NOVARTIS

衛署藥輸字第 022462 號

復乳納 膜衣錠 2.5 毫克

Femara® film-coated tablets 2.5mg

非類固醇芳香化**酶**抑制劑（動情素合成抑制劑）；抗腫瘤劑

本藥須由醫師處方使用

組成與劑型

主成分：4,4'-[(1H-1,2,4-triazol-l-yl)-methylene]bis-benzonitrile（INN/USAN = letrozole）。

每一膜衣錠含 2.5 毫克 letrozole。

賦形劑部份請見「賦形劑」節。

外觀：暗黃色、圓形、兩面略凸、邊緣呈斜角膜衣錠，一面印有 “FV” 字樣，另一面印有 “CG” 字樣。

適應症

- 停經後荷爾蒙接受器呈陽性反應的初期乳癌病人之輔助治療。
- 接受抗動情激素治療失敗的自然或人工停經後之末期乳癌病人之治療，停經後之局部晚期或轉移性乳癌婦女患者之第一線治療用藥。
- 荷爾蒙接受器呈陽性及 LN metastasis positive 之乳癌病人作為 Tamoxifen 輔助療法之後的延伸治療。

用法用量

成人和老人

建議劑量為每日一次 Femara 2.5 毫克。在輔助性及延伸性輔助治療方面，Femara 的治療應持續 5 年或直到腫瘤復發，視何種情況先發生而定。對轉移性疾病的病患，Femara 治療應持續，除非腫瘤惡化時才停止。老年病患無需調整劑量。

兒童

不適用。

肝或腎功能不全之病患

肝或腎功能不全（肌酸酐廓清率≧ 10 mL/min）之病患無需調整劑量。然而，嚴重性肝功能損害之患者（Child-Pugh 分級屬於 C 級者），必須在嚴謹監控下使用 Femara（見「藥物動力學」）。

禁忌症

- 對本品主成分或任一種賦形劑過敏者
- 停經前內分泌仍有作用之狀態；孕婦；哺乳者 (見「懷孕及授乳」和「臨床前安全性數據」)。

警語及注意事項

腎功能不全

本品未曾用於肌酸酐廓清率 < 10 mL/min 之病人進行研究，此類病人在投予 Femara 前，應審慎考慮可能之風險及效益。

肝功能不全

嚴重性肝功能損害之患者（Child-Pugh 分級屬於 C 級者），其 Femara 曝露於全身的量及最終半衰期，均大約是健康受試者的兩倍，所以這類患者必須在嚴謹監控下使用 Femara（請詳見「藥物動力學」方面）。

對骨頭的影響

使用 Femara 已出現骨質疏鬆和 / 或骨折的案例報告，故建議在治療期間監視整體骨骼的健康（請詳見「副作用」和「藥效動力學」方面）。

交互作用

使用 cimetidine 和 warfarin 進行臨床交互作用研究顯示，同時投予本品與此等藥品，不會產生顯著臨床上之藥物交互作用。

根據臨床試驗之資料，並無證據顯示本藥與其他常用之處方藥有臨床相關之交互作用。

目前尚無本品與其他抗癌藥物併用的臨床經驗。

Letrozole 在體外會抑制 cytochrome P_{450}-isoenzymes 2A6 並適度抑制 2C19。CYP2A6 在藥物代謝上並非扮演主要的角色。於體外試驗，letrozole 濃度高於所觀察到的血漿穩定狀態濃度約 100 倍，並不能有效的抑制 diazepam（一種 CYP2C19 的受質）的代謝。因此，臨床上與 CYP2C19 相關之交互作用不大可能發生。然而，併用其體內分佈主要依賴這些輔**酶**代謝且其治療指數狹窄的藥物時仍應小心。

孕婦和授乳婦

懷孕

懷孕期間禁止使用 Femara (見「禁忌症」)。

少數生殖缺陷 (唇裂融合、生殖器不明) 的案例被通報於使用 Femara 的懷孕婦女 (見「臨床前安全性數據」)。

具有生育能力的婦女

醫生必須與具有懷孕能力的婦女，討論必要的適當避孕法 (包括停經前或停經不久的婦女) 直到她們的停經階段完全確立。(見「臨床前安全性數據」)。

授乳

禁止在授乳期間使用 Femara (見「禁忌症」)。

對開車與操作機器的影響

由於已發現使用 Femara 會造成疲勞和頭昏，並有少數病例指出會造成睏倦，所以建議患者開車或操作機器時需注意。

副作用

Femara 在所有研究中，作為未期乳癌之第一線及第二線藥物，早期乳癌之輔助療法，以及已接受標準 tamoxifen 輔助療法的婦女之延伸性輔助治療上均有良好的耐受性。大約有三分之一以 Femara 治療轉移性疾病及作為術前輔助療法之患者及約 75% 接受輔助治療的患者（於治療期中位數 60 個月時之 Femara 組和 Tamoxifen 組雙方）可能會經歷不良副作用，且預期有大約 80% 的患者在接受延伸性輔助治療時（於治療期中位數 60 個月時之 Femara 組和安慰劑組雙方）可能會產生不良反應。一般而言，所觀察到的不良反應大部份在性質上是輕度或中度的，主要和動情素的缺乏有關。

臨床試驗中，在治療移轉性疾病及作為術前輔助療法上，最常通報的副作用包括熱潮紅、關節痛、噁心及疲勞。許多副作用可歸因藥物造成之動情素缺乏的正常藥理結果（例如熱潮紅、禿頭及陰道出血）。

以下列於表 1 的不良藥物反應，是由 Femara 的臨床試驗及上市後的使用經驗所累積。

表 1

副作用發生頻率之評級，最常發生者為首，利用以下文字代表不同的發生率：極常見（≧ 1/10），常見（≧ 1/100，<1/10），不常見（≧ 1/1000，<1/100），罕見（≧ 1/10000，<1/1000），極罕見（<1/10000），包括個案的報告。

感染及寄生蟲感染
不常見：尿道感染
良性及惡性及未特定腫瘤（包括囊腫及息肉）
不常見：腫瘤疼痛 [6]
血液及淋巴系統疾病
不常見：白血球減少
代謝及營養性疾病
常　見：食慾缺乏、食慾增加、高膽固醇血症
不常見：全身性水腫
精神疾病
常　見：抑鬱
不常見：焦慮 [1]
神經系統疾病
常　見：頭痛、頭昏
不常見：腦卒、失眠、記憶力受損、感覺遲鈍 [2]、味覺干擾、腦血管意外、腕道症候群
眼部疾病
不常見：白內障、眼部發炎、視線模糊
心臟疾病
不常見：心悸、心搏過速
血管疾病
不常見：血栓性靜脈炎 [3]、高血壓、缺血性心臟疾病 [7, 8]
罕　見：肺部栓塞、動脈栓塞、腦血管栓塞
呼吸道、胸廓及縱膈的疾病
不常見：呼吸困難
胃腸道疾病
常　見：噁心、嘔吐、消化不良、便秘、腹瀉
不常見：腹部疼痛、口乾
肝膽疾病
不常見：肝臟酵素增加
極罕見：肝炎
皮膚及皮下組織疾病
常　見：禿頭、增加出汗、發疹 [4]
不常見：搔癢、皮膚乾燥、蕁麻疹
極罕見：血管水腫、過敏反應、中毒性表皮壞死症、多型性紅斑
肌肉骨骼、結締組織疾病
極常見：關節疼痛
常　見：肌痛、骨骼疼痛、骨質疏鬆、骨折
不常見：關節炎
未　知 [9]：板機指
腎臟及泌尿道疾病
不常見：增加排尿頻率
生殖系統及乳房疾病
不常見：陰道出血、陰道分泌物、陰道乾燥、胸部疼痛
全身性疾病及給藥部位的症狀
極常見：熱潮紅
常　見：疲勞 [5] 末梢水腫
不常見：發燒、黏膜乾燥、口渴
研究
常　見：體重增加
不常見：體重減輕

* 包括：
(1) 包括神經緊張、易怒
(2) 包括感覺異常、感覺減退
(3) 包括表層及深部血栓靜脈炎
(4) 包括紅疹、斑丘疹、牛皮癬及蕁麻疹
(5) 包括虛弱與不適
(6) 僅見於用在轉移性疾病 / 術前輔助治療
(7) 在輔助治療中，無論其發生原因，下列不良反應分別發生於 Femara 組及 Tamoxifen 組：血栓栓塞（2.1% 比 3.6%）、狹心症（1.1 % 比 1.0%）、心肌梗塞（1.0 % 比 0.5%）及心衰竭（0.8% 比 0.5%）(見「藥效動力學」－輔助治療)。
(8) 於延伸性輔助治療時，在 letrozole 治療期中位數 60 個月時，以及安慰劑治療期中位數 37 個月時，Femara 和安慰劑組 (排除所有轉至 Femara 案例) 所通報的藥物不良反應 (ADR) 分別為：新產生或病況惡化心絞痛 (1.4% 比 1.0%)；需進行手術之心絞痛 (0.8% 比 0.6%)；心肌梗塞 (1.0% 比 0.7%)；血栓事件 (0.9% 比 0.3%)；中風 / 短暫性腦缺血發作 (TIA) (1.5% 比 0.8%) (見「藥效動力學」－延伸性輔助治療)。
(9) 根據上市後使用經驗。分類為「未知」是由於無法得知被通報使用 Femara 的患者人數多寡而無法評估發生頻率。

過量

曾有被孤立的 Femara 過量的個案報告。

未知有任何特定用藥過量的處理方法；用藥過量時的處置以症狀治療和支持性療法為原則。

藥效動力學

藥效動力學作用

在腫瘤組織之成長需依賴動情素的病例中，去除動情素則可使腫瘤生長受抑制；停經後婦女的動情素主要來自於芳香化**酶**的作用，芳香化**酶**將腎上腺雄性素，主要包括 androstenedione 和睪固酮轉化為雌素酮（E1）和雌二酮（E2）；因此，可經由特異性抑制芳香化**酶**，使周邊組織和癌組織本身所製造的動情素被抑制。

本品是一種非類固醇芳香化**酶**抑制劑，其經由競爭性結合至芳香化**酶**細胞色素 P_{450} 亞單位血基質而抑制芳香化**酶**，結果導致全部組織合成之動情素減低。

若用於健康停經後婦女，單劑 0.1、0.5 和 2.5 毫克 letrozole 可抑制血清雌素酮和睾情素醇分別達基線值之 75-78% 和 78%；在 48 至 78 小時後可達最大抑制效果。

用於晚期乳癌的停經後病人，每日劑量 0.1 毫克至 5 毫克，發現所有病人均可抑制雌二酮，睾情素醇和雌素酮硫酸鹽之血漿濃度達基線值之 75-95% 抑制；0.5 毫克或更高劑量的抑制效果更大，雌素酮和雌素酮硫酸鹽量分析常低於可分析的量，顯示此劑量有很大的動情素抑制作用。所有病患在治療期間，抑制動情素的作用都能持續。

Letrozole 具有高度專一性的芳香化**酶**抑制作用，未見有損害腎上腺性類固醇生合成的情形。未發現血漿中 cortisol、醛類脂醇 (aldosterone)、11-deoxycortisol、17-hydroxy-progesterone 及親腎上腺皮質激素 (ACTH) 濃度變化有臨床上相關，或每日以 0.1-5 毫克治療停經後病人，亦未見血漿中腎素活性的改變。每日以 0.1、0.25、0.5、1、2.5 及 5 毫克治療 6 週及 12 週後，檢驗親腎上腺皮質激素刺激作用，並未減少醛類脂醇或 cortisol 的生成。因此無需補充糖性類皮質酮及礦物皮質酮。

於健康停經後婦女每日服用 0.1、0.5 及 2.5 毫克 letrozole 單劑，血漿中雄性素 (androstenedione 及睪固酮）濃度未改變，或停經後病人每日以 0.1-5 毫克治療，血漿中 androstenedione 濃度亦未改變，顯示抑制動情素的生合成，不會導致雄性素前驅物質的蓄積。病人血漿中黃體素 (LH) 及濾泡激素 (FSH) 的量不受 letrozole 的影響，甚至甲狀腺刺激素 (TSH)、T4 及 T3 攝取試驗評估，亦未見甲狀腺功能受影響。

輔助治療

BIG 1-98 試驗期中分析之療效結果

BIG 1-98 是一項多中心、雙盲試驗，包含超過 8000 名初期乳癌已切除且荷爾蒙接受體陽性的停經婦女隨機分配至下列其中一組：

- A. Tamoxifen 治療 5 年
- B. Femara 治療 5 年
- C. Tamoxifen 治療 2 年後以 Femara 治療 3 年
- D. Femara 治療 2 年後以 Tamoxifen 治療 3 年

本試驗旨在探討兩項主要問題：5 年 Femara 治療是否優於 5 年 tamoxifen 治療 (主要核心分析與單一治療組分析)，以及在兩年時轉換為內分泌治療，是否優於 5 年持續使用同一藥物治療 (循序治療分析)。

主要療效評估指標為無病存活率 (DFS)，次要療效評估指標為整體存活率 (OS)，遠端無病存活率 (DDFS)、全身性無病存活 (SDFS)、侵入性對側乳癌以及發生遠處轉移時間 (TDM)。

追蹤期中位數 26 個月的療效結果

表 2 數據反映主要核心分析 (PCA)，包括來自未轉換藥物治療組的數據 (治療組 A 和 B)，以及截取兩治療組進行轉換藥物後 30 天 (治療組 C 和 D) 的數據。本分析是於治療期中位數 24 個月以及追蹤期中位數 26 個月時進行。除了整體存活率以及對側乳癌之外，Femara 治療 5 年的所有的療效評估指標均優於 tamoxifen 治療。

表 2：在追蹤期中位數 26 個月之無病存活率及整體存活率（PCA ITT 族群）
（BIG 1-98 試驗期中分析）

	Femara N=4003	Tamoxifen N=4007	危險比率 (95%CI)	P值[1]
無病存活率(主要) -案例數(按計畫的定義，總數)	351	428	0.81(0.70, 0.93)	0.0030
遠處轉移時間(次要)	184	249	0.73(0.60, 0.88)	0.0012
遠處無病存活率(次要)	265	318	0.82 (0.70, 0.97)	0.0204
整體存活率(次要) -死亡人數(總數)	166	192	0.86(0.70, 1.06)	0.1546
全身性無病存活率(次要)	323	383	0.83(0.72, 0.97)	0.0172
侵入性對側乳癌(次要)	19	31	0.61(0.35, 1.08)	0.0910

CI =信賴區間

[1] 經時序檢驗，以隨機選擇分組，並採用曾接受輔助化學療法者。

BIG 1-98 試驗提前解盲後之長期安全及療效結果

追蹤期中位數 73 個月之單一治療組分析 (MAA) 結果

單一治療組分析 (MAA) 只針對單一治療組數據進行分析，僅提供 Femara 單一治療相對於 tamoxifen 單一治療在臨床方面長期有效性的適當更新 (表 3)。2005 年，依據表 2 所示之主要核心分析 (PCA) 數據，以及獨立數據監測委員會之建議，將 tamoxifen 單一治療組除盲，並允許患者轉換藥物至 Femara 治療。接受隨機分配至 tamoxifen 的患者中有 26% 的病人，選擇轉換藥物為 Femara 治療，其中含極少數患者轉換藥物至其他芳香化**酶**抑制劑。為探索此種選擇性交換藥物的影響，將單一治療組分析 (MAA) 的 (tamoxifen 治療組中) 設限追蹤時間於選擇性交換藥物日期直至現在的分析彙總列出 (表 4)。

在追蹤期中位數 73 個月和治療期中位數 60 個月，相較於 tamoxifen，Femara 的無病存活率 (DFS) 事件風險有顯著下降 (單一治療組分析 (MAA) 的意向治療 (ITT) 族群分析：HR 0.88；95% CI 0.78, 0.99；P = 0.03)；確認 2005 年 PCA 結果。無病存活率 (DFS) 設限分析顯示類似效益 (HR 0.85；95% CI 0.75, 0.96)。同樣地，經由更新性分析，確認 Femara 在遠端無病存活率事件風險的減少 (HR 0.87 0.76, 1.00)，以及遠處轉移時間增加 (HR 0.85; 95% CI 0.72, 1.00)，具有較佳的表現。此外，以意向治療 (ITT) 分析整體存活率具顯著性趨向。整體存活率設限分析顯示 Femara 明顯效益較佳 (HR 0.82 0.70, 0.96)。

表 3：在追蹤期中位數 73 個月之無病狀態及整體存活率（MAA ITT 人數）
BIG 1-98 試驗解盲後長期追蹤療效分析

	Femara N=2463	Tamoxifen N=2459	危險比率 (95%CI)	P值[1]
無病存活率(主要) -案例數(按計畫的定義，總數)	509	565	0.88 (0.78, 0.99)	0.03
遠處轉移時間(次要)	257	298	0.85 (0.72, 1.00)	0.045
遠處無病存活率(轉移) (次要)	385	432	0.87 (0.76, 1.00)	0.049
整體存活率(次要) -死亡人數(總數)	303	343	0.87 (0.75, 1.02)	0.08
全身無病性存活 (次要)	465	512	0.89 (0.79, 1.01)	0.065
侵入性對側乳癌(次要)	34	44	0.76 (0.49, 1.19)	0.2
DFS的設限分析	509	543	0.85 (0.75, 0.96)	-
整體存活率的設限分析	338	338	0.82 (0.70, 0.96)	-

CI =信賴區間

[1] 經時序檢驗，以隨機選擇分組，並採用曾接受輔助化學療法者。

循序治療分析

於追蹤期中位數 48 個月時所進行的循序治療分析 (STA)，主要是針對試驗的第 2 項主要研究問題。循序治療分析 (STA) 的主要分析，是交換藥物 (等同單一藥物治療組則為相同時間點) + 30 天 (STA-S)，每組配對比較是以雙尾檢定進行分析，顯著水準為 2.5%。此外，亦會進行隨機分配 (STA-R) 至追蹤期中位數 67 個月的探索性分析，每組的比較結果，以危險比率和 99% 信賴區間總結表示。

於追蹤期中位數 48 個月時，循序治療分析 (STA) 結果，顯示交換藥物後任何時間點相較於單一藥物治療，均未有顯著差異性 (例如：[Tamoxifen 治療 2 年後換] Femara 治療 3 年相對於 tamoxifen 治療超過 2 年，無病存活率 (DFS) HR 0.89；97.5% CI 0.68, 1.15，而 [Femara 治療 2 年後換] tamoxifen 治療 3 年相對於 Femara 治療超過 2 年，無病存活率 (DFS) HR 0.93；97.5% CI 0.71, 1.22。於追蹤期中位數 67 個月時，循序治療分析 (STA) 結果，顯示隨機分配後於任何時間點相較於單一藥物治療，均未有顯著差異性 (例如：tamoxifen 治療 2 年後以 Femara 治療 3 年相對於 Femara 治療 5 年，無病存活率 (DFS) HR 1.10；99% CI 0.86, 1.41；Femara 治療 2 年後以 tamoxifen 治療 3 年相對於 Femara 治療 5 年，DFS HR 0.96; 99% CI 0.74, 1.24)。未有證據顯示 Femara 和 tamoxifen 循序治療優於 Femara 單一藥物治療 5 年。

治療期中位數 60 個月的安全性數據

在 BIG 1-98 試驗中，治療期中位數 60 個月所觀察到的副作用與藥物安全性特性一致。依據兩種藥物之已知的藥理學性質與副作用特性，某些特定的不良反應所做的前瞻性的分析。

不良反應的分析不考慮是否與藥物相關。大部份通報的不良反應 (約 75% 患者通報至少有 1 項以上的 AE) 為 CTC (通用毒性標準) 標準第 2 版 /CTCAE 第 3 版的第 1 級和第 2 級。若考慮治療期間所有等級之不良反應，Femara 組發生率高於 tamoxifen 組者有：高膽固醇症 (52% 比 29%)、骨折 (10.1% 比 7.1%)、心肌梗塞 (1.0% 比 0.5%)、骨質疏鬆 (5.1% 比 2.7%) 和關節疼痛 (25.2% 比 20.4%)。

Tamoxifen 組發生率較 Femara 組高的不良反應有：熱潮紅 (38% 比 33%)、夜間盜汗 (17% 比 15%)、陰道出血 (13% 比 5.2%)、便秘 (2.9% 比 2.0%)、血栓事件 (3.6% 比 2.1%)、子宮內膜增生 / 子宮內膜癌 (2.9% 比 0.3%) 以及子宮內膜增生病變 (1.8% 比 0.3%)。

早期乳癌輔助療法，試驗 D2407

試驗 D2407 是一項第 3 期、開放性、隨機分配、多中心試驗，旨在比較 letrozole 和 tamoxifen 輔助治療和 tamoxifen 對於骨質密度 (BMD)、骨標記和空腹血清脂質所做的影響。共有 262 位荷爾蒙敏感性且原發性乳癌已切除之停經女性，接受隨機分配至每日 letrozole 2.5 毫克治療 5 年，或每日 tamoxifen 20 毫克治療 2 年後轉換為每日 letrozole 2.5 毫克治療 3 年。

主要評估指標為比較 letrozole 相較於 tamoxifen 對腰椎 (L2-L4) 骨質密度 (BMD) 的影響，以 2 年時腰椎骨質密度 (BMD) 相對於基期的變化百分比來評估。

在第 24 個月，letrozole 治療組腰椎 (L2-L4) BMD 中位數下降 4.1%，相較於 tamoxifen 治療組中位數增加 0.3% (差異 = 4.4%)。在 2 年時，整體來說，letrozole 和 tamoxifen 之間的腰椎骨質密度 (BMD) 中位數差異，tamoxifen 有明顯較佳的統計意義 (P < 0.0001)。目前數據顯示，基期有正常骨質密度 (BMD) 的患者，並未在第 2 年時發生骨質疏鬆，只有 1 位於基期時骨質缺乏 (T 值為 -1.9) 的患者，於治療期間產生骨質疏鬆 (由中央審查進行評估)。

整體髖部骨質密度 (BMD) 結果與腰椎骨質密度 (BMD) 結果相似，但差異性較不明顯。在 2 年時，整體骨質密度 (BMD) 安全性族群和所有分層類別，有觀察到 tamoxifen 組明顯表現較佳 (P < 0.0001)。在 2 年期間，letrozole 治療組有 20 位患者 (15%) 而 tamoxifen 治療組則有 22 位患者 (17%) 通報骨折。

在 tamoxifen 治療組，在 6 個月後相較於基期的總膽固醇量中位數減少 16%；類似減少現象於 24 個月的後續回診也觀察到。在 letrozole 治療組，相對來說總膽固醇量中位數值穩定，未在任何回診中觀察到明顯的提高。於任何時間點，2 組之間差異具統計顯著性且較有利於 tamoxifen (P < 0.0001)。

延伸性輔助治療

在一項多個醫學中心、雙盲、隨機、安慰劑對照試驗中 (CFEM345G MA-17)，將 5100 位仍在無疾病狀態，且已完成 tamoxifen 輔助治療 (4.5 到 6 年) 之接受雌激性的停經患者或未知的原發性乳癌患者，隨機分配至 Femara 或安慰劑組。

於追蹤期中位數約 28 個月時 (25% 的患者接受追蹤長達 38 個月) 所進行的主要分析顯示，與安慰

劑相比，Femara 明顯減少了 42% 的復發風險（危險比率 0.58；p=0.00003）。敏感度分析證實了有力的數據。不論淋巴結狀態如何，無病存活率（DFS）之統計上明顯的療效較傾向於 letrozole（淋巴結陰性，危險比率 0.48，p=0.002；淋巴結陽性，危險比率 0.61，p=0.002）。

當試驗於 2003 年除盲時，獨立數據監測委員會建議安慰劑組婦女若無疾病者，可轉換至 Femara 藥物治療 5 年。2008 年進行更新最後分析時，1551 位女性（其中 60% 符合轉換藥物資格）於完成輔助 tamoxifen 療法後中位數 31 個月，從安慰劑組轉換至 Femara。轉換 Femara 藥物治療期中位數為 40 個月。

於追蹤期中位數 62 個月時進行的更新最後分析，即使除盲後有安慰劑組 60% 符合資格患者轉換至 Femara 藥物治療的，仍證實 Femara 相較於安慰劑能明顯降低乳癌風險復發風險。Femara 治療組的治療期中位數為 60 個月，安慰劑組治療期中位數則為 37 個月。2004 年和 2008 年分析結果，顯示 Femara 治療組有相同的計畫書明訂 4 年無病存活率 (DFS)，證實試驗數據穩定和 Femara 的良好長期治療功效。在更新性分析中，安慰劑組 4 年無病存活率 (DFS) 的增加，清楚反映了轉換藥物至 Femara 對 60% 患者帶來的影響。此轉換藥物結果也解釋了治療差異明顯弱化的現象。

在原始分析中，在次要的試驗終點之整體存活率上（OS），共計報告了 113 死亡案例（Femara 51 例，安慰劑 62 例）。整體而言，之前在治療組之間在 OS 上沒有明顯差異（危險比率 0.82；p=0.29）。包括之前已接受化學治療或之前無接受化學治療的患者，在淋巴結陽性疾病方面，Femara 可減少大約 40% 的任何原因引起之死亡風險（危險比率 0.61；p=0.035），但是在淋巴結陰性患者（危險比率 1.36；p=0.385）及之前接受或未接受過化學治療的患者則未見明顯的差異。歸納的結果參見表 4 和表 5：

表 4：無疾病狀態及整體存活率（修正的 ITT 人數）

	2004分析–追蹤期中位數28個月（MA-17試驗解盲前期中分析）			2008最新分析[1]–追蹤期中位數62個月(MA-17試驗解盲後長期追蹤資料分析)		
	Letrozole	安慰劑	危險比率 (95%CI)[2]	Letrozole	安慰劑	危險比率 (95%CI)[2]
	N=2582	N=2586	P值	N=2582	N=2586	P 值
無病存活率(按試驗計畫的定義)[3]						
			0.58			0.75
案例數	92 (3.6%)	155 (6.0%)	(0.45, 0.76)	209 (8.1%)	286 (11.1%)	(0.63, 0.89)
			0.00003			0.001
4年無病存活率	94.4%	89.8%		94.4%	91.4%	
無病存活率(包括任何導致死亡的原因)						
			0.62			0.89
案例數	122 (4.7%)	193 (7.5%)	(0.49, 0.78)	344 (13.3%)	402 (15.5%)	(0.77, 1.03)
			0.00003			0.120
5年無病存活率	90.5%	80.8%		88.8%	86.7%	
遠處轉移						
			0.61			0.88
案例數	57 (2.2%)	93 (3.6%)	(0.44, 0.84)	142 (5.5%)	169 (6.5%)	(0.70, 1.10)
			0.003			0.246
整體存活率						
			0.82			1.13
死亡人數	51 (2.0%)	62 (2.4%)	(0.56, 1.19)	236 (9.1%)	232 (9.0%)	(0.95, 1.36)
			0.291			0.175
死亡人數[4]	--	--	--	236[5] (9.1%)	170[6] (6.6%)	0.78 (0.64, 0.96)
對側乳癌						
			0.60			0.64[7]
侵略性(總計)	15 (0.6%)	25 (1.0%)	(0.31, 1.14)	33 (1.3%)	51 (2.0%)	(0.41, 1.00)
			0.117			0.049

HR = 危險比；CI = 信賴區間

[1] 當試驗於 2003 年除盲時，隨機分配至安慰劑組的 1551 位患者 (其中 60% 符合轉換藥物條件 – 即無疾病者) 於隨機分配後中位數 31 個月時轉換至 letrozole 治療組。此處所列舉的分析，依據意向治療 (ITT) 原則並未包括轉換藥物治療。

[2] 依接受器狀態、淋巴結狀態和先前輔助化療進行分層。

[3] 計畫書定義之無病存活事件：局部區域復發、遠處轉移或對側乳癌。

[4] 安慰劑組探索性分析、於轉換藥物時的設限追蹤時間 (若有發生時)。

[5] 追蹤期中位數 62 個月。

[6] 至轉換藥物 (若有發生時) 為止的追蹤期中位數 37 個月。

[7] 勝算比和勝算比的 95% 信賴區間 (CI)。

表 5：依接受體狀態、淋巴結狀態、先前的化學治療之無疾病狀態和整體存活率（修正的 ITT 人口）

	2004 分析 – 追蹤期中位數 28 個月（MA-17 試驗解盲前期中分析）		2008 分析 – 追蹤期中位數 62 個月[1] (MA-17試驗解盲後長期追蹤資料分析)	
	危險比率 (95%CI)[2]	P 值	危險比率 (95%CI)[2]	P 值
無病存活率 (按試驗計畫的定義)				
接受體狀態陽性	0.57 (0.44, 0.75)	0.00003	0.74 (0.62, 0.89)	0.001
淋巴結狀態				
陰性	0.48 (0.30, 0.78)	0.002	0.67 (0.49, 0.93)	0.015
陽性	0.61 (0.44, 0.83)	0.002	0.78 (0.62, 0.97)	0.027
化學治療				
無	0.58 (0.40, 0.84)	0.003	0.71 (0.54, 0.92)	0.010
已接受	0.59 (0.41, 0.84)	0.003	0.79 (0.62, 1.01)	0.055
整體存活率				
淋巴結狀態				
陰性	1.36 (0.68, 2.71)	0.385	1.34 (0.99, 1.81)	0.058
陽性	0.61 (0.38, 0.97)	0.035	0.96 (0.75, 1.21)	0.710

HR = 危險比；CI = 信賴區間

[1] 包括試驗於 2003 年除盲後，從安慰劑組交換藥物至 letrozole 組的 60% 符合交換藥物條件患者

[2] 來自 Cox 迴歸模型

在更新性分析中，如表 4 所示，即便有 60% 安慰劑組患者轉換至 Femara 治療組，Femara 相較於安慰劑顯著降低了罹患侵入性對側乳癌的機會。整體存活率則未有顯著差異。

一項設限追蹤時間於轉換藥物日期 (若有發生時) 的探索性分析，顯示 Femara 相較於安慰劑明顯降低所有原因造成的死亡率風險 (表 4)。

在 <65 歲和≥ 65 歲的患者之間並沒有療效或安全性上的差異。

在更新的 Femara 安全性報告中，未顯示任何新發現的不良事件，與 2004 年通報項目一致。

下列不良反應不論其原因為何，與使用安慰劑時相比，Femara 有較顯著的出現 – 熱潮紅 (Femara 組 61% 比安慰劑組 51%)，關節痛 / 關節炎 (41% 比 27%)，發汗 (35% 比 30%)，高膽固醇血症 (24% 比 15%) 和肌肉痛 (1.8% 比 94%)。這些不良事件大部分發生於治療的第一年。在轉換至 Femara 的安慰劑組患者中，觀察到的一般不良反應類似模式。在治療期間，服用 Femara 的患者，其骨質疏鬆之發生率明顯高於安慰劑組 (12.2% 比 6.4 %)。在治療期間，服用 Femara 的患者，其臨床的骨折發生率明顯高於安慰劑組 (10.4% 比 5.8%)。在轉換至 Femara 的患者中，於使用 Femara 治療期間，5.4% 的患者出現初次診斷的骨質疏鬆，而 7.7% 的患者出現骨折。若患者≥ 65 歲，不論治療為何，均較容易發生骨折和骨質疏鬆。

來自骨骼次研究的更新結果 (追蹤期中位數為 61 個月)，顯示在 2 年時，相較於基期，接受 Femara 治療的患者，髖部骨質密度 (BMD) 降低 3.8% 比例中位數，而安慰劑組為 2.0% (P = 0.022)。任何時間點的治療，對於腰椎骨質密度 (BMD) 的改變未有顯著差異。來自脂質子研究的更新結果 (追蹤期中位數為 62 個月)，顯示於任何時間點，Femara 和安慰劑兩者間的任何脂質檢驗值，未有明顯差異。於更新性分析中，Femara 組與安慰劑組於治療期至轉換藥物為止，心血管事件的發生率 (包括腦血管和血栓事件) 為 9.8% 與 7.8%，具統計上顯著性差異。

於試驗治療期，原提供的不良事件名詞列表中，最常通報事件為：中風 / 暫時性腦缺血 (letrozole 組，1.5%；轉換藥物前的安慰劑組，0.8%)；新產生或病況惡化心絞痛 (letrozole，1.4%；轉換藥物前的安慰劑組，1.0%)；心肌梗塞 (letrozole，1.0%；轉換藥物前的安慰劑組，0.7%)；血栓事件 (letrozole，0.9%；轉換藥物前的安慰劑組，0.3%)。Femara 組相較於轉換藥物前的安慰劑組，前者血栓事件以及中風 / 暫時性腦缺血通報頻率明顯較高。對於安全性結果的解釋，應考慮由於約有 60% 安慰劑患者轉換至 Femara 治療組，造成 letrozole (60 個月) 與安慰劑 (37 個月) 治療期中位數的差異。

第一線治療

有一個良好對照設計的雙盲試驗，比較 Femara 2.5 毫克與 tamoxifen 當成第一線治療時，對於停經後罹患局部或轉移性乳癌婦女的效果差異。在受試的 907 位患者中，Femara 組不論在至疾病進程所需要的時間 (主要的評估項目)、整體的腫瘤主要反應、至治療失敗所需要的時間及臨床治療利益上，均優於 tamoxifen 組的患者：試驗結果請詳見表 6。

表 6：32 個月之後的中位數結果

	Femara	Tamoxifen	P值
至疾病進程的時間(中位數)	9.4個月	6.0個月	<0.0001
整體的腫瘤客觀反應率(比率)	32%	21%	0.0002
整體的腫瘤主要反應之期間(中位數)	25個月	23個月	0.0578
至治療失敗的時間(中位數)	9.1個月	5.7個月	<0.0001
臨床治療利益(比率)	50%	38%	0.0004

Femara 組無論是至疾病進程的時間及客觀反應率，均顯著地較 tamoxifen 組長 / 高，與接受者的狀態無關（表 7）。

表 7：接受器狀態

	Femara	Tamoxifen	P值
ER和/或PgR呈陽性反應者			
至疾病進程的時間（中位數）	9.4個月	6.0個月	<0.0001
整體的腫瘤主要反應率	33%	22%	0.0019
未知/陰性反應者			
至疾病進程的時間(中位數)	9.2個月	6.0個月	0.0402
整體的腫瘤主要反應	30%	20%	0.0309

ER：動情素接受器

PgR：黃體激素接受器

對於主要患病部位的藥效如表 8 所述：

表 8：對主要患病部位的藥效

主要患病部位	Femara N = 453	Tamoxifen N = 454	P值
軟組織：	N = 113	N = 115	
至疾病進程的時間(中位數)	12.1個月	6.4個月	0.0456
整體的腫瘤客觀反應率	50%	34%	0.0171
骨骼：	N = 145	N = 131	
至疾病進程的時間(中位數)	9.5個月	6.2個月	0.0262
整體的腫瘤客觀反應率	23%	15%	0.0891
臟器：	N = 195	N = 208	
至疾病進程的時間(中位數)	8.3個月	4.6個月	0.0005
整體的腫瘤客觀反應率	28%	17%	0.0095
轉移至肝臟：	N = 60	N = 55	
至疾病進程的時間(中位數)	3.8個月	3.0個月	0.0232
整體的腫瘤客觀反應率	10%	11%	0.8735
整體的臨床獲益比例	28%	16%	0.1292
整體的存活(中位數)(包括交叉治療)	19個月	12個月	0.0727

注意：“轉移至肝臟”歸類於病患之主要患病部位為“臟器”的分組下。

研究設計允許患者交叉進行其他治療或自研究中退出。大約有 50% 的患者交叉以其他方法治療，實際上交叉在 36 個月內完成。交叉的中位數時間為 17 個月 (Femara 到 tamoxifen)，及 13 個月 (tamoxifen 到 Femara)。Femara 作為乳癌晚期患者之第一線治療，與早期存活的受益之相關性甚於 tamoxifen。Femara 的中位數存活率為 34 個月，tamoxifen 的中位數存活率為 30 個月。經過前 24 個月的研究（重覆的經時序檢驗），服用 Femara 而存活的患者數量上顯著地較多，見表 9。

表 9：整體的存活率 - 患者存活、死亡、交叉治療

	Femara (n=458)			Tamoxifen (n=458)			經時序檢驗
月數	存活	死亡	以tamoxifen交叉治療	存活	死亡	以Femara交叉治療	P值
6	426	31	51	406	52	74	0.0167
12	378	79	129	343	114	145	0.0038
18	341	115	185	297	159	179	0.0010
24	286	166	208	263	193	198	0.0246
30	241	209	225	227	227	217	0.0826
36	156	243	233	169	251	224	0.2237
42	70	267	238	85	266	226	0.4820
48	24	277		27	272	228	0.6413
54	6	277		6	276		*0.5303

* 整體經時序檢驗 p 值

治療的效果由共變數“之前的抗動情素療法”，分析詳列於表 10。

表 10：根據之前的抗動情素療法之結果

	有之前的荷爾蒙治療			無之前的荷爾蒙治療		
終點	Femara N=84	Tamoxifen N=83	P值	Femara N=369	Tamoxifen N=371	P值
至疾病進程所需的時間(中位數)	8.9個月	5.9個月	0.0033	9.5個月	6.0個月	0.0003
整體的腫瘤客觀反應率	26%	8%	0.0038	33%	24%	0.0039
臨床利益	46%	31%	0.0464	51%	40%	0.0026
	N=86	N=83		N=372	N=375	
整體存活時間(中位數)包括交叉治療	28個月	30個月	0.6558	34個月	30個月	0.3756
	N=45	N=43		N=174	N=186	
第一線治療的存活(未進行交叉治療的患者)(中位數)	33個月	18個月		33個月	19個月	

未進行另一種相對藥物之交叉治療的患者，Femara 的存活率中位數為 35 個月（n=219，95% 信賴區間為 29-43 個月）相對 tamoxifen 為 20 個月（n=229，95% 信賴區間為 16-26 個月）。

Femara 組之內泌素治療的總時間（至化療時間）顯著地較長（中位數 16.3 個月，95% 信賴區間為 15-18 個月）甚於 tamoxifen（中位數 9.3 個月，95% 信賴區間為 8-12 個月）（經時序檢驗 p=0.0047）。

Letrozole 第一線治療組之卡氏評級惡化 20 分或以上的患者明顯地較少（19%），而 tamoxifen 組較多（25%）（風險比 p=0.0208）。

第二線治療

有兩個良好對照設計的雙盲試驗，以停經後患有末期乳癌且之前曾接受抗動情激素治療的婦女為試驗對象，進行以兩種 letrozole 的劑量（2.5 毫克與 0.5 毫克），分別與 megestrol acetate 及 aminoglutethimide 之間的比較試驗。

結果證實 Femara 2.5 毫克不論在整體的腫瘤主要反應率（24% 比 16%，p=0.04）、至治療失敗的時間（p=0.04），都比 megestrol acetate 理想，且具統計上差異。至於至疾病進程的時間，則 Femara 2.5 毫克與 megestrol acetate 無統計上的差異（p=0.07）；兩組之間整體的存活率亦無統計上的差異（p=0.2）。

另一個試驗中，Femara 2.5 毫克組在至疾病進程所需的時間（p=0.008）、至治療失敗所需的時間（p=0.003），及整體的存活率（p=0.002）方面，在統計上則有意義地優於 aminoglutethimide 組。兩組的治療反應率，統計上則無明顯的差異（p=0.06）。

手術前治療

一項為期 4 個月，將 337 位患者隨機分配至 Femara 2.5 毫克組或 tamoxifen 組的雙盲試驗中，根據臨床的評估，Femara 組的整體客觀反應率為 55%，而 tamoxifen 組僅為 36%（p<0.001）。此結果是因最保守的方法評估，亦被超音波 (p=0.042) 及乳房放射線攝影檢查 (p<0.001) 所確認；證實 Femara 組比 tamoxifen 組有更多的患者，變成適合進行乳房保留手術（Femara 組有 45%，而 tamoxifen 組為 35%；p=0.022）。

藥物動力學

吸收

Letrozole 能很快經由胃腸道完全吸收（平均絕對生體可用率：99.9%），食物會稍微降低吸收率（T_{max} 中間值：空腹時為 1 小時，飽餐時為 2 小時；平均 C_{max}：空腹時為 129 ± 20.3 nmol/L，飽餐時為 98.7 ± 18.6 nmol/L），但吸收程度（AUC）未改變。對吸收率輕微的影響並未影響其臨床療效，故服用 letrozole 與用餐時間無關。

分佈

Letrozole 的血漿蛋白結合率約 60%，主要和 albumin 結合（55%）。紅血球中 letrozole 的濃度約為血漿中濃度的 80%。投予碳 14 標示的 letrozole 2.5 毫克，檢測放射性，血漿中約有 82% 為原形藥。顯示體內代謝物很少。Letrozole 能快速並廣泛地分佈在組織中，其穩定期的擬似分佈容積約為 1.87 ± 0.47 L/kg。

代謝及排除

Letrozole 主要的排除路徑為經由代謝成不具藥理活性的 carbinol 代謝物而清除（CLm = 2.1 L/h），但和肝血流比較（90 L/h），其相對代謝速率很低。細胞色素 P_{450} 異酵素 (Cytochrome P_{450} isoenzymes) 3A4 及 2A6 能將 letrozole 轉化成代謝物。未確認的次要代謝物及直接由腎和糞便的排泄僅屬 letrozole 排除的一小部份。健康停經後的受試者服用碳 14 標示的 letrozole 2.5 毫克兩週後，尿中測得的放射活性為 88.2 ± 7.6%，糞便中為 3.8 ± 0.9%。故 216 小時後，至少有 75% 的放射活性仍能在尿中測到（劑量的 84.7 ± 7.8%）是歸因於 glucuronide 之 carbinol 代謝物，約有 9% 為二種未確定的代謝物，6% 為 letrozole 原形藥。

於血漿的擬似最終清除半衰期約 2 天。每天口服 2.5 毫克後，2-6 週可達穩定期。穩定期的血漿濃度較單次投予 2.5 毫克高約 7 倍，由於此濃度比以單一劑量推算的穩定期濃度高出 1.5-2 倍，故可得知每日投予 2.5 毫克 letrozole 的藥物動力學稍微呈非線性狀態。因穩定期濃度能長時間維持，故得知 letrozole 無連續蓄積作用。

年齡不影響 letrozole 的藥物動力學。

特殊族群

在一包含不同腎功能狀態（24 小時 creatinine 清除率 9-116 ml/min）受試者的研究中，投予 2.5 毫克單劑，並不影響 letrozole 的藥物動力學。對肝功能程度不同的受試者做類似的試驗，中度肝功能障礙受試者（Child-Pugh 分級屬 B 級者）的 AUC 值比正常人高出 37%，但仍在肝功能正常的受試者的 AUC 值範圍內。在一項以八位患有肝硬化及嚴重肝損害（Child-Pugh 分級屬 C 級者）患者，在給予單次口服 letrozole 劑量後，其曲線下面積及半衰期，皆比另外八位健康受試者各高出 95% 及 187%。由此可見併有嚴重肝損害的乳癌患者，其體內 letrozole 的濃度比沒有併發嚴重肝損害的乳癌患者高。然而，由於每天給予 5 毫克或 10 毫克的 letrozole，並不會增加其危險性；因此，對於嚴重肝損害的乳癌患者，並不須減低 letrozole 的劑量，但是必須在嚴密的監控下使用 letrozole。此外，在 359 名末期乳癌患者的試驗，letrozole 的濃度並不受腎功能損害（creatinin 清除率 20-50 ml/min）或肝功能損害的影響。

臨床前安全性資料

以標準動物種類所進行之各種前臨床安全性試驗中，沒有任何全身性或目標器官毒性的證據。

將囓齒動物曝露於 2000 毫克 / 公斤的 letrozole 下顯示急性毒性的程度很低。在狗的試驗中，100 毫克 / 公斤的 letrozole 會造成中度毒性的徵兆。

在長達 12 個月大白鼠和狗的重覆劑量毒性試驗中，觀察到的主要結果均歸因於藥物本身的藥理活性。對兩種動物沒有不良反應的濃度是 0.3 毫克 / 公斤。

在年輕大鼠的動物試驗，letrozole 藥理學作用對於骨骼、神經內分泌和生殖結果有影響，雄性於最低劑量 (0.003 毫克 / 公斤 / 天) 開始，其骨骼生長和成熟有降低，雌性於最低劑量 (0.003 毫克 / 公斤) 開始，其骨骼生長和成熟有增加。雌性於相同劑量下，骨質密度 (BMD) 亦有下降。在相同試驗中，所有劑量均有顯現生育力下降情形，合併腦垂體肥大、睪丸改變 (包括細曲精管上皮退化) 以及雌性生殖道萎縮。除了雌性的骨骼大小和雄性睪丸形態改變之外，所有作用是部份可逆的。

體外和體內對 letrozole 的致突變可能性的研究均沒有顯示任何基因毒性的徵兆。

在一項為期 104 週的大白鼠致癌性試驗中，在雌鼠沒有見到與治療相關的腫瘤。在雌鼠，在所有的 letrozole 劑量下發現良性和惡性乳房腫瘤的發生率減少。

在接受治療的動物中，口服 letrozole 會導致妊娠中 Sprague-Dawley 大白鼠在胎兒畸形 (圍頂頭和中樞脊椎骨融合) 發生率輕微的增加。類似的畸形並未見於紐西蘭大白兔。但是，無法顯示這是藥理性質所間接造成的結果（抑制雌激素生合成），或是 letrozole 本身的直接作用 (見「禁忌症」和「懷孕及授乳」)。

前臨床試驗結果限制在與已知的藥理活性相關的作用，這是在人類使用上唯一從動物試驗中獲得之安全性事項。

賦形劑

Colloidal anhydrous silica, microcrystalline cellulose, lactose monohydrate, magnesium stearate, maize starch, sodium starch glycollate, hydroxypropyl methylcellulose, polyethylene glycol 8000, talc, titanium dioxide (E171), iron oxide yellow (E172)。

配伍禁忌

無適用者。

儲存

見外包裝。

包裝上的有效期過後禁止使用。

使用及操作指示

並無特殊之使用及操作指示。

注意：藥品必須置於兒童無法取得之處。

製造廠：Novartis Pharma Stein AG
廠　址：(P) Schaffhauserstrasse CH-4332, Stein, Switzerland
　　(O) CH-4002, Basel, Switzerland
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NOVARTIS

Femara®

Non-steroidal aromatase inhibitor (inhibitor of estrogen biosynthesis); antineoplastic agent.

COMPOSITION AND PHARMACEUTICAL FORM

Active substance: 4,4'-[(1H-1,2,4-triazol-1-yl)-methylene]bis-benzonitrile (INN/USAN= letrozole).

Each film-coated tablet contains 2.5 mg letrozole.

For a full list of excipients, see section EXCIPIENTS.

Coated tablet, dark yellow, round, slightly biconvex with bevelled edges. One side bears the imprint "FV", the other "CG".

INDICATIONS

- Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.
- Extended adjuvant treatment of early breast cancer in post menopausal women who have received prior standard adjuvant tamoxifen therapy
- First-line treatment in postmenopausal women with hormone-dependent advanced breast cancer.
- Treatment of advanced breast cancer in women with natural or artificially induced postmenopausal status, who have previously been treated with antioestrogens.
- Pre-operative therapy in postmenopausal women with localised hormone receptor positive breast cancer, to allow subsequent breast-conserving surgery in women not originally considered candidates for this type of surgery. Subsequent treatment after surgery should be in accordance with standard of care.

DOSAGE AND ADMINISTRATION

Adult and elderly patients

The recommended dose of Femara is 2.5 mg once daily. In the adjuvant and extended adjuvant setting, treatment with Femara should continue for 5 years or until tumor relapse occurs, whichever comes first. In patients with metastatic disease, treatment with Femara should continue until tumor progression is evident. No dose adjustment is required for elderly patients.

Children

Not applicable.

Patients with hepatic and/or renal impairment

No dosage adjustment is required for patients with hepatic impairment or renal impairment (creatinine clearance ≥10 mL/min.). However, patients with severe hepatic impairment (Child-Pugh score C) should be kept under close supervision (see section PHARMACOKINETICS).

CONTRAINDICATIONS

- Known hypersensitivity to the active substance or to any of the excipients.
- Premenopausal endocrine status; pregnancy, lactation (see sections PREGNANCY AND LACTATION and PRECLINICAL SAFETY DATA).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Renal impairment

Femara has not been investigated in patients with creatinine clearance <10 mL/min. The potential risk/benefit to such patients should be carefully considered before administration of Femara.

Hepatic impairment

In patients with severe hepatic impairment (Child-Pugh score C), systemic exposure and terminal half-life were approximately doubled compared to healthy volunteers. Such patients should therefore be kept under close supervision (see section PHARMACOKINETICS).

Bone effects

Osteoporosis and/or bone fractures have been reported with the use of Femara. Therefore monitoring of overall bone health is recommended during treatment (see sections UNDESIRABLE EFFECTS and PHARMACODYNAMICS).

INTERACTIONS

Clinical interaction studies with cimetidine and warfarin indicated that the coadministration of Femara with these drugs does not result in clinically significant drug interactions.

A review of the clinical trial database indicated no evidence of other clinically relevant interaction with other commonly prescribed drugs.

There is no clinical experience to date on the use of Femara in combination with other anti-cancer agents.

Letrozole inhibits *in vitro* the cytochrome P_{450}-isozymes 2A6, and moderately 2C19. CYP2A6 does not play a major role in drug metabolism. In *in vitro* experiments letrozole, was not able to substantially inhibit the metabolism of diazepam (a substrate of CYP2C19) at concentrations approximately 100-fold higher than those observed in plasma at steady state. Thus, clinically relevant interactions with CYP2C19 are unlikely to occur. However, caution should be used in the concomitant administration of drugs whose disposition is mainly dependent on these isoenzymes and whose therapeutic index is narrow.

PREGNANCY AND LACTATION

Pregnancy

Femara is contraindicated during pregnancy (see section CONTRAINDICATIONS).

Isolated cases of birth defects (labial fusion, ambiguous genitalia) have been reported in pregnant women exposed to Femara (see also section PRECLINICAL SAFETY DATA).

Women of child-bearing potential

The physician needs to discuss the necessity of adequate contraception with women who have the potential to become pregnant including women who are perimenopausal or who recently became postmenopausal, until their postmenopausal status is fully established (see section PRECLINICAL SAFETY DATA).

Lactation

Femara is contraindicated during lactation (see section CONTRAINDICATIONS).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Since fatigue and dizziness have been observed with the use of Femara and somnolence has been reported uncommonly, caution is advised when driving or using machines.

UNDESIRABLE EFFECTS

Femara was generally well tolerated across all studies as first-line and second-line treatment for advanced breast cancer, as adjuvant treatment of early breast cancer and as extended adjuvant treatment in women who have received prior standard tamoxifen therapy. Approximately one third of the patients treated with Femara in the metastatic and neoadjuvant settings, approximately 75% of the patients in the adjuvant setting (both Femara and tamoxifen arms, at a median treatment duration of 60 months), and approximately 80% of the patients in the extended adjuvant setting (both Femara and placebo arms, at a median treatment duration of 60 months) experienced adverse reactions. Generally, the observed adverse reactions are mainly mild or moderate in nature, and most are associated with estrogen deprivation.

The most frequently reported adverse reactions in the clinical studies were hot flushes, arthralgia, nausea and fatigue. Many adverse reactions can be attributed to the normal pharmacological consequences of estrogen deprivation (e.g. hot flushes, alopecia and vaginal bleeding). The following adverse drug reactions, listed in Table 1, were reported from clinical studies and from post marketing experience with Femara.

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10,000, <1/1000); very rare (<1/10,000), including isolated report.

Table 1

Infections and infestations	
Uncommon	Urinary tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon	Tumor pain[6)]
Blood and the lymphatic system disorders	
Uncommon	Leukopenia
Metabolism and nutrition disorders	
Common	Anorexia, appetite increase, hypercholesterolemia
Uncommon	General edema
Psychiatric disorders	
Common	Depression
Uncommon	Anxiety[1)]
Nervous system disorders	
Common	Headache, dizziness
Uncommon	Somnolence, insomnia, memory impairment, dysesthesia[2)], taste disturbance, cerebrovascular accident, carpal tunnel syndrome
Eye disorders	
Uncommon	Cataract, eye irritation, blurred vision
Cardiac disorders	
Uncommon	Palpitations, tachycardia
Vascular disorders	
Uncommon	Thrombophlebitis[3)], hypertension, ischemic cardiac events[7,8)]
Rare	Pulmonary embolism, arterial thrombosis, cerebrovascular infarction
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnea, cough
Gastrointestinal disorders	

Common	Nausea, vomiting, dyspepsia, constipation, diarrhea
Uncommon	Abdominal pain, stomatitis, dry mouth
Hepatobiliary disorders	
Uncommon	Increased hepatic enzymes
Very rare	Hepatitis
Skin and subcutaneous tissue disorders	
Common	Alopecia, increased sweating, rash[4)]
Uncommon	Pruritus, dry skin, urticaria
Very rare	Angioedema, anaphylactic reaction, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia
Common	Myalgia, bone pain, osteoporosis, bone fractures
Uncommon	Arthritis
Not known[(9)]	Trigger finger
Renal and urinary disorders	
Uncommon	Increased urinary frequency
Reproductive system and breast disorders	
Uncommon	Vaginal bleeding, vaginal discharge, vaginal dryness, breast pain
General disorders and administration site conditions	
Very common	Hot flushes
Common	Fatigue[5)], peripheral edema
Uncommon	Pyrexia, mucosal dryness, thirst
Investigations	
Common	Weight increase
Uncommon	Weight loss

1) including nervousness, irritability
2) including paresthesia, hypoesthesia
3) including superficial and deep thrombophlebitis
4) including erythematous, maculopapular, psoriaform and vesicular rash
5) including asthenia and malaise
6) in metastatic/neoadjuvant setting only
7) in the adjuvant setting, irrespective of causality, the following adverse events occurred in the Femara and tamoxifen groups respectively: thromboembolic events (2.1% vs. 3.6%), angina pectoris (1.1% vs. 1.0%), myocardial infarction (1.0% vs. 0.5%) and cardiac failure (0.8% vs. 0.5%) (see section PHARMACODYNAMICS- Adjuvant treatment).
8) In the extended adjuvant setting, at a median treatment duration of 60 months for letrozole and 37 months for placebo, the following ADRs were reported for Femara and placebo (excluding all switches to Femara) respectively: new or worsening angina (1.4% vs. 1.0%); angina requiring surgery (0.8% vs. 0.6%); myocardial infarction (1.0% vs 0.7%); thromboembolic event (0.9% vs. 0.3%); stroke/TIA (1.5% vs 0.8%) (see section PHARMACODYNAMICS- Extended adjuvant treatment)
9) Based on post-marketing experience. Because the unknown size of the patient population exposed to Femara, it is not possible to reliably estimate their frequency which is therefore quoted as “not known”.

OVERDOSE

Isolated cases of overdosage with Femara have been reported.

No specific treatment for overdosage is known; treatment should be symptomatic and supportive.

PHARMACODYNAMICS

Pharmacodynamic effects

The elimination of estrogen-mediated stimulatory effects is a prerequisite for tumor response in cases where the growth of tumor tissue depends on the presence of estrogens. In postmenopausal women, estrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens - primarily androstenedione and testosterone - to estrone (E1) and estradiol (E2). The suppression of estrogen biosynthesis in peripheral tissues and the cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme.

Letrozole is a non-steroidal aromatase inhibitor. It inhibits the aromatase enzyme by competitively binding to the hem of the cytochrome P450 subunit of the enzyme, resulting in a reduction of estrogen biosynthesis in all tissues.

In healthy postmenopausal women, single doses of 0.1 mg, 0.5 mg and 2.5 mg letrozole suppress serum estrone and estradiol by 75 to 78% and 78% from baseline, respectively. Maximum suppression is achieved in 48 to 78 hours.

In postmenopausal patients with advanced breast cancer, daily doses of 0.1 to 5 mg suppress plasma concentration of estradiol, estrone, and estrone sulphate by 75 to 95% from baseline in all patients treated. With doses of 0.5 mg and higher, many values of estrone and estrone sulphate are below the limit of detection in the assays, indicating that higher estrogen suppression is achieved with these doses. Estrogen suppression was maintained throughout treatment in all these patients.

Letrozole is highly specific in inhibiting aromatase activity. Impairment of adrenal steroidogenesis has not been observed. No clinically relevant changes were found in the plasma concentrations of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxy-progesterone, and ACTH, or in plasma renin activity among postmenopausal patients treated with a daily dose of letrozole 0.1 to 5 mg. The ACTH stimulation test performed after 6 and 12 weeks of treatment with daily doses of 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 2.5 mg, and 5 mg did not indicate any attenuation of aldosterone or cortisol production. Thus, glucocorticoid and mineralocorticoid supplementation is not necessary.

No changes were noted in plasma concentrations of androgens (androstenedione and testosterone) among healthy postmenopausal women after 0.1 mg, 0.5 mg, and 2.5 mg single doses of letrozole or in plasma concentrations of androstenedione among postmenopausal patients treated with daily doses of 0.1 to 5 mg, indicating that the blockade of estrogen biosynthesis does not lead to accumulation of androgenic precursors. Plasma levels of LH and FSH are not affected by letrozole in patients, nor is thyroid function as evaluated by TSH, T4 and T3 uptake.

Adjuvant treatment

Study BIG 1-98

BIG-98 is a multicenter, double-blind study which randomized over 8,000 postmenopausal women with resected receptor-positive early breast cancer, to one of the following arms:

A. tamoxifen for 5 years

B. Femara for 5 years

C. tamoxifen for 2 years followed by Femara for 3 years

D. Femara for 2 years followed by tamoxifen for 3 years

This study was designed to investigate two primary questions: whether Femara for 5 years was superior to tamoxifen for 5 years (Primary Core Analysis and Monotherapy Arms Analysis) and whether switching endocrine treatments at 2 years was superior to continuing the same agent for a total of 5 years (Sequential Treatments Analysis).

The primary endpoint was disease free survival (DFS), secondary endpoints were overall survival (OS), distant disease free survival (DDFS), systemic disease-free survival (SDFS), invasive contralateral breast cancer, and time to distant metastasis (TDM).

Efficacy results at a median follow-up of 26 months

Data in Table 2 reflects result of the Primary Core Analysis (PCA) including data from non-switching arms (arms A and B) together with data truncated 30 days after the switch in the two switching arms (arms C and D). This analysis was conducted at a median treatment duration of 24 months and a median follow-up of 26 months. Femara for 5 years was superior to tamoxifen in all endpoints except overall survival and contralateral breast cancer.

Table 2 Disease-free and overall survival (PCA ITT population) at a median follow-up of 26 months

	Femara N=4003	**Tamoxifen** N=4007	**Hazard Ratio (95% CI)**	***P*-Value[1]**
Disease-free survival (primary) - events (protocol definition, total)	351	428	0.81 (0.70, 0.93)	0.0030
Time to distant metastases (secondary)	184	249	0.73 (0.60, 0.88)	0.0012
Distant disease free survival (secondary)	265	318	0.82 (0.70, 0.97)	0.0204
Overall survival (secondary) - number of deaths (total)	166	192	0.86 (0.70, 1.06)	0.1546
Systemic disease-free survival (secondary)	323	383	0.83 (0.72, 0.97)	0.0172
Contralateral breast cancer (invasive) (secondary)	19	31	0.61 (0.35, 1.08)	0.0910

CI = confidence interval,

[1] Logrank test, stratified by randomization option and use of prior adjuvant chemotherapy

MAA efficacy results at a median follow-up of 73 months

The Monotherapy Arms Analysis (MAA) which include data for the monotherapy arms only provides the clinically appropriate long-term update of the efficacy of Femara monotherapy compared to tamoxifen monotherapy (Table 3). In 2005, based on the PCA data presented in Table 2 and on recommendations by the independent Data Monitoring Committee, the tamoxifen monotherapy arms were unblinded and patients were allowed to cross over to Femara. 26% of patients randomized to tamoxifen elected to cross over to Femara – including a very small number of patients who crossed over to other aromatase inhibitors. To explore the impact of this selective crossover, analyses censoring follow-up at the date of the selective crossover (in the tamoxifen arm) are summarized for the MAA (Table 4).

At a median follow-up of 73 months and a median treatment duration of 60 months, the risk of a DFS event was significantly reduced with Femara compared with tamoxifen (MAA ITT analysis: HR 0.88; 95% CI 0.78, 0.99; *P*=0.03); confirming the 2005 PCA results. Censored analysis of DFS shows similar benefit (HR 0.85; 95% CI 0.75, 0.96). Similarly, the updated analysis confirmed the superiority of Femara in reducing the risk of distant disease free survival events (HR 0.87 0.76, 1.00) and increased time to distant metastases (HR 0.85; 95% CI 0.72, 1.00). Additionally, overall survival trended towards significance in the ITT analysis. Censored analysis of overall survival shows a significantly greater benefit (HR 0.82 0.70, 0.96) in favour of Femara.

Table 3 **Disease-free and overall survival (MAA ITT population) at a median follow up of 73 months**

	Femara N=2463	Tamoxifen N=2459	Hazard Ratio (95 % CI)	*P*-Value[1]
Disease-free survival (primary) - events (protocol definition, total)	509	565	0.88 (0.78, 0.99)	0.03
Time to distant metastases (secondary)	257	298	0.85 (0.72, 1.00)	0.045
Distant disease-free survival (metastases) (secondary)	385	432	0.87 (0.76, 1.00)	0.049
Overall survival (secondary) - number of deaths (total)	303	343	0.87 (0.75, 1.02)	0.08
Systemic disease-free survival (secondary)	465	512	0.89 (0.79, 1.01)	0.065
Contralateral breast cancer (invasive) (secondary)	34	44	0.76 (0.49, 1.19)	0.2
Censored analysis of DFS	509	543	0.85 (0.75, 0.96)	-
Censored analysis of Overall survival	338	338	0.82 (0.70, 0.96)	-

CI = confidence interval,

[1] Logrank test, stratified by randomization option and use of prior adjuvant chemotherapy

Sequential Treatments Analyses

The Sequential Treatments Analysis (STA) conducted at a median follow up of 48 months addresses the second primary question of the study. The primary analysis for the STA was from switch (or equivalent time-point in monotherapy arms) + 30 days (STA-S) with a two-sided test applied to each pair-wise comparison at the 2.5% level. Additional, exploratory analyses were conducted from randomization (STA-R) at a median follow up of 67 months, with the results for each comparison summarized by hazard ratios and 99% confidence intervals.

At a median follow up of 48 months there were no significant differences in any endpoint from switch in the Sequential Treatments Analysis with respect to either monotherapy (e.g. [Tamoxifen 2 years followed by] Femara 3 years versus tamoxifen beyond 2 years, DFS HR 0.89; 97.5% CI 0.68, 1.15 and [Femara 2 years followed by] tamoxifen 3 years versus Femara beyond 2 years, DFS HR 0.93; 97.5% CI 0.71, 1.22). At a median follow up of 67 months overall, there were no significant differences in any endpoint from randomization in the Sequential Treatments Analysis (e.g. tamoxifen 2 years followed by Femara 3 years versus Femara 5 years, DFS HR 1.10; 99% CI 0.86, 1.41; Femara 2 years followed by tamoxifen 3 years versus Femara 5 years, DFS HR 0.96; 99% CI 0.74, 1.24). There was no evidence that a sequence of Femara and tamoxifen was superior to Femara alone given for 5 years.

Safety data at a median treatment duration of 60 months

In study BIG-98 at a median treatment duration of 60 months, the side effects seen were consistent with the safety profile of the drug. Certain adverse reactions were prospectively specified for analysis, based on the known pharmacologic properties and side effect profiles of the two drugs.

Adverse events were analyzed irrespective of drug relationship. Most adverse events reported (approximately 75% of patients reporting 1 or more AE) were Grade 1 and Grade 2 applying the CTC criteria Version 2.0/ CTCAE, version 3.0. When considering all grades during study treatment, a higher incidence of events was seen for Femara compared to tamoxifen regarding hypercholesterolemia (52% vs. 29%), fractures (10.1% vs. 7.1%), myocardial infarctions (1.0% vs. 0.5%), osteoporosis (5.1% vs. 2.7%) and arthralgia (25.2% vs. 20.4%).

A higher incidence was seen for tamoxifen compared to Femara regarding hot flushes (38% vs. 33%), night sweating (17% vs. 15%), vaginal bleeding (13% vs 5.2%), constipation (2.9% vs 2.0%), thromboembolic events (3.6% vs 2.1%), endometrial hyperplasia/cancer (2.9% vs. 0.3%), and endometrial proliferate disorders (1.8% vs 0.3%).

Adjuvant Therapy in Early Breast Cancer, Study D2407

Study D2407 is a phase III, open-label, randomized, multicenter study designed to compare the effects of adjuvant treatment with letrozole to tamoxifen on bone mineral density (BMD), bone markers and fasting serum lipid profiles. A total of 262 postmenopausal women with hormone sensitive resected primary breast cancer were randomly assigned to either letrozole 2.5 mg daily for 5 years or tamoxifen 20 mg daily for 2 years followed by 3 years of letrozole 2.5 mg daily.

The primary objective was to compare the effects on lumbar spine (L2-L4) BMD of letrozole versus tamoxifen, evaluated as percent change from baseline lumbar spine BMD at 2 years.

At 24 months, the lumbar spine (L2-L4) BMD showed a median decrease of 4.1% in the letrozole arm compared to a median increase of 0.3% in the tamoxifen arm (difference = 4.4%). At 2 years, overall the median difference in lumbar spine BMD change between letrozole and tamoxifen was statistically significant in favor of tamoxifen (P<0.0001). The current data indicates that no patient with a normal BMD at baseline became osteoporotic at year 2 and only 1 patient with osteopenia at baseline (T score of -1.9) developed osteoporosis during the treatment period (assessment by central review).

The results for total hip BMD were similar to those for lumbar spine BMD. The differences, however, were less pronounced. At 2 years, a significant difference in favor of tamoxifen was observed in the overall BMD safety population and all stratification categories (P<0.0001). During the 2 year period, fractures were reported by 20 patients (15%) in the letrozole arm, and 22 patients (17%) in the tamoxifen arm.

In the tamoxifen arm, the median total cholesterol levels decreased by 16% after 6 months compared to baseline; a similar decrease was also observed at subsequent visits up to 24 months. In the letrozole arm, the median total cholesterol levels were relatively stable over time, with no significant increase at a single visit. The differences between the 2 arms were statistically significant in favour of tamoxifen at each time point (P<0.0001).

Extended adjuvant treatment

In a multicenter, double-blind, randomized, placebo-controlled study (CFEM345G MA-17), performed in over 5,100 postmenopausal patients with receptor-positive or unknown primary breast cancer patients who had remained disease-free after completion of adjuvant treatment with tamoxifen (4.5 to 6 years) were randomly assigned either Femara or placebo.

The primary analysis conducted at a median follow-up of around 28 months (25% of the patients being followed-up for up to 38 months) showed that Femara significantly reduced the risk of recurrence by 42% compared with placebo (hazard ratio 0.58; P=0.00003). Sensitivity analyses confirmed the robustness of the data. The statistically significant benefit in DFS in favour of letrozole was observed regardless of nodal status – node negative, hazard ratio 0.48, P=0.002; node positive, hazard ratio 0.61, P=0.002.

The independent Data and Safety Monitoring Committee recommended that women who were disease-free in the placebo arm be allowed to switch to Femara for up to 5 years when the study was unblinded in 2003. In the updated, final analysis conducted in 2008, 1551 women (60% of those eligible to switch) switched from placebo to Femara at a median 31 months after completion of adjuvant tamoxifen therapy. Median duration of Femara after switch was 40 months.

The updated final analysis conducted at a median follow-up of 62 months confirmed the significant reduction in the risk of breast cancer recurrence with Femara compared with placebo, despite 60% of eligible patients in the placebo arm switching to Femara after the study was unblinded. In the Femara arm, median duration of treatment was 60 months; in the placebo arm, median duration of treatment was 37 months. The protocol-specified 4-year DFS rate was identical in the Femara arm for both the 2004 and the 2008 analyses, confirming the stability of the data and robust effectiveness of Femara long-term. In the placebo arm, the increase in 4-year DFS rate at the updated analysis clearly reflects the impact of 60% of the patients having switched to Femara. This switching also accounts for the apparent dilution in treatment difference.

In the original analysis, for the secondary endpoint overall survival (OS) a total 113 deaths were reported (51 Femara, 62 placebo). Overall, there was no significant difference between treatments in OS (hazard ratio 0.82; P=0.29). In node positive disease, Femara significantly reduced the risk of all-cause mortality by approximately 40% (hazard ratio 0.61; P=0.035), whereas no significant difference was seen in patients with node negative disease (hazard ratio 1.36; P=0.385), in patient with prior chemotherapy or in patients with no prior chemotherapy. See Tables 4 and 5 that summarize the results:

Table 4 **Disease-free and overall survival (Modified ITT population)**

	2004 analysis – median follow-up 28 months			2008 final update analysis[1] – median follow-up 62 months		
	Letrozole N=2582	Placebo N=2586	HR (95% CI)[2] *P* value	Letrozole N=2582	Placebo N=2586	HR (95% CI)[2] *P* value
Disease-free survival (protocol definition)[3]						
Events	92 (3.6%)	155 (6.0%)	0.58 (0.45, 0.76) 0.00003	209 (8.1%)	286 (11.1%)	0.75 (0.63, 0.89) 0.001
4-year DFS rate	94.4%	89.8%		94.4%	91.4%	
Disease-free survival including deaths from any cause						
Events	122 (4.7%)	193 (7.5%)	0.62 (0.49, 0.78) 0.00003	344 (13.3%)	402 (15.5%)	0.89 (0.77, 1.03) 0.120
5-year DFS rate	90.5%	80.8%		88.8%	86.7%	
Distant metastases						
Events	57 (2.2%)	93 (3.6%)	0.61 (0.44, 0.84) 0.003	142 (5.5%)	169 (6.5%)	0.88 (0.70, 1.10) 0.246
Overall survival						
Deaths	51 (2.0%)	62 (2.4%)	0.82 (0.56, 1.19) 0.291	236 (9.1%)	232 (9.0%)	1.13 (0.95, 1.36) 0.175

Deaths[4]	–	--	–	236[5] (9.1%)	170[6] (6.6%)	0.78 (0.64, 0.96)
Contralateral breast cancer						
Invasive (total)	15 (0.6%)	25 (1.0%)	0.60 (0.31, 1.14) 0.117	33 (1.3%)	51 (2.0%)	0.64[7] (0.41, 1.00) 0.049

HR = Hazards ratio; CI = Confidence Interval

[1] When the study was unblinded in 2003, 1551 patients in the randomized placebo arm (60% of those eligible to switch – i.e. who were disease-free) switched to letrozole at a median 31 months after randomization. The analyses presented here ignore the switching under the ITT principle.

[2] Stratified by receptor status, nodal status and prior adjuvant chemotherapy.

[3] Protocol definition of disease-free survival events: loco-regional recurrence, distant metastasis or contralateral breast cancer.

[4] Exploratory analysis, censoring follow-up times at the date of switch (if it occurred) in the placebo arm.

[5] Median follow-up 62 months.

[6] Median follow-up until switch (if it occurred) 37 months.

[7] Odds ratio and 95% CI for the odds ratio.

Table 5 Disease-free and overall survival by receptor status, nodal status and previous chemotherapy (Modified ITT population)

	2004 analysis – median follow-up 28 months		2008 analysis – median follow-up 62 months1	
	HR (95% CI)[2]	*P* value	HR (95% CI)[2]	*P* value
Disease-free survival (protocol definition)				
Receptor status positive	0.57 (0.44, 0.75)	0.00003	0.74 (0.62, 0.89)	0.001
Nodal status				
Negative	0.48 (0.30, 0.78)	0.002	0.67 (0.49, 0.93)	0.015
Positive	0.61 (0.44, 0.83)	0.002	0.78 (0.62, 0.97)	0.027
Chemotherapy				
None	0.58 (0.40, 0.84)	0.003	0.71 (0.54, 0.92)	0.010
Received	0.59 (0.41, 0.84)	0.003	0.79 (0.62, 1.01)	0.055
Overall survival				
Nodal status				
Negative	1.36 (0.68, 2.71)	0.385	1.34 (0.99, 1.81)	0.058
Positive	0.61 (0.38, 0.97)	0.035	0.96 (0.75, 1.21)	0.710

HR = Hazards ratio; CI = Confidence Interval

[1] Including 60% of eligible patients who switched from placebo to letrozole after the study was unblinded in 2003

[2] From Cox regression models

In the updated analysis, as shown in Table 4, there was a significant reduction in the odds of an invasive contralateral breast cancer with Femara compared with placebo, despite 60% of the patients in the placebo arm having switched to Femara. There was no significant difference in overall survival.

An exploratory analysis censoring follow-up times at the date of switch (if it occurred) showed a significant reduction in the risk of all-cause mortality with Femara compared with placebo (Table 4).

There was no difference in efficacy or safety between patients aged <65 versus ≥65 years.

The updated safety profile of Femara did not reveal any new adverse event and was entirely consistent with the profile reported in 2004.

The following adverse events irrespective of causality were reported significantly more often with Femara than with placebo – hot flushes (Femara, 61% versus placebo, 51%), arthralgia/arthritis (41% versus 27%), sweating (35% versus 30%), hypercholesterolemia (24% versus 15%) and myalgia (18% versus 9.4%). The majority of these adverse events were observed during the first year of treatment. In the patients in the placebo arm who switched to Femara, a similar pattern of general adverse events was observed. The incidence of osteoporosis during treatment was significantly higher for Femara than for placebo (12.2% versus 6.4%). The incidence of clinical fractures during treatment was significantly higher for Femara than for placebo (10.4% versus 5.8%). In patients who switched to Femara, newly diagnosed osteoporosis during treatement with Femara was reported in 5.4% of patients while fractures were reported in 7.7% of patients. Irrespective of treatment, patients ≥65 years experienced more bone fractures and more osteoporosis. Updated results (median follow-up was 61 months) from the bone sub-study demonstrated that, at 2 years, compared to baseline, patients receiving Femara had a median decrease of 3.8% in hip Bone Mineral Density (BMD) compared to 2.0% in the placebo group (*P*=0.022). There was no significant difference between treatments in changes in lumbar spine BMD at any time. Updated results (median follow-up was 62 months) from the lipid sub-study showed for any of the lipid measurements no significant difference between the Femara and placebo groups at any time. In the updated analysis, the incidence of cardiovascular events (including cerebrovascular and thromboembolic events) during treatment with Femara versus placebo until switch was 9.8% vs 7.8%, a statistically significant difference.

Amongst the pre-printed, check-listed terms during study treatment, the most frequently reported events were: stroke/transient ischemic attack (letrozole, 1.5%; placebo until switch, 0.8%); new or worsening angina (letrozole, 1.4%; placebo until switch, 1.0%); myocardial infarction (letrozole, 1.0%; placebo until switch, 0.7%); thromboembolic events (letrozole, 0.9%; placebo until switch, 0.3%). The reported frequency of thromboembolic events as well as of stroke/transient ischemic attack was significantly higher for Femara than placebo until switch. The interpretation of safety results should consider that there was an unbalance in the median duration of treatment with letrozole (60 months) compared with placebo (37 months) due to the switch from placebo to Femara which occurred in approximately 60% of the patients.

First-line treatment

One well-controlled double-blind trial was conducted comparing Femara 2.5 mg to tamoxifen as first-line therapy in postmenopausal women with locally advanced or metastatic breast cancer. In 907 women, Femara was superior to tamoxifen in time to progression (primary endpoint) and in overall objective response, time to treatment failure and clinical benefit. Specific results are presented in Table 6.

Table 6 Results at a median follow-up of 32 months

	Femara	Tamoxifen	*P*-value
Time to progression (median)	9.4 months	6.0 months	<0.0001
Overall objective tumor response (rate)	32%	21%	0.0002
Duration of overall objective tumor response (median)	25 months	23 months	0.0578
Time to treatment failure (median)	9.1 months	5.7 months	<0.0001
Clinical benefit (rate)	50%	38%	0.0004

Both time to progression and objective response rate were significantly longer/higher for Femara than for tamoxifen irrespective of receptor status (Table 7).

Table 7 Receptor status

	Femara	Tamoxifen	*P*-value
Receptor Status:			
ER and/or PgR+:			
Time to progression (median)	9.4 months	6.0 months	<0.0001
Overall objective tumor response (rate)	33%	22%	0.0019
Unknown/negative:			
Time to progression (median)	9.2 months	6.0 months	0.0402
Overall objective tumor response (rate)	30%	20%	0.0309

ER: estrogen receptor

PgR: progesterone receptor

The efficacy by dominant disease site is described in Table 8:

Table 8 Efficacy by dominant disease site

Dominant disease site	Femara n=453	Tamoxifen n=454	*P*-value
Soft tissue:	**n=113**	**n=115**	
Time to progression (median)	12.1 months	6.4 months	0.0456
Overall objective tumor response	50%	34%	0.0171
Bone:	**n=145**	**n=131**	
Time to progression (median)	9.5 months	6.2 months	0.0262
Overall objective tumor response	23%	15%	0.0891
Viscera:	**n=195**	**n=208**	
Time to progression (median)	8.3 months	4.6 months	0.0005
Overall objective tumor response	28%	17%	0.0095
Liver metastasis:	**n=60**	**n=55**	
Time to progression (median)	3.8 months	3.0 months	0.0232
Overall objective tumor response	10%	11%	0.8735
Rate of overall clinical benefit	28%	16%	0.1292
Overall survival (median) (including	19 months	12 months	0.0727

Dominant disease site	Femara n=453	Tamoxifen n=454	*P*-value
crossover)			

Note: "Liver metastasis" is a subset of patients with dominant site of disease in viscera.

Study design allowed patients to crossover upon progression to the other therapy or discontinue from the study. Approximately 50% of patients crossed over to the opposite treatment arm and crossover was virtually completed by 36 months. The median time to crossover was 17 months (Femara to tamoxifen) and 13 months (tamoxifen to Femara). Femara treatment in the first line therapy of advanced breast cancer patients is associated with an early survival advantage over tamoxifen. The median survival was 34 months for Femara and 30 months for tamoxifen. A significantly greater number of patients were alive on Femara versus tamoxifen throughout the first 24 months of the study (repeated log rank test), see Table 9.

Table 9 Overall survival – Patients alive, died, crossed treatments

	Femara (n=458)			Tamoxifen (n=458)			Logrank
Months	**Alive**	**eaths**	**Crossed to tamoxifen**	**Alive**	**Deaths**	**Crossed to letrozole**	***P*-value**
6	426	31	51	406	52	74	0.0167
12	378	79	129	343	114	145	0.0038
18	341	115	185	297	159	179	0.0010
24	286	166	208	263	193	198	0.0246
30	241	209	225	227	227	217	0.0826
36	156	243	233	169	251	224	0.2237
42	70	267	238	85	266	226	0.4820
48	24	277		27	272	228	0.6413
54	6	277		6	276		*0.5303

* Overall log rank test *P*-value

The treatment effects analysed by the covariate "prior adjuvant antioestrogen therapy" are detailed in Table 10.

Table 10 Results according to prior adjuvant antioestrogen therapy

	Prior hormone therapy			No prior hormone therapy		
Endpoint	**Femara**	**Tamoxifen**	***P*-value**	**Femara**	**Tamoxifen**	***P*-value**
	n=84	**n=83**		**n=369**	**n=371**	
Time to progressio n (median)	8.9 months	5.9 months	0.0033	9.5 months	6.0 months	0.0003
Overall objective tumor response	26%	8%	0.0038	33%	24%	0.0039
Clinical benefit	46%	31%	0.0464	51%	40%	0.0026
	n=86	**n=83**		**n=372**	**n=375**	
Overall survival (median) including crossover	28 months	30 months	0.6558	34 months	30 months	0.3756
	n=45	**n=43**		**n=174**	**n=186**	
Survival first-line (patients who did not crossover) (median)	33 months	18 months		33 months	19 months	

In patients who did not crossover to the opposite treatment arm, median survival was 35 months with Femara (n=219, 95% CI 29 to 43 months) vs. 20 months with tamoxifen (n=229, 95% CI 16 to 26 months).

The total duration of endocrine therapy (time to chemotherapy) was significantly longer for Femara (median 16.3 months, 95% CI 15 to 18 months) than for tamoxifen (median 9.3 months, 95% CI 8 to 12 months) (logrank *P*=0.0047).

Worsening of Karnofsky Performance Score (KPS) by 20 points or more occurred in significantly fewer patients on letrozole first-line (19%) than tamoxifen first-line (25%) (odds ratio, *P*=0.0208).

Second-line treatment

Two well-controlled clinical trials were conducted, comparing two letrozole doses (Femara 0.5 mg and 2.5 mg) to megestrol acetate and to aminoglutethimide, respectively, in postmenopausal women with advanced breast cancer previously treated with antioestrogens.

Statistically significant differences were observed in favour of Femara 2.5 mg compared with megestrol acetate in overall objective tumor response rate (24% vs 16%, *P*=0.04), and in time to treatment failure (*P*=0.04). Time to progression was not significantly different between Femara 2.5 mg and megestrol acetate (*P*=0.07). Overall survival was not significantly different between the 2 arms (*P*=0.2).

In the second study, Femara 2.5 mg was statistically superior to aminoglutethimide for time to progression (*P*=0.008), time to treatment failure (*P*=0.003), and overall survival (*P*=0.002). The response rate was not significantly different between Femara 2.5 mg and aminoglutethimide (*P*=0.06).

Pre-operative treatment

A double blind trial was conducted in 337 patients randomized to either Femara 2.5 mg for 4 months or tamoxifen for 4 months. There were 55% objective responses in the Femara-treated patients versus 36% for the tamoxifen-treated patients (*P* <0.001) based on clinical assessment. This finding was consistently confirmed by ultrasound (*P*=0.042) and mammography (*P* <0.001), giving the most conservative assessment of response. This response was reflected in a statistically significantly higher number of patients in the Femara group who became suitable for and underwent breast-conserving therapy (45% of patients in the Femara group versus 35% of patients in the tamoxifen group, *P*=0.022).

PHARMACOKINETICS

Absorption

Letrozole is rapidly and completely absorbed from the gastrointestinal tract (mean absolute bioavailability: 99.9%). Food slightly decreases the rate of absorption (median t_{max}: 1 hour fasted versus 2 hours fed; and mean C_{max}: 129 ± 20.3 nmol/L fasted versus 98.7 ± 18.6 nmol/L fed), but the extent of absorption (AUC) is not changed. The minor effect on the absorption rate is not considered to be of clinical relevance, and therefore letrozole may be taken without regard to meal times.

Distribution

Plasma protein binding of letrozole is approximately 60%, mainly to albumin (55%). The concentration of letrozole in erythrocytes is about 80% of that in plasma. After administration of 2.5 mg ^{14}C-labelled letrozole, approximately 82% of the radioactivity in plasma was unchanged compound. Systemic exposure to metabolites is therefore low. Letrozole is rapidly and extensively distributed to tissues. Its apparent volume of distribution at steady state is about 1.87 ± 0.47 L/kg.

Metabolism and elimination

Metabolic clearance to a pharmacologically inactive carbinol metabolite is the major elimination pathway of letrozole (CL_m= 2.1 L/h), but is relatively slow when compared to hepatic blood flow (about 90 L/h). The cytochrome P_{450} isoenzymes 3A4 and 2A6 were found to be capable of converting letrozole to this metabolite. Formation of minor unidentified metabolites, and direct renal and faecal excretion play only a minor role in the overall elimination of letrozole. Within 2 weeks after administration of 2.5 mg ^{14}C-labelled letrozole to healthy postmenopausal volunteers, 88.2 ± 7.6% of the radioactivity was recovered in urine and 3.8 ± 0.9% in faeces. At least 75% of the radioactivity recovered in urine up to 216 hours (84.7 ± 7.8% of the dose) was attributed to the glucuronide of the carbinol metabolite, about 9% to two unidentified metabolites, and 6% to unchanged letrozole.

The apparent terminal elimination half-life in plasma is about 2 days. After daily administration of 2.5 mg, steady-state levels are reached within 2 to 6 weeks. Plasma concentrations at steady state are approximately 7 times higher than concentrations measured after a single dose of 2.5 mg, while they are 1.5 to 2 times higher than the steady-state values predicted from the concentrations measured after a single dose, indicating a slight non-linearity in the pharmacokinetics of letrozole upon daily administration of 2.5 mg. Since steady-state levels are maintained over time, it can be concluded that no continuous accumulation of letrozole occurs.

Age had no effect on the pharmacokinetics of letrozole.

Special populations

In a study involving volunteers with varying degrees of renal function (24-hour creatinine clearance 9 to 116 mL/min), no effect on the pharmacokinetics of letrozole was found after a single dose of 2.5 mg. In a similar study involving subjects with varying degrees of hepatic function, the mean AUC values of the volunteers with moderate hepatic impairment (Child-Pugh score B) was 37% higher than in normal subjects, but still within the range seen in subjects without impaired function. In a study comparing the pharmacokinetics of letrozole after a single oral dose in eight subjects with liver cirrhosis and severe hepatic impairment (Child-Pugh score C) to those in healthy volunteers (n=8), AUC and $t_{1/2}$ increased by 95 and 187%, respectively. Breast-cancer patients with severe hepatic impairment are thus expected to be exposed to higher levels of letrozole than patients without severe hepatic dysfunction. However, since in patients dosed at 5 or 10 mg/day no increase in toxicity was observed, a dose reduction in patients with severe hepatic impairment appears not to be warranted, although such patients should be kept under close supervision. In addition, in two well-controlled studies involving 359 patients with advanced breast cancer, no effect of renal impairment (calculated creatinine clearance: 20 to 50 mL/min) or hepatic dysfunction was found on the letrozole concentration.

PRECLINICAL SAFETY DATA

In a variety of preclinical safety studies conducted in standard animal species, there was no evidence of systemic or target organ toxicity.

Letrozole showed a low degree of acute toxicity in rodents exposed to up to 2,000 mg/kg. In dogs, letrozole caused signs of moderate toxicity at 100 mg/kg.

In repeated-dose toxicity studies in rats and dogs up to 12 months, the main findings observed can be attributed to the pharmacological action of the compound. The no-adverse effect level was 0.3 mg/kg in both species.

The pharmacological effects of letrozole resulted in skeletal, neuroendocrine and reproductive findings in a juvenile rat study. Bone growth and maturation were decreased from the lowest dose (0.003 mg/kg/day) in males and increased from the lowest dose (0.003 mg/kg) in females. Bone Mineral Density (BMD) was also decreased at that dose in females. In the same study, decreased fertility at all doses was accompanied by hypertrophy of the hypophysis, testicular changes which included a degeneration of the seminiferous tubular epithelium and atrophy of the female reproductive tract. With the exception of bone size in females and morphological changes in the testes, all effects were at least partially reversible.

Both in vitro and in vivo investigations on letrozole's mutagenic potential revealed no indications of any genotoxicity.

In a 104-week rat carcinogenicity study, no treatment-related tumors were noted in male rats. In female rats, a reduced incidence of benign and malignant mammary tumors at all the doses of letrozole was found.

Oral administration of letrozole to gravid Sprague-Dawley rats resulted in a slight increase in the incidence of fetal malformation (domed head and fused centrum/vertebrae) among the animals treated. Similar malformations were not seen in New Zealand White rabbits. However, it was not possible to show whether this was an indirect consequence of the pharmacological properties (inhibition of estrogen biosynthesis), or a direct effect of letrozole in its own right (see recommendations in sections CONTRAINDICATIONS and PREGNANCY AND LACTATION).

Preclinical observations were confined to those associated with the recognized pharmacological action, which is the only safety concern for human use derived from animal studies.

EXCIPIENTS

Colloidal anhydrous silica, microcristalline cellulose, lactose monohydrate, magnesium stearate, maize starch, sodium starch glycollate, hydroxypropyl methylcellulose, polyethylene glycol 8000, talc, titanium dioxide (E 171), iron oxide yellow (E 172).

Pharmaceutical formulations may vary between countries.

INCOMPATIBILITIES

Not applicable.

STORAGE

See folding box.

Femara should not be used after the date marked “EXP” on the pack.

INSTRUCTIONS FOR USE AND HANDLING

No specific instructions for use/handling.

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

Manufacturer:

See folding box.

International Package Leaflet

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