals cannot be excluded. No differences in efficacy were observed in geriatric patients for the CINV indication and none are expected for geriatric PONV patients. However, Aloxi efficacy in geriatric patients has not been adequately evaluated.

8.6 Renal Impairment

Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. Total systemic exposure increased by approximately 28% in severe renal impairment relative to healthy subjects. Dosage adjustment is not necessary in patients with any degree of renal impairment.

8.7 Hepatic Impairment

Hepatic impairment does not significantly affect total body clearance of palonosetron compared to the healthy subjects. Dosage adjustment is not necessary in patients with any degree of hepatic impairment.

8.8 Race

Intravenous palonosetron pharmacokinetics was characterized in twenty-four healthy Japanese subjects over the dose range of 3 – 90 mcg/kg. Total body clearance was 25% higher in Japanese subjects compared to Whites, however, no dose adjustment is required. The pharmacokinetics of palonosetron in Blacks has not been adequately characterized.

10 OVERDOSAGE

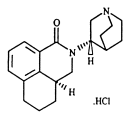
There is no known antidote to ALOXI. Overdose should be managed with supportive care.

Fifty adult cancer patients were administered palonosetron at a dose of 90 mcg/kg (equivalent to 6 mg fixed dose) as part of a dose ranging study. This is approximately 25 times the recommended dose of 0.25 mg. This dose group had a similar incidence of adverse events compared to the other dose groups and no dose response effects were observed.

Dialysis studies have not been performed, however, due to the large volume of distribution, dialysis is unlikely to be an effective treatment for palonosetron overdose. A single intravenous dose of palonosetron at 30 mg/kg (947 and 474 times the human dose for rats and mice, respectively, based on body surface area) was lethal to rats and mice. The major signs of toxicity were convulsions, gasping, pallor, cyanosis and collapse.

11 DESCRIPTION

ALOXI (palonosetron hydrochloride) is an antiemetic and antinauseant agent. It is a serotonin-3 (5-HT_3) receptor antagonist with a strong binding affinity for this receptor. Chemically, palonosetron hydrochloride is: (3a<u>S</u>)-2-[(<u>S</u>)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*benz[*de*]isoquinoline hydrochloride. The empirical formula is $C_{19}H_{24}N_2O.HCl$, with a molecular weight of 332.87. Palonosetron hydrochloride exists as a single isomer and has the following structural formula:



Palonosetron hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, soluble in propylene glycol, and slightly soluble in ethanol and 2-propanol.

ALOXI injection is a sterile, clear, colorless, non pyrogenic, isotonic, buffered solution for intravenous administration. ALOXI injection is available as 5 mL single use vial or 1.5 mL single use vial. Each 5 mL vial contains 0.25 mg palonosetron base as 0.28 mg palonosetron hydrochloride, 207.5 mg mannitol, disodium edetate and citrate buffer in water for intravenous administration.

Each 1.5 mL vial contains 0.075 mg palonosetron base as 0.084 mg palonosetron hydrochloride, 83 mg mannitol, disodium edetate and citrate buffer in water for intravenous administration.

The pH of the solution in the 5 mL and 1.5 mL vials is 4.5 to 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Palonosetron is a 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors.

Cancer chemotherapy may be associated with a high incidence of nausea and vomiting, particularly when certain agents, such as cisplatin, are used. 5-HT_3 receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. It is thought that chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine and that the released serotonin then activates 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex.

Postoperative nausea and vomiting is influenced by multiple patient, surgical and anesthesia related factors and is triggered by release of 5-HT in a cascade of neuronal events involving both the central nervous system and the gastrointestinal tract. The 5-HT_3 receptor has been demonstrated to selectively participate in the emetic response.

12.2 Pharmacodynamics

The effect of palonosetron on blood pressure, heart rate, and ECG parameters including QTc were comparable to ondansetron and dolasetron in CINV clinical trials. In PONV clinical trials the effect of palonosetron on the QTc interval was no different from placebo. In non-clinical studies palonosetron possesses the ability to block ion channels involved in ventricular de- and re-polarization and to prolong action potential duration.

The effect of palonosetron on QTc interval was evaluated in a double blind, randomized, parallel, placebo and positive (moxifloxacin) controlled trial in adult men and women. The objective was to evaluate the ECG effects of I.V. administered palonosetron at single doses of 0.25, 0.75 or 2.25 mg in 221 healthy subjects. The study demonstrated no significant effect on any ECG interval including QTc duration (cardiac repolarization) at doses up to 2.25 mg.

12.3 Pharmacokinetics

After intravenous dosing of palonosetron in healthy subjects and cancer patients, an initial decline in plasma concentrations is followed by a slow elimination from the body. Mean maximum plasma concentration (C_{max}) and area under the concentration-time curve ($AUC_{0-\infty}$) are generally dose-proportional over the dose range of 0.3–90 mcg/kg in healthy subjects and in cancer patients. Following single I.V. dose of palonosetron at 3 mcg/kg (or 0.21 mg/70 kg) to six cancer patients, mean (±SD) maximum plasma concentration was estimated to be 5630 ± 5480 ng/L and mean AUC was 35.8 ± 20.9 h•mcg/L.

Following I.V. administration of palonosetron 0.25 mg once every other day for 3 doses in 11 cancer patients, the mean increase in plasma palonosetron concentration from Day 1 to Day 5 was 42±34%. Following I.V. administration of palonosetron 0.25 mg once daily for 3 days in 12 healthy subjects, the mean (±SD) increase in plasma palonosetron concentration from Day 1 to Day 3 was 110±45%.

After intravenous dosing of palonosetron in patients undergoing surgery (abdominal surgery or vaginal hysterectomy), the pharmacokinetic characteristics of palonosetron were similar to those observed in cancer patients.

Distribution

Palonosetron has a volume of distribution of approximately 8.3 ± 2.5 L/kg. Approximately 62% of palonosetron is bound to plasma proteins.

Metabolism

Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palonosetron and 6-S-hydroxy-palonosetron. These metabolites each have less than 1% of the 5-HT_3 receptor antagonist activity of palonosetron. *In vitro* metabolism studies have suggested that CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates.

Elimination

After a single intravenous dose of 10 mcg/kg [^{14}C]-palonosetron, approximately 80% of the dose was recovered within 144 hours in the urine with palonosetron representing approximately 40% of the administered dose. In healthy subjects, the total body clearance of palonosetron was 0.160 ± 0.035 L/h/kg and renal clearance was 0.067± 0.018 L/h/kg. Mean terminal elimination half-life is approximately 40 hours.

Specific populations

Pediatric Patients

Single-dose I.V. ALOXI pharmacokinetic data was obtained from a subset of pediatric cancer patients that received 10 mcg/kg or 20 mcg/kg. When the dose was increased from 10 mcg/kg to 20 mcg/kg a dose-proportional increase in mean AUC was observed. Following single dose intravenous infusion of Aloxi 20 mcg/kg, peak plasma concentrations (C_T) reported at the end of the 15 minute infusion were highly variable in all age groups and tended to be lower in patients < 6 years than in older patients. Median half-life was 29.5 hours in overall age groups and ranged from about 20 to 30 hours across age groups after administration of 20 mcg/kg.

The total body clearance (L/h/kg) in patients 12 to 17 years old was similar to that in healthy adults. There are no apparent differences in volume of distribution when expressed as L/kg.

Table 3: Pharmacokinetics Parameters in Pediatric Cancer Patients following intravenous infusion of ALOXI at 20 mcg/kg over 15 min

PK Parameter [a]	Pediatric Age Group			
	<2 y	2 to <6 y	6 to <12 y	12 to <17 y
	N=12	N=42	N=38	N=44
C_T [b], ng/L	9025 (197)	9414 (252)	16275 (203)	11831 (176)
		N=5	N=7	N=10
$AUC_{0-\infty}$, h·mcg/L		103.5 (40.4)	98.7 (47.7)	124.5 (19.1)
	N=6	N=14	N=13	N=19
Clearance [c], L/h/kg	0.31 (34.7)	0.23 (51.3)	0.19 (46.8)	0.16 (27.8)
Vss [c], L/kg	6.08 (36.5)	5.29 (57.8)	6.26 (40.0)	6.20 (29.0)

a Geometric Mean (CV) except for t1/2 which is median values .
b C_T is the plasma palonosetron concentration at the end of the 15 minute infusion.
c Clearance and Vss calculated from 10 and 20 mcg/kg and are weight adjusted

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week carcinogenicity study in CD-1 mice, animals were treated with oral doses of palonosetron at 10, 30 and 60 mg/kg/day. Treatment with palonosetron was not tumorigenic. The highest tested dose produced a systemic exposure to palonosetron (Plasma AUC) of about 150 to 289 times the human exposure (AUC= 29.8 h•mcg/L) at the recommended intravenous dose of 0.25 mg. In a 104-week carcinogenicity study in Sprague-Dawley rats, male and female rats were treated with oral doses of 15, 30 and 60 mg/kg/day and 15, 45 and 90 mg/kg/day, respectively. The highest doses produced a systemic exposure to palonosetron (Plasma AUC) of 137 and 308 times the human exposure at the recommended dose. Treatment with palonosetron produced increased incidences of adrenal benign pheochromocytoma and combined benign and malignant pheochromocytoma, increased incidences of pancreatic Islet cell adenoma and combined adenoma and carcinoma and pituitary adenoma in male rats. In female rats, it produced hepatocellular adenoma and carcinoma and increased the incidences of thyroid C-cell adenoma and combined adenoma and carcinoma.

Palonosetron was not genotoxic in the Ames test, the Chinese hamster ovarian cell (CHO/HGPRT) forward mutation test, the *ex vivo* hepatocyte unscheduled DNA synthesis (UDS) test or the mouse micronucleus test. It

was, however, positive for clastogenic effects in the Chinese hamster ovarian (CHO) cell chromosomal aberration test.

Palonosetron at oral doses up to 60 mg/kg/day (about 1894 times the recommended human intravenous dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

14 CLINICAL STUDIES

14.1 Chemotherapy-Induced Nausea and Vomiting in Adults

Efficacy of single-dose palonosetron injection in preventing acute and delayed nausea and vomiting induced by both moderately and highly emetogenic chemotherapy was studied in three Phase 3 trials and one Phase 2 trial. In these double-blind studies, complete response rates (no emetic episodes and no rescue medication) and other efficacy parameters were assessed through at least 120 hours after administration of chemotherapy. The safety and efficacy of palonosetron in repeated courses of chemotherapy was also assessed.

Moderately Emetogenic Chemotherapy

Two Phase 3, double-blind trials involving 1132 patients compared single-dose I.V. ALOXI with either single-dose I.V. ondansetron (study 1) or dolasetron (study 2) given 30 minutes prior to moderately emetogenic chemotherapy including carboplatin, cisplatin ≤ 50 mg/m², cyclophosphamide < 1500 mg/m², doxorubicin > 25 mg/m², epirubicin, irinotecan, and methotrexate > 250 mg/m². Concomitant corticosteroids were not administered prophylactically in study 1 and were only used by 4-6% of patients in study 2. The majority of patients in these studies were women (77%), White (65%) and naïve to previous chemotherapy (54%). The mean age was 55 years.

Highly Emetogenic Chemotherapy

A Phase 2, double-blind, dose-ranging study evaluated the efficacy of single-dose I.V. palonosetron from 0.3 to 90 mcg/kg (equivalent to < 0.1 mg to 6 mg fixed dose) in 161 chemotherapy-naïve adult cancer patients receiving highly-emetogenic chemotherapy (either cisplatin ≥ 70 mg/m² or cyclophosphamide > 1100 mg/m²). Concomitant corticosteroids were not administered prophylactically. Analysis of data from this trial indicates that 0.25 mg is the lowest effective dose in preventing acute nausea and vomiting induced by highly emetogenic chemotherapy.

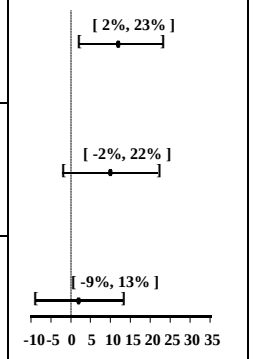
A Phase 3, double-blind trial involving 667 patients compared single-dose I.V. ALOXI with single-dose I.V. ondansetron (study 3) given 30 minutes prior to highly emetogenic chemotherapy including cisplatin ≥ 60 mg/m², cyclophosphamide > 1500 mg/m², and dacarbazine. Corticosteroids were co-administered prophylactically before chemotherapy in 67% of patients. Of the 667 patients, 51% were women, 60% White, and 59% naïve to previous chemotherapy. The mean age was 52 years.

Efficacy Results

The antiemetic activity of ALOXI was evaluated during the acute phase (0-24 hours) [Table 4], delayed phase (24-120 hours) [Table 5], and overall phase (0-120 hours) [Table 6] post-chemotherapy in Phase 3 trials.

Table 4: Prevention of Acute Nausea and Vomiting (0-24 hours): Complete Response Rates

Chemotherapy	Study	Treatment Group	N [a]	% with Complete Response	p-value [b]	97.5% Confidence Interval ALOXI minus Comparator [c]
Moderately Emetogenic	1	ALOXI 0.25 mg	189	81	0.009	[2%, 23%]
		Ondansetron 32 mg I.V.	185	69		
	2	ALOXI 0.25 mg	189	63	NS	[-2%, 22%]
		Dolasetron 100 mg I.V.	191	53		
Highly Emetogenic	3	ALOXI 0.25 mg	223	59	NS	[-9%, 13%]
		Ondansetron 32 mg I.V.	221	57		

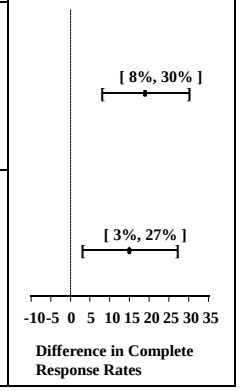


a Intent-to-treat cohort
b 2-sided Fisher's exact test. Significance level at α=0.025.
c These studies were designed to show non-inferiority. A lower bound greater than –15% demonstrates non-inferiority between ALOXI and comparator.

These studies show that ALOXI was effective in the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy. In study 3, efficacy was greater when prophylactic corticosteroids were administered concomitantly. Clinical superiority over other 5-HT3 receptor antagonists has not been adequately demonstrated in the acute phase.

Table 5: Prevention of Delayed Nausea and Vomiting (24-120 hours): Complete Response Rates

Chemotherapy	Study	Treatment Group	N [a]	% with Complete Response	p-value [b]	97.5% Confidence Interval ALOXI minus Comparator [c]
Moderately Emetogenic	1	ALOXI 0.25 mg	189	74	<0.001	[8%, 30%]
		Ondansetron 32 mg I.V.	185	55		
	2	ALOXI 0.25 mg	189	54	0.004	[3%, 27%]
		Dolasetron 100 mg I.V.	191	39		

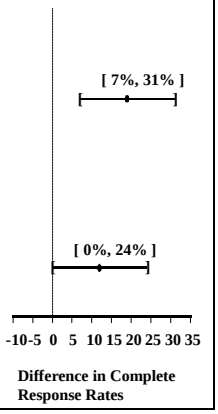


a Intent-to-treat cohort
b 2-sided Fisher's exact test. Significance level at α=0.025.
c These studies were designed to show non-inferiority. A lower bound greater than –15% demonstrates non-inferiority between ALOXI and comparator.

These studies show that ALOXI was effective in the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy.

Table 6: Prevention of Overall Nausea and Vomiting (0-120 hours): Complete Response Rates

Chemotherapy	Study	Treatment Group	N [a]	% with Complete Response	p-value [b]	97.5% Confidence Interval ALOXI minus Comparator [c]
Moderately Emetogenic	1	ALOXI 0.25 mg	189	69	<0.001	
		Ondansetron 32 mg I.V.	185	50		[7%, 31%]
	2	ALOXI 0.25 mg	189	46	0.021	
		Dolasetron 100 mg I.V.	191	34		[0%, 24%]



a Intent-to-treat cohort
b 2-sided Fisher's exact test. Significance level at α=0.025.
c These studies were designed to show non-inferiority. A lower bound greater than –15% demonstrates non-inferiority between ALOXI and comparator.

These studies show that ALOXI was effective in the prevention of nausea and vomiting throughout the 120 hours (5 days) following initial and repeat courses of moderately emetogenic cancer chemotherapy.

14.2 Chemotherapy-Induced Nausea and Vomiting in Pediatrics

One double-blind, active-controlled clinical trial was conducted in pediatric cancer patients. The total population (N = 327) had a mean age of 8.3 years (range 2 months to 16.9 years) and were 53% male; and 96% white. Patients were randomized and received a 20 mcg/kg (maximum 1.5 mg) intravenous infusion of ALOXI 30 minutes prior to the start of emetogenic chemotherapy (followed by placebo infusions 4 and 8 hours after the dose of palonosetron) or 0.15 mg/kg of intravenous ondansetron 30 minutes prior to the start of emetogenic chemotherapy (followed by ondansetron 0.15 mg/kg infusions 4 and 8 hours after the first dose of ondansetron, with a maximum total dose of 32 mg). Emetogenic chemotherapies administered included doxorubicin, cyclophosphamide (<1500 mg/m^2), ifosfamide, cisplatin, dactinomycin, carboplatin, and daunorubicin. Adjuvant corticosteroids, including dexamethasone, were administered with chemotherapy in 55% of patients.

Complete Response in the acute phase of the first cycle of chemotherapy was defined as no vomiting, no retching, and no rescue medication in the first 24 hours after starting chemotherapy. Efficacy was based on demonstrating non-inferiority of intravenous palonosetron compared to intravenous ondansetron. Non-inferiority criteria were met if the lower bound of the 97.5% confidence interval for the difference in Complete Response rates of intravenous palonosetron minus intravenous ondansetron was larger than -15%. The non-inferiority margin was 15%.

Efficacy Results

As shown in Table 7, intravenous ALOXI 20 mcg/kg (maximum 1.5 mg) demonstrated non-inferiority to the active comparator during the 0 to 24 hour time interval.

Table 7: Prevention of Acute Nausea and Vomiting (0-24 hours): Complete Response Rates

I.V. ALOXI 20 mcg/kg (N=165)	I.V. Ondansetron 0.15 mg/kg x 3 (N=162)	Difference [97.5% Confidence Interval]*: I.V. ALOXI minus I.V. Ondansetron Comparator
59.4%	58.6%	0.36% [-11.7%, 12.4%]

* To adjust for multiplicity of treatment groups, a lower-bound of a 97.5% confidence interval was used to compare to -15%, the negative value of the non-inferiority margin.

In patients that received ALOXI at a lower dose than the recommended dose of 20 mcg/kg, non-inferiority criteria were not met.

14.3 Postoperative Nausea and Vomiting

In one multicenter, randomized, stratified, double-blind, parallel-group, phase 3 clinical study (Study 1), palonosetron was compared with placebo for the prevention of PONV in 546 patients undergoing abdominal and gynecological surgery. All patients received general anesthesia. Study 1 was a pivotal study conducted predominantly in the US in the out-patient setting for patients undergoing elective gynecologic or abdominal laparoscopic surgery and stratified at randomization for the following risk factors: gender, non-smoking status, history of post operative nausea and vomiting and/or motion sickness.

In Study 1 patients were randomized to receive palonosetron 0.025 mg, 0.050 mg or 0.075 mg or placebo, each given intravenously immediately prior to induction of anesthesia. The antiemetic activity of palonosetron was evaluated during the 0 to 72 hour time period after surgery.

Of the 138 patients treated with 0.075 mg palonosetron in Study 1 and evaluated for efficacy, 96% were women; 66% had a history of PONV or motion sickness; 85% were non-smokers. As for race, 63% were White, 20% were Black, 15% were Hispanic, and 1% were Asian. The age of patients ranged from 21 to 74 years, with a mean age of 37.9 years. Three patients were greater than 65 years of age.

Co-primary efficacy measures were Complete Response (CR) defined as no emetic episode and no use of rescue medication in the 0-24 and in the 24-72 hours postoperatively.

Secondary efficacy endpoints included:

- Complete Response (CR) 0-48 and 0-72 hours
- Complete Control (CC) defined as CR and no more than mild nausea
- Severity of nausea (none, mild, moderate, severe)

The primary hypothesis in Study 1 was that at least one of the three palonosetron doses were superior to placebo.

Results for Complete Response in Study 1 for 0.075 mg palonosetron versus placebo are described in the following table.

Table 8: Prevention of Postoperative Nausea and Vomiting: Complete Response (CR), Study 1, Palonosetron 0.075 mg Vs Placebo

Treatment	n/N (%)	Palonosetron Vs Placebo	
		Δ	p-value*
Co-primary Endpoints			
CR 0-24 hours			
Palonosetron	59/138 (42.8%)	16.8%	0.004
Placebo	35/135 (25.9%)		
CR 24-72 hours			
Palonosetron	67/138 (48.6%)	7.8%	0.188
Placebo	55/135 (40.7%)		

* To reach statistical significance for each co-primary endpoint, the required significance limit for the lowest p-value was p<0.017.
Δ Difference (%): palonosetron 0.075 mg minus placebo

Palonosetron 0.075 mg reduced the severity of nausea compared to placebo. Analyses of other secondary endpoints indicate that palonosetron 0.075 mg was numerically better than placebo, however, statistical significance was not formally demonstrated.

A phase 2 randomized, double-blind, multicenter, placebo-controlled, dose ranging study was performed to evaluate I.V. palonosetron for the prevention of post-operative nausea and vomiting following abdominal or vaginal hysterectomy. Five I.V. palonosetron doses (0.1, 0.3, 1.0, 3.0 and 30 µg/kg) were evaluated in a total of 381 intent-to-treat patients. The primary efficacy measure was the proportion of patients with CR in the first 24 hours after recovery from surgery. The lowest effective dose was palonosetron 1 µg/kg (approximately 0.075 mg) which had a CR rate of 44% versus 19% for placebo, p=0.004. Palonosetron 1 µg/kg also significantly reduced the severity of nausea versus placebo, p=0.009.

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC # 62856-797-01, ALOXI Injection 0.25 mg/5 mL (free base) single-use vial individually packaged in a carton.

NDC # 62856-798-01, ALOXI Injection 0.075 mg/1.5 mL (free base) single-use vial packaged in a carton containing 5 vials.

Storage

- Store at controlled temperature of 20–25°C (68°F–77°F). Excursions permitted to 15–30°C (59-86°F).
- Protect from freezing.
- Protect from light.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labelling (Patient Information).

Instructions for Patients

Patients should be advised to report to their physician all of their medical conditions, including any pain, redness, or swelling in and around the infusion site *[see Adverse Reactions (6.3)]*.

Advise patients of the possibility of serotonin syndrome, especially with concomitant use of Aloxi and another serotonergic agent such as medications to treat depression and migraines. Advise patients to seek immediate medical attention if the following symptoms occur: changes in mental status, autonomic instability, neuromuscular symptoms with or whithout gastrointestinal symptoms [*see Warnings and Precautions (5.2)*].

Patients should be instructed to read the Patient Information.
