裕利股份有限公司　　函

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發文日期：中華民國112年06月15日

發文字號：112 裕字-第000996號

主　　旨：本公司銷售台灣百靈佳殷格翰股份有限公司之藥品「Glyxambi Film-Coated Tablets 25/5 mg（糖順平膜衣錠25/5毫克)」(衛部藥輸字第027073號)仿單變更事宜，如說明段。

說　　明：

一、本公司銷售台灣百靈佳殷格翰股份有限公司之藥品「Glyxambi Film-Coated Tablets 25/5 mg (糖順平膜衣錠 25/5 毫克)」(衛部藥輸字第027073 號)，承蒙　貴院採用，特此致謝。

二、接獲原廠通知，上述產品**自批號 301012 起**仿單變更，變更內容請參考附件仿單變更前後對照表。

三、特此通知，敬請轉知相關單位，造成不便懇請見諒，並請繼續支持本公司為禱。

附件：原廠公文及相關資料。

裕利股份有限公司
負責人 凱珀斯

Boehringer Ingelheim

台灣百靈佳殷格翰股份有限公司 函

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受文者：裕利股份有限公司、吉程股份有限公司

發文日期：中華民國 112 年 5 月 31 日
發文字號：(112) 百總字第 078 號
附　　件：

請 貴公司函轉 Glyxambi® 25/5 mgTablets (即 糖順平®膜衣錠 25/5 毫克)使用單位為荷，行文內容如下：

主旨： 有關 Glyxambi® 25/5 mgTablets (即 糖順平®膜衣錠 25/5 毫克)之仿單變更，詳細說明如下，請查照！

說明：

一、 承蒙 貴院支持與採購 Glyxambi® 25/5 mgTablets (即 糖順平®膜衣錠 25/5 毫克，以下簡稱為『本產品』)，謹此致上十二萬分謝意。

二、 本產品仿單變更，起始批號 301012 將陸續供應至貴院使用。

三、

仿單段落	變更前仿單	變更後仿單
--	**衛部藥輸字第 027074 號** **衛部藥輸字第 027073 號**	**10/5 毫克: 衛部藥輸字第 027074 號** **25/5 毫克: 衛部藥輸字第 027073 號**
1.3 劑型	--	膜衣錠。
2. 適應症	~~適應症與用法~~ GLYXAMBI 錠劑適用於配合飲食控制及運動，以改善下列第二型糖尿病人者的血糖控制：使用 metformin 合併 empagliflozin 或 linagliptin 未能達到適當血糖控制者；或已在使用 empagliflozin 及 linagliptin 合併治療者。	GLYXAMBI 錠劑適用於配合飲食控制及運動，以改善下列第二型糖尿病人者的血糖控制：使用 metformin 合併 empagliflozin 或 linagliptin 未能達到適當血糖控制者；或已在使用 empagliflozin 及 linagliptin 合併治療者。
7. 交互作用	表 3 與 GLYXAMBI 臨床上相關	**表 1 與 GLYXAMBI 臨床上相關**

	的交互作用	**的交互作用**
8.2 臨床試驗經驗	併用 empagliflozin (每日劑量 10 mg 或 25 mg) 與 linagliptin (每日劑量 5 mg) 的安全性，已於有效藥物對照的臨床試驗中進行評估，總計涵蓋 1363 位第二型糖尿病病人，治療期間最長 52 週。依據這些試驗的統合分析結果，同時併用 empagliflozin 及 linagliptin 最常見的不良反應如表 1 所示。 **表 1 Empagliflozin 併用 Linagliptin 治療組內發生率 ≥5% 的不良反應** ...[a]試驗預設之不良事件類別，包括但不限於泌尿道感染、無症狀之菌尿症、膀胱炎 *低血糖* 表 2 說明 empagliflozin 及 linagliptin 治療 52 週的低血糖事件。 **表 2 總體 a 和嚴重 b 低血糖不良反應發生率**	併用 empagliflozin (每日劑量 10 mg 或 25 mg) 與 linagliptin (每日劑量 5 mg) 的安全性，已於有效藥物對照的臨床試驗中進行評估，總計涵蓋 1363 位第二型糖尿病病人，治療期間最長 52 週。依據這些試驗的統合分析結果，同時併用 empagliflozin 及 linagliptin 最常見的不良反應如表 2 所示。 **表 2 Empagliflozin 併用 Linagliptin 治療組內發生率 ≥5% 的不良反應** ...[a]試驗預設之不良反應類別，包括但不限於泌尿道感染、無症狀之菌尿症、膀胱炎 *低血糖* 表 3 說明 empagliflozin 及 linagliptin 治療 52 週的低血糖事件。 **表 3 總體[a]和嚴重[b]低血糖不良反應發生率**
8.3 上市後經驗	在 linagliptin及empagliflozin 上市後曾發現其他不良反應，由於這些反應是由不確定人數之族群自發通報，因此通常無法可靠估計發生率，也無法確立與藥物暴露量之間的因果關係。 • 急性胰臟炎，包括致命的胰臟炎 *[詳見適應症及*	在 linagliptin 及 empagliflozin 上市後曾發現其他不良反應，由於這些反應是由不確定人數之族群自發通報，因此通常無法可靠估計發生率，也無法確立與藥物暴露量之間的因果關係。 • *胃腸道疾病*：急性胰臟炎，包括致命的胰臟炎

	使用方法 (1)]。 • 酮酸中毒。 • 尿路敗血症與腎盂腎炎 • 會陰部壞死性筋膜炎(弗尼爾氏壞疽) • 過敏反應，包括急性過敏、血管性水腫和鱗片狀脫皮。 • 嚴重和行動不便之關節疼痛 • 大皰性類天皰瘡 • 急性腎損傷 • 皮膚反應 • 口腔潰瘍、口腔炎	[詳見適應症 (2)]、便祕、口腔潰瘍、口腔炎 • *免疫系統疾病*：過敏反應，包括急性過敏、血管性水腫和鱗片狀脫皮 • *感染*：會陰部壞死性筋膜炎(弗尼爾氏壞疽) 、尿路敗血症與腎盂腎炎 • *代謝及營養疾病*：酮酸中毒 • *肌肉骨骼與結締組織疾病*：嚴重和行動不便之關節疼痛 • *腎臟及泌尿系統疾病*：急性腎損傷 • *皮膚及皮下組織疾病*：大皰性類天皰瘡、皮膚反應(如: 皮疹、蕁麻疹)
9. 過量	GLYXAMBI 用藥過量時，請立即就診。~~依病人的臨床狀況而定，採用一般支持性措施(例如移除胃腸道中尚未吸收的物質、進行臨床監測，以及給予支持性治療)。~~目前尚未針對血液透析清除 empagliflozin 的效果進行研究，以血液透析或腹膜透析清除 linagliptin 則不太可行。	GLYXAMBI 用藥過量時，請立即就診。目前尚未針對血液透析清除 empagliflozin 的效果進行研究，以血液透析或腹膜透析清除 linagliptin 則不太可行。
12. 臨床試驗資料	**Linagliptin 心血管安全性試驗** **CARMELINA** CARMELINA 試驗，針對第二型糖尿病成人病人且具有大血管或腎臟疾病病史之病人族群，評估 TRAJENTA 對 心血管風險的影響… …47%受試者為中度腎功能不全(eGFR 30 至<60 mL／min／1.73	**Linagliptin 心血管安全性試驗** **CARMELINA** CARMELINA 試驗，針對第二型糖尿病成人病人且具有大血管或腎臟疾病病史之病人族群，評估 linagliptin 對心血管風險的影響… …47%受試者為中度腎功能不全(eGFR 30 至<60 mL／min／1.73 m^2)及 15%為重度腎功能不全

	m2)及 15%為重度腎功能不全 (eGFR <30 mL／min／1.73 m2)。 重大心臟血管綜合不良事件發生率於兩個治療組別: 安慰劑組每 1000 病人年發生 56.3 次事件相較於 linagliptin 治療組每 1000 病人年發生 57.5 次事件。	(eGFR <30 mL／min／1.73 m2)。 重大心臟血管綜合不良事件發生率於兩個治療組別: 安慰劑組每 1000 病人年發生 56.3 次事件相較於 linagliptin 治療組每 1000 病人年發生 57.7 次事件。
13.2 效期	--	如包裝所示。
14. 病人使用須知	低血糖 請告知病人 GLYXAMBI 與磺醯尿素類藥物或胰島素併用時，會增加低血糖症的發生風險，因此可能須降低磺醯尿素類藥物或胰島素的劑量，以減少低血糖症的風險[請參閱警語及注意事項 (5.1.5)]。	併用胰島素與胰島素促泌劑時發生的低血糖 請告知病人 GLYXAMBI 與胰島素促泌劑(例如 磺醯尿素類藥物) 或胰島素併用時，會增加低血糖症的發生風險，因此可能須降低胰島素促泌劑或胰島素的劑量，以減少低血糖症的風險*[請參閱警語及注意事項(5.1.5)]*。
15. 其他	**製造廠** **Boehringer Ingelheim Pharma GmbH & Co. KG** **Binger Strasse 173, 55216** **Ingelheim am Rhein, Germany** **國外許可證持有者** **Boehringer Ingelheim International GmbH** **Ingelheim am Rhein, Germany** **藥商** **台灣百靈佳殷格翰股份有限公司** **台北市民生東路三段 2 號 12 樓**	共用仿單產品: 糖順平® 膜衣錠 10/5 毫克 Glyxambi® 10/5mg Film-Coated Tablets (衛部藥輸字第 027074 號) 糖順平® 膜衣錠 25/5 毫克 Glyxambi® 25/5mg Film-Coated Tablets (衛部藥輸字第 027073 號) 修訂日期 2022 年 5 月 核定日期 2022 年 9 月 **製造廠** **Boehringer Ingelheim**

	修訂日期 2021 年 7 月 核定日期 2022 年 2 月	**Pharma GmbH & Co. KG** **Binger Strasse 173, 55216** **Ingelheim am Rhein,** **Germany** **國外許可證持有者** **Boehringer Ingelheim** **International GmbH** **Ingelheim am Rhein,** **Germany** **藥商** **台灣百靈佳殷格翰股份有限公司** **台北市民生東路三段 2 號 12 樓**

四、 敬請 貴院諒解因仿單變更所造成的不便，前述說明若有其他疑問與意見，尚請不吝來電賜教。

敬祝醫安！

內文至此

敬祝商祈

台灣百靈佳殷格翰股份有限公司

代表人：邱建誌

格列平®膜衣錠 10/5 毫克
格列平®膜衣錠 25/5 毫克
Glyxambi® 10/5mg Film-Coated Tablets
Glyxambi® 25/5mg Film-Coated Tablets

10/5 毫克：衛部藥輸字第 027074 號

25/5 毫克：衛部藥輸字第 027073 號

本藥須由醫師處方使用

1. 性狀

1.1 有效成分及含量

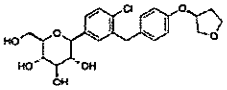
GLYXAMBI 錠劑為口服型藥物含有：empagliflozin 及 linagliptin。

Empagliflozin

Empagliflozin 是一種鈉-葡萄糖共同運送蛋白 2 (SGLT2) 抑制劑。

Empagliflozin 的化學名為 D-Glucitol,1,5-anhydro-1-C- [4-chloro-3- [[4- [[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S)。

分子式為 $C_{23}H_{27}ClO_7$，分子量為 450.91，結構式為：



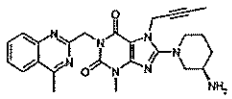
Empagliflozin 為白色至淡黃色，不具吸濕性的乾粉。水溶性極低，略溶於甲醇，微溶於酒精和乙醇；在 50% 乙醇/水中為可溶；在甲苯中幾不溶。

Linagliptin

Linagliptin 是一種糖肽胜肽酶-4 (DPP-4) 酵素抑制劑。

Linagliptin 的化學名為 1H-Purine-2,6-dione, 8- [(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1- [(4-methyl-2-quinazolinyl)methyl]-

分子式為 $C_{25}H_{28}N_8O_2$，分子量為 472.54，結構式為：



Linagliptin 為白色至淡黃色，不具吸濕性的固體粉質。水溶性極低，可溶於甲醇，略溶於酒精，在異丙醇中幾不溶，在丙酮中幾不溶。

GLYXAMBI

GLYXAMBI 錠劑有兩種劑量，含有 empagliflozin 10 mg 或 25 mg，加上 linagliptin 5 mg。

1.2 賦形劑

GLYXAMBI 的非活性成分如下：膜衣錠核心：甘露醇、預糊化澱粉、玉米澱粉、共聚維酮、交聚維酮、滑石粉、硬脂酸鈣。膜衣：經再甲基維素、甘露醇、滑石、二氧化鈦、聚乙二醇；氧化鐵，黃色 (10 mg/5 mg)，或氧化鐵，紅色 (25 mg/5 mg)。

1.3 劑型

膜衣錠。

1.4 錠品外觀

GLYXAMBI 為 empagliflozin 及 linagliptin 的複合劑：

- 10 mg empagliflozin/5 mg linagliptin 為淺黃色、圓弧三角形、平面、邊緣斜切的膜衣錠，一面壓印百靈佳殷格翰公司標誌，另一面壓印數字「10/5」。
- 25 mg empagliflozin/5 mg linagliptin 為淺粉紅色、圓弧三角形、平面、邊緣斜切的膜衣錠，一面壓印百靈佳殷格翰公司標誌，另一面壓印數字「25/5」。

2. 適應症

GLYXAMBI 錠劑適用於配合飲食控制及運動，以改善下列第二型糖尿病人者的血糖控制：使用 metformin 合併 empagliflozin 或 linagliptin 未能達到適當血糖控制者；或已在使用 empagliflozin 及 linagliptin 合併治療者。

Empagliflozin 用於具第二型糖尿病且已有心血管疾病的成人病人時，可降低心血管原因死亡的風險。然而，本品糖順平用於具第二型糖尿病且已有心血管疾病的成人病人時，其降低心血管原因死亡的風險的有效性尚未被建立。

使用上的限制
GLYXAMBI 不建議用於第一型糖尿病人，其可能會增加這類病人酮酸中毒的風險。*[詳見警語及注意事項 (5.1.2)]*。

由於尚未針對具有胰臟炎病史的病人進行 GLYXAMBI 的試驗，因此目前仍不瞭解具有胰臟炎病史之病人使用 GLYXAMBI，是否會增加發生胰臟炎的風險 *[詳見警語及注意事項 (5.1.1)]*。

3. 用法及用量

3.1 用法用量

3.1.1 開始使用糖順平前

- 開始使用糖順平前請先評估腎功能，並遵照臨床指示*[請參閱警語及注意事項 (5.1.3)]*。
- 針對體液容量減少的病人，建議在開始服用糖順平前先矯正此一狀況 *[請參閱警語及注意事項 (5.1.3) 及特殊族群注意事項(6.5, 6.7)]*。

3.1.2 建議劑量

GLYXAMBI 的建議劑量為每日早上一次，每次 10 mg empagliflozin/5 mg linagliptin，可與食物一起服用，亦可空腹服用。GLYXAMBI 可增加至每日一次 25 mg empagliflozin/5 mg linagliptin，做為額外的血糖控制。

3.3 特殊族群用法用量
腎功能不全病人的建議劑量
腎絲球過濾率估計值 (eGFR) 低於 30 mL/min/1.73 m² 的病人，不應使用 GLYXAMBI。

腎絲球過濾率估計值大於或等於 30 mL/min/1.73 m² 的病人，無須調整劑量。

若腎絲球過濾率估計值持續低於 30 mL/min/1.73 m²，應停用 GLYXAMBI *[詳見警語及注意事項 (5.1.3、5.1.5) 與特殊族群注意事項 (6.7)]*。

4. 禁忌

GLYXAMBI 不可用於有下列狀況的病人：

- 患有重度腎功能不全、末期腎病或正接受透析 *[詳見特殊族群注意事項 (6.7)]*。
- 曾對 empagliflozin、linagliptin 或 GLYXAMBI 中任何賦形劑出現嚴重過敏反應，例如急性過敏、血管性水腫、類片狀脫皮、蕁麻疹、曾發生支氣管過敏 *[詳見警語及注意事項 (5.1.8)、副作用/不良反應 (8)]*。

5. 警語及注意事項

5.1 警語/注意事項

5.1.1 胰臟炎
曾有服用 linagliptin 的病人發生急性胰臟炎的報告。在 CARMELINA 試驗*[詳見臨床試驗資料 (12)]*中，有 9 名 (0.3%) 接受 linagliptin 治療的病人和 5 名 (0.1%) 接受安慰劑治療的病人發生急性胰臟炎。在 CARMELINA 試驗中，有 2 名接受 linagliptin 治療的病人發生急性胰臟炎並因而致死。linagliptin 的上市後報告，曾發生急性胰臟炎的病例，包括致命的胰臟炎。

持續對注意胰臟炎的可能徵象和症狀，若懷疑出現胰臟炎，請立即停止使用 GLYXAMBI 並開始給予適當的治療。目前仍不瞭解有胰臟炎病史之病人使用 GLYXAMBI，是否會增加發生胰臟炎的風險。

5.1.2 酮酸中毒
過去在對使用第二型鈉-葡萄糖輸送蛋白 (SGLT2) 抑制劑（包含 empagliflozin）的第一型和第二型糖尿病病人進行上市後監測時，以及在臨床試驗中，曾發現酮酸中毒的案例；注意一種嚴重、威脅生命且必須緊急住院治療的疾病。使用 empagliflozin 的病人曾有報告致死的酮酸中毒案例。在以第一型糖尿病病人為研究對象的安慰劑對照試驗中，相比於接受安慰劑的病人，接受 SGLT2 抑制劑治療的病人，酮酸中毒風險增加。GLYXAMBI 不建議用於治療第一型糖尿病病人 *[詳見適應症 (2)]*。

接受 GLYXAMBI 治療的病人如果有出現意度代謝性酸中毒的跡象和症狀，無論其血糖濃度多高，均應評估是否發生酮酸中毒。因為即使血糖濃度低於 250 mg/dL，仍可能發生 GLYXAMBI 相關酮酸中毒。如果懷疑酮酸中毒，應停用 GLYXAMBI、評估病人，並立即開始進行治療。治療酮酸中毒時，可能需要給予胰島素、水分和補充碳水化合物。

許多上市後報告顯示，尤其是在第一型糖尿病病人中，當有未即時發現酮酸中毒的情形，也因此延遲治療，其原因就是病人的血糖濃度低於一般糖尿病酮酸中毒預期呈現的血糖濃度（經常低於 250 mg/dL）。病人就診時的跡象與症狀符合脫水及重度代謝性酸中毒之診斷，包括噁心、嘔吐、腹痛、全身不適、[illegible]促。在部分但並非全部案例中，曾發現病人較易發生酮酸中毒的因素，例如胰島素劑量調降、急性[illegible]病、熱量攝取減少、手術、可能導致胰島素不足的胰臟疾患（例如第一型糖尿病、胰臟炎或胰臟手術病史），以及酗酒。

開始使用 GLYXAMBI 前，請先考慮病人病史中可能使其較易發生酮酸中毒的因素，包括任何原因引起的胰臟胰島素不足、熱量攝取低下、以及54酒。病人進行預定手術時，考慮暫時前至少三天暫時停用 Glyxambi。*[詳見臨床特性(10.2)與藥物動力學特性 (11)]*。考慮監測酮酸中毒並在已知較易發生酮酸中毒的其他臨床情況下（例如因急性疾病或術後而長時間禁食時）暫時停用 GLYXAMBI。再開始使用 Glyxambi 前須確認發生酮酸中毒的風險因子已解決。應監測病人酮酸酮體中毒的徵象與症狀，並請病人在出現這些症狀時，應停止使用 Glyxambi 並就醫。

5.1.3 體液容量減少
Empagliflozin 可引發血管內容積減少，有時連帶發生暫有症狀的低血壓或血清肌酸酐急性略開的變化*[請參閱臨床試驗經驗(8.2)]*。上市後報告曾有接受 SGLT2 抑制劑包含 empagliflozin 的第二類型糖尿病病人，出現急性腎損傷，有些病人需要住院及血液透析。腎功能不全的病人(eGFR 低於 60 mL/min/1.73 m²)、年長的病人、或正在使用環利尿劑的病人可能發生體液容量減少或低血壓的風險增加。病人具有上述一個或多個特性時，在開始糖順平治療之前，請評估體液狀態及腎功能，體液容量減少的病人，開始糖順平治療之前，請先矯正此情形。開始糖順平治療之後，請監測體液容量減少之徵象和症狀以及腎功能。

5.1.4 尿路感染與腎盂腎炎
在上市後使用經驗中，曾通報使用 SGLT2 抑制劑（包含 empagliflozin）的病人發生嚴重泌尿道感染（包括尿路敗血症及需要住院的腎盂腎炎）的案例。SGLT2 抑制劑的治療會提高泌尿道感染的風險。請評估病人是否有泌尿道感染的徵象和症狀，並於必要時立即給予治療 *[詳見副作用/不良反應 (8)]*。

5.1.5 併用胰島素與胰島素促泌劑時發生的低血糖
胰島素與胰島素促泌劑已知都可能引發低血糖。在臨床試驗中，較教於安慰劑，empagliflozin 或 linagliptin 與胰島素促泌劑（例如磺醯尿素類藥物）或胰島素併用時的低血糖症發生率較高。因此，與 GLYXAMBI 併用時，可能須降低胰島素促泌劑或胰島素的劑量，以減少低血糖症的風險。

5.1.6 會陰部壞死性筋膜炎(弗尼爾氏壞疽)
會陰部壞死性筋膜炎(弗尼爾氏壞疽)是一種罕見但嚴重且可能危及性命的壞死性感染，需要緊急手術治療。在接受 SGLT2 抑制劑(包括 empagliflozin)之糖尿病病人的上市後監測中，曾發現會陰部壞死性筋膜炎的罕見案例：在女性與男性皆有病例，其中嚴重者也有可能住院、多次手術甚或死亡。

對於接受糖順平治療和有出現生殖器或會陰區域疼痛或壓痛、紅腫或敏感性快速發展成身體不適的病人，皆應評估是否發生壞死性筋膜炎。如有懷疑，應立即以廣效性抗生素進行治療，如有必要，可進行手術清創。停用糖順平，密切監測血糖濃度，並提供適當的血糖控制替代療法。

5.1.7 生殖器黴菌感染
Empagliflozin 可能會提高生殖器黴菌感染的風險 *[詳見臨床試驗經驗(8.2)]*。過去有慢性或復發性生殖器黴菌感染病史的病人，會有較高的機會發生生殖器黴菌感染，應視情況監測及治療。

5.1.8 過敏反應
linagliptin 上市後，曾通報發生嚴重過敏反應的病例，包括急性過敏、血管性水腫和蕁麻疹脫症。這些反應主要[illegible]開始 linagliptin 治療後 3 個月內，有些病例發生在第一次劑量之後。

[illegible]化雙肽胜肽酶-4 (DPP-4) 抑制劑，也曾發生血管性水腫的病例。對其他 DPP-4 抑制劑曾有血管性水腫病[illegible]人，應特別審慎。目前仍不瞭解這類病人使用 GLYXAMBI 是否會增加血管性水腫的風險。

[illegible]後使用 [illegible] empagliflozin 治療的病人有嚴重過敏反應（例如血管性水腫）。

和果發生過敏反應，請停止 GLYXAMBI，按照適當的標準照護進行治療，並監測直至徵兆和症狀消失。GLYXAMBI 禁用於對 empagliflozin、linagliptin 或 GLYXAMBI 中任何賦形劑有嚴重過敏反應者*[請參閱禁忌(4)]*。

5.1.9 低密度脂蛋白膽固醇 (LDL-C) 上升

使用 empagliflozin 可能會導致 LDL-C 升高 *[詳見臨床試驗經驗(6.2)]*。應視情況監測及治療。

5.1.10 嚴重和行動不便之關節疼痛

雙肽基肽酶-4(DPP-4)抑制劑的上市後報告中曾有嚴重和行動不便之關節疼痛的案例。這些病人是在開始用藥後第 1 天或數年後發生關節痛症狀。大多數病人在停藥後症狀即緩解。有些案例在停藥、症狀緩解後再用藥或換用其他 DPP-4 抑制劑時，再發生關節痛症狀。考慮 DPP-4 抑制劑可能造成嚴重關節疼痛，若發生，思停藥。

5.1.11 大皰性類天皰瘡 (Bullous Pemphigoid)

在 CARMELINA 試驗中*[詳見臨床試驗資料(12)]*，有 7 名 (0.2%) 接受 linagliptin 治療的病人發生大皰性類天皰瘡，其中 3 人 (0.1%) 需要住院治療；接受安慰劑治療者則無此種病例。DPP-4 抑制劑的上市後報告中曾有需要住院的大皰性類天皰瘡案例。在所報告的病例中，病人通常可在接受局部或全身性免疫抑制治療前停止使用 DPP-4 抑制劑之後復原。請告知病人，應通報在接受 GLYXAMBI 時出現的水泡或糜爛。若懷疑有大皰性類天皰瘡，應停止使用 GLYXAMBI，並考慮轉診皮膚科醫師接受診斷及適當的治療。

6. 特殊族群注意事項

6.1 懷孕

風險摘要

由於 empagliflozin 的動物研究資料顯示有不良腎臟影響，因此不建議在懷孕第二孕期和第三孕期時使用 GLYXAMBI。

在懷孕婦女使用 GLYXAMBI、linagliptin 或 empagliflozin 的現有資料極少。因此無法確認對定藥物與重大先天缺陷和流產風險之間是否具有相關性。懷孕期間糖尿病控制不佳可能對母體和胎兒造成風險*(詳見「臨床考量」一節)*。

在動物試驗中，在相當於人類第二孕期晚期和第三孕期的大鼠腎臟發育期間使用 empagliflozin (總暴露量為人類治療劑量的其中一項成分之一)時，導致不良腎臟變化。因為最大臨床劑量 13 倍的劑量引發可逆原的腎盂和腎小管擴張。懷孕的大鼠併用 linagliptin 和 empagliflozin 時，未觀察到對發育有不良影響*(詳見「資料」一節)*。

在有孕前糖尿病且 HbA1c >7 的女性，美小松出現重大先天缺陷的背景風險估計值為 6%-10%，在 HbA1c >10 的女性則高達 20%-25%，但不知道此類群的流產背景風險估計值。在美國一般族群之經臨床確認的懷孕中，重大先天缺陷與流產的背景風險估計值分別為 2%-4%與 15%-20%。

臨床考量

*疾病相關的懷孕風險和疾病相關胎兒風險：*懷孕期間若患有控制欠佳之糖尿病，會提高母體發生糖尿病酮酸血症、子癲前症、自發性流產、早產、死產和生產併發症的風險。控制欠佳之糖尿病之會提高胎兒發生重大先天缺陷、死產和巨嬰症相關疾病的風險。

資料

動物實驗數據

在大鼠器官形成期間使用合併劑量最高 empagliflozin 700 mg/kg/天，和上 linagliptin 140 mg/kg/天 (分別為臨床劑量的 253 倍和 353 倍)，結果並不具致畸胎性。尚未針對 GLYXAMBI 的併用或分進行出生前和出生後的生長試驗。

Empagliflozin：

在授出生後第 21 天 (PND 21) 開始，以 1、10、30 和 100 mg/kg/天每日劑量對年幼大鼠直接地用 empagliflozin 至 PND 90 為止，在 100 mg/kg/日的每日劑量下 (根據 AUC)，約為最大臨床劑量 25 mg 的 13 倍) 曾觀察到其腎臟重量增加以及腎小管和腎盂擴張現象。在 13 週的不用藥恢復期結束後，對未觀察到上述發現。這些結果是在大鼠腎臟發育期間(相當於人類腎臟發育的第二孕期晚期和第三孕期)暴露於藥物時發生。

在大鼠和兔子的胚胎胎兒發育研究中，empagliflozin 是在相當於人類器官形成期(第一孕期)的時期地用，在最高至 300 mg/kg 的每日劑量 (根據 AUC 計算，大鼠與兔子使用劑量分別相當於最大臨床劑量 25 mg 的 48 與 128 倍) 下未對發育造成不良影響。在引發大鼠母體毒性的更高劑量下，使用 700 mg/kg 的每日劑量 (相當於最大臨床劑量 25 mg 的 154 倍)，胎兒四肢骨骼畸形的發例會增加。Empagliflozin 可通過大鼠胎盤進入胎兒組織。然兔子使用較高的 empagliflozin 劑量 (700 mg/kg 的每日劑量，相當於最大臨床劑量 25 mg 的 139 倍) 曾引發母體及胎兒毒性。

在懷孕大鼠的產前和產後發育研究中，使用 empagliflozin 最高劑量至 100 mg/kg/天 (約相當於最大臨床劑量 25 mg 的 16 倍)，自妊娠第 6 天開始地用至泌乳第 20 天 (斷奶) 為止，並未產生母體毒性。在劑量 30 mg/kg/天 (約相對於最大臨床劑量 25 mg 的 4 倍) 以上，觀察到幼鼠的體重減輕。

Linagliptin：

於懷孕 Wistar Han 大鼠與兔為拉格先的器官形成期間使用 linagliptin (劑量分別最高達一天 240 mg/kg 與 150 mg/kg)時，皆未觀察到不良的發育結果。根據基底量計算，在大鼠與兔子使用的這些劑量約分別為最高臨床劑量 5 mg 的 943 與 1943 倍。在 Wistar Han 大鼠懷孕第 6 天到泌乳第 21 天期間、使用人體最高建議劑量 49 倍的 linagliptin 劑量時 (根據基底量計算)，並未在幼鼠觀察到不良的功能、行為或生殖結果。

在懷孕的大鼠和兔子經口服投藥之後，linagliptin 可通過胎盤進入幼胎。

6.2 哺乳

風險摘要

關於 GLYXAMBI 或其個別成分是否會進入人類的乳汁以及其對哺乳嬰兒或乳汁生成有何影響，目前尚無相關資料。Empagliflozin 和 linagliptin 會分泌到授乳中大鼠的乳汁內*(詳見「資料」一節)*。由於人類的腎臟是在子宮內到出生後 2 年內逐漸成熟 (此時可能因哺乳而暴露)，因此人類腎臟的發育可能成幼風險之中。

因為 GLYXAMBI 可能對接受哺乳的嬰兒造成嚴重的不良反應(包括 empagliflozin 可能影響出生後的腎臟發育)，應告知病人，不建議在哺乳期間使用 GLYXAMBI。

資料

在授乳第 18 天的母大鼠地用單劑口服藥物之後，大鼠胎兒組織中存在的 empagliflozin 濃度低。在大鼠乳汁中，乳汁對血漿中藥物濃度比平均值在 0.634-5 範圍內，而且在用藥後 2 至 24 小時期間皆大於 1。乳汁對血漿中藥物濃度比平均值最大值 5 發生在用藥後 8 小時，顯示 empagliflozin 會容積在乳汁內，年幼大鼠直接暴露於 empagliflozin 時，會對其成熟期間發育中的腎臟造成風險(腎盂和腎小管擴張)。

6.4 小兒

GLYXAMBI 在兒童病人使用的安全性及有效性，尚未獲得確立。

6.5 老年人

GLYXAMBI

Empagliflozin 會引起滲透性利尿，可能影響 75 歲以上病人的水合狀態[請參閱警語及注意事項 (5.1.3)]。

Empagliflozin

在以 empagliflozin 使用於第二型糖尿病的試驗中，總計有 2721 名接受 empagliflozin 治療的病人年滿 65 歲以及 491 名年滿 75 歲。試驗裡，75 歲以上的病人發生體液容量減少相關不良反應，在安慰劑、empagliflozin 10 mg 和 empagliflozin 25 mg 各組一天服用一次的情形下，分別為 2.1%、2.3%和 4.4%；75 歲以上的病人泌尿道感染的發生率、在安慰劑、empagliflozin 10 mg 和 empagliflozin 25 mg 各組一天服用一次的情形下，分別為 10.5%、15.7%和 15.1%。

Linagliptin

在 linagliptin 臨床試驗中，其中有 1085 位接受 linagliptin 治療的病人為 65 歲以上，另有 131 位病人為 75 歲以上。民這些臨床試驗觀察到，linagliptin 的安全性或療效，整體上老年病人及較年輕的成年病人並無差異。

6.6 肝功能不全

GLYXAMBI 可用於肝功能不全病人*[詳見藥物動力學特性 (11)]*。

6.7 腎功能不全

Empagliflozin

Empagliflozin 25 mg 的降血糖效益會隨著病人腎功能的惡化而減弱。腎功能不全*[詳見警語及注意事項 (5.1.3)]*、體液容量減少不良反應、泌尿道感染相關不良反應等風險、都會隨著腎功能惡化而提高。

Empagliflozin 的療效及安全性試驗並未納入正接受透析的 ESRD 病人，亦沒有納入 eGFR 低於 30 mL/min/1.73 m^2 的病人。Empagliflozin 並用於正在接受透析的病人*[詳見適應症(2)與禁忌(4)]*。

7. 交互作用

表 1 與 GLYXAMBI 臨床上相關的交互作用

利尿劑	
臨床上的影響	Empagliflozin 與利尿劑併用會造成尿量和排尿次數增加，可能進而提升體液容量減少的可能性
處置	在開始 GLYXAMBI 治療之前，請評估體液狀態及腎功能。體液減少的病人，開始 GLYXAMBI 治療之前，請先矯正此情形。開始 GLYXAMBI 治療之後，監測體液減少之徵象和症狀以及腎功能。
胰島素或胰島素促泌劑	
臨床上的影響	在一個臨床試驗中，與安慰劑相比，Empagliflozin 或 Linagliptin 與胰島素或胰島素促泌劑(例如:sulfonylurea)併用時，有較高比例發生低血糖症。
處置	GLYXAMBI 與胰島素促泌劑(例如磺醯尿素類藥物)或胰島素併用時，可能須降低胰島素促泌劑或胰島素的劑量，以減少低血糖症的風險
尿中葡萄糖檢測陽性	
臨床上的影響	SGLT2 抑制劑會增加尿中葡萄糖排出量而使尿中葡萄糖檢測呈現陽性。

處置	使用 SGLT2 抑制劑的病人，不建議以檢測尿中葡萄糖監測血糖控制，因為 SGLT2 抑制劑會增加尿中的葡萄糖排出量而使尿中葡萄糖檢測呈現陽性。請以其他方法監測血糖控制。
干擾 1,5-anhydroglucitol (1,5-AG) 分析	
臨床上的影響	針對使用 SGLT2 抑制劑的病人，1,5-AG 的測量值在其血糖控制的評估上並不可靠
處置	不建議以 1,5-AG 分析監測血糖控制。請以其他方法監測血糖控制。
P-糖蛋白 (P-glycoprotein) 或 CYP3A4 酵素之誘發劑	
臨床上的影響	Rifampin 可降低 linagliptin 的暴露量，顯示與強效 P-糖蛋白 (P-gp) 或 CYP3A4 誘發劑併用時，其療效可能降低。
處置	linagliptin 若須與強效 P-gp 或 CYP3A 誘發劑併用時，應考慮改用其他替代療法

8. 副作用/不良反應

8.1 臨床重要副作用/不良反應

下列主要不良反應將描述如下及於單內其他部分：

- 脫碳美 *[請參閱警語及注意事項 (5.1.1)]*
- 酮酸中毒 *[請參閱警語及注意事項 (5.1.2)]*
- 體液容量減少 *[請參閱警語及注意事項 (5.1.3)]*
- 泌尿道感染與腎盂腎炎 *[請參閱警語及注意事項 (5.1.4)]*
- 併用胰島素與胰島素促泌劑時發生的低血糖 *[請參閱警語及注意事項 (5.1.5)]*
- 會陰部壞死性筋膜炎(奈克羅氏壞疽) *[請參閱警語及注意事項(5.1.6)]*
- 生殖器黴菌感染 *[請參閱警語及注意事項 (5.1.7)]*
- 過敏反應 *[請參閱警語及注意事項 (5.1.8)]*
- 低密度脂蛋白膽固醇 (LDL-C) 上升 *[請參閱警語及注意事項 (5.1.9)]*
- 嚴重和行動不便之關節疼痛 *[請參閱警語及注意事項 (5.1.10)]*
- 大皰性類天皰瘡 *[請參閱警語及注意事項 (5.1.11)]*

8.2 臨床試驗經驗

由於臨床試驗是在各種不同的狀況下進行，因此在某一種藥物的臨床試驗中所觀察到的不良反應發生率，無法與在另一藥物的臨床試驗中所觀察到的不良反應發生率直接進行比較，亦無法反映實際臨床狀況中的發生率。

Empagliflozin 及 Linagliptin

併用 empagliflozin (每日劑量 10 mg 或 25 mg) 與 linagliptin (每日劑量 5 mg) 的安全性，已於有效藥物對照的臨床試驗中進行評估，總計涵蓋 1363 位第二型糖尿病病人，治療期間最長 52 週。根據這些試驗的統合分析結果，同時併用 empagliflozin 及 linagliptin 最常見的不良反應如表 2 所示。

表 2　Empagliflozin 併用 Linagliptin 治療組內發生率 ≥5% 的不良反應

不良反應	GLYXAMBI (%) 10 mg/5 mg n=272	GLYXAMBI (%) 25 mg/5 mg n=273
泌尿道感染 *	12.5	11.4
鼻咽炎	5.9	6.6
上呼吸道感染	7.0	7.0

*試驗預設之不良事件類別，包括但不限於泌尿道感染、陰莖或之菌尿症、腎盂炎

Empagliflozin

接受 empagliflozin 的病人，發生率≥2% 且高於安慰劑組的不良反應 (10 mg、25 mg、安慰劑)：泌尿道感染 (9.3%, 7.6%, 7.6%)；女性生殖器黴菌感染 (5.4%, 6.4%, 1.5%)；上呼吸道感染 (3.1%, 4.0%, 3.8%)；排尿增加 (3.4%, 3.2%, 1.0%)；血脂異常 (3.9%, 2.9%, 3.4%)；關節痛 (2.4%, 2.3%, 2.2%)；男性生殖器黴菌感染 (3.1%, 1.6%, 0.4%)；噁心 (2.3%, 1.1%, 1.4%)。

口渴（包括多渴症）在安慰劑、empagliflozin 10 mg 和 empagliflozin 25 mg 組內的通報比例分別為 0%、1.7%和 1.5%。

Empagliflozin 會引起滲透性利尿，進而導致血管內容量減少，以及體液容量減少相關不良反應。有 3 個病人 (1.1%)接受 Glyxambi 與 metformin 治療時發生體液容量減少(低血壓與暈厥)相關事件。

Linagliptin

linagliptin 5 mg 治療組內發生率≥2% 且高於安慰劑組的不良反應包括：鼻咽炎 (7.0%, 6.1%)；腹瀉 (3.3%, 3.0%)；咳嗽 (2.1%, 1.4%)。

在 Linagliptin 單藥療法臨床試驗中所報告的其他不良反應包括過敏 (例如蕁麻疹、血管性水腫、局部脫皮、支氣管過敏) 和肌痛。

在臨床試驗中，接受 linagliptin 治療的胰臟炎發生率為每一萬病人年暴露量中出現 15.2 例，對照藥物 (安慰劑和活性對照物行磺醯尿素類) 組內發生率為每一萬病人年暴露量中出現 3.7 例。另有三個胰臟炎病例是在使用最後一劑 linagliptin 之後發生的。

低血糖

表 3 說明 empagliflozin 及 linagliptin 治療 52 週的低血糖事件。

表 3　總體[a]和嚴重[b]低血糖不良反應發生率

Metformin 輔助療法 (52 週)	GLYXAMBI (%) 10 mg/5 mg (n=136)	GLYXAMBI (%) 25 mg/5 mg (n=137)
總體	2.2	3.6
嚴重	0	0

[a]總體低血糖事件：血漿或毛細血管葡萄糖 70 mg/dL 以下或需要協助
[b]嚴重低血糖事件：需要協助，不論血糖值高低

實驗室檢測

Empagliflozin 及 Linagliptin

併用 empagliflozin 及 linagliptin 治療的病人，實驗室檢測結果的變化包括腎臟和血球容積比高於基準點數值。

Empagliflozin

*血清肌酸酐升高及 eGFR 降低：*開始以 empagliflozin 治療的幾週內，會請發血清肌酸酐升高及 eGFR 降低的情形，之後這些變化趨於穩定。在一項以中度腎功能不全病人為對象的試驗中，觀察到較大的平均變化量。在一項長期的心血管結果試驗中，血清肌酸酐升高及 eGFR 降低的情形一般不超過 0.1 mg/dL 及-9.0 mL/min/1.73 m²，於第四週時，停止治療後數值回復，指測使用 empagliflozin 後，急性血液動力學變化在腎功能變化中扮演一定的角色。

*低密度脂蛋白膽固醇 (LDL-C) 上升：*在接受 empagliflozin 治療的病人中，曾觀察到低密度脂蛋白膽固醇 (LDL-C) 出現與劑量有關的上升現象。在接受安慰劑、empagliflozin 10 mg、empagliflozin 25 mg 治療的病人中，LDL-C 分別上升 2.3%、4.6%、6.5% *[詳見警語及注意事項 (5.1,9)]*。平均基準點 LDL-C 濃度在各治療組之間的範圍為 90.3 到 90.6 mg/dL。

*血球容積比增加：*安慰劑組的血球容積比中位數減少 1.3%；empagliflozin 10 mg 治療組增加 2.8%、empagliflozin 25 mg 治療組增加 2.8%。安慰劑、empagliflozin 10 mg、empagliflozin 25 mg 組內一開始血球容積比在參考範圍內的病人，分別有 0.6%、2.7%、3.5% 於治療結束時超過參考範圍的上限。

Linagliptin

*尿酸增加：*Linagliptin 治療組較常見且發生率高於安慰劑組至少 1% 的實驗室檢測值變化為尿酸增加 (安慰劑組 1.3%，linagliptin 治療組 2.7%)。

*脂肪酶增加：*在一項針對有微量白蛋白尿或巨量白蛋白尿的第二型糖尿病病人進行之安慰劑對照的 linagliptin 臨床試驗中，linagliptin 治療組從基期至 24 週的脂肪酶濃度平均增加 30%，安慰劑組則平均增加 2%。Linagliptin 治療組與安慰劑組脂肪酶濃度高於正常值上限 3 倍的病人分別有 8.2%與 1.7%。

*澱粉酶增加：*在第二型糖尿病病人的比較 linagliptin 和 glimpiride 之心血管安全性臨床試驗，linagliptin 治療組與 glimpiride 治療組中澱粉酶濃度高於正常值上限 3 倍的病人分別有 1%與 0.5%。

在沒有其他胰臟炎徵兆和症狀，使用 linagliptin 發生脂肪酶和澱粉酶濃度升高的臨床意義尚不清楚。

8.3 上市後經驗

在 linagliptin 及 empagliflozin 上市後曾經說其他不良反應，由於這些反應是由不確定人數之族群自發通報，因此通常無法可靠估計發生率，也無法確立與藥物暴露量之間的因果關係。

- *胃腸道疾病：*急性胰臟炎，包括致命的胰臟炎 [詳見過敏症 (2)]，便秘，口渴清痛，口腔炎
- *免疫系統疾病：*過敏反應，包括急性過敏、血管性水腫和藥片狀脫皮
- *感染：*會陰部壞死性筋膜炎 (弗尼爾氏壞疽)，尿路敗血症與腎盂腎炎
- *代謝及營養疾病：*酮酸中毒
- *肌肉骨骼與結締組織疾病：*肢重和行動不便之關節疼痛
- *腎臟及泌尿系統疾病：*急性腎損傷
- *皮膚及皮下組織疾病：*大疱性類天疱瘡、皮膚反應 (如：皮疹、蕁麻疹)

9. 過量

GLYXAMBI 用藥過量時，請立即就診。目前尚未針對血液透析清除 empagliflozin 的效果進行研究，以血液透析或腹膜透析清除 linagliptin 則不大可行。

10. 藥理特性

10.1 作用機轉

GLYXAMBI

GLYXAMBI 含有：empagliflozin (鈉-葡萄糖共同運送蛋白 2 [SGLT2] 抑制劑) 及 linagliptin (雙肽基肽酶-4 [DPP-4] 抑制劑)。

Empagliflozin

鈉-葡萄糖共同運送蛋白 2 (SGLT2) 是負責再吸收由腎絲球過濾回標稱原之葡萄糖的主要轉運通道。Empagliflozin 是一種 SGLT2 抑制劑，藉由抑制 SGLT2，empagliflozin 可減少腎臟對已過濾之葡萄糖的再吸收作用，降低腎臟的葡萄糖閾值，進而增加尿糖排泄量。

Linagliptin

Linagliptin 是一種 DPP-4 抑制劑，而 DPP-4 是分解腸泌素荷爾蒙類升糖素肽胰 1 (GLP-1) 和葡萄糖依賴型促胰島素多肽 (GIP) 的酵素。因此，linagliptin 可使活性腸泌素荷爾蒙的濃度增高，在葡萄糖依賴性的狀態刺激胰島素的釋出，並降低循環中的升糖素濃度，這兩種腸泌素荷爾蒙均參與了葡萄糖體內平衡的生理調節作用。平時即有基本濃度的低量腸泌素荷爾蒙分泌，但其濃度可於用餐後立即上升。在血糖濃度正常與升高時，GLP-1 與 GIP 皆可增加胰島素的生合成以及從胰臟β細胞的分泌，此外，GLP-1 亦可降低胰臟α細胞的升糖素分泌，而依附細的葡萄糖輸出量降低。

10.2 藥效學理特性

Empagliflozin

<u>葡萄糖自尿液排出</u>

第二型糖尿病病人使用一劑 empagliflozin 後，尿糖排泄量會立即增加，效果可維持至 4 週治療期結束時：每日一次 10 mg empagliflozin 治療組平均約 64 克，每日一次 25 mg 組平均約 78 克。從健康受試者口服單劑 empagliflozin10mg、25mg 的數據顯示，平均而言，尿糖排泄量增加情形約 3 天回到基準點。

<u>尿液排出量</u>

在一項為期 5 天的試驗中，每天一次 empagliflozin 25 mg 治療組平均 24 小時排尿量，第 1 天相較於基準點增加 341 毫升，第 5 天增加 135 毫升。

<u>心臟電生理學</u>

在一項隨機分配、安慰劑及活性藥物對照、交叉設計的試驗中，共有 30 名健康受試者接受單一劑口服 empagliflozin 25 mg、empagliflozin 200 mg (最高建議劑量的 8 倍)、moxifloxacin 和安慰劑。empagliflozin 25 mg 或 200 mg 組並未觀察到校正 QT 間期 (QTc) 延長。

Linagliptin

Linagliptin 與 DPP-4 的結合具可逆性，可提高腸泌素荷爾蒙的濃度。Linagliptin 在葡萄糖依賴性狀態下增加胰島素的分泌，並降低升糖素的分泌，因此可產生較理想的葡萄糖體內平衡調節。在體外實驗中，在相當於治療暴露量的濃度下，linagliptin 選擇性與 DPP-4 結合而抑制其活性，對 DPP-8 或 DPP-9 活性則無作用。

<u>心臟電生理學</u>

在一項隨機分配、安慰劑及活性藥物對照、4 向交叉設計的試驗中，共有 36 名健康受試者接受單一劑口服 linagliptin 5 mg、linagliptin 100 mg (最高建議劑量的 20 倍)、moxifloxacin 和安慰劑。5 mg 建議劑量[illegible]0 mg 劑量組，均未觀察到校正 QT 間期 (QTc) 延長。100 mg 組的 linagliptin 最高血漿濃度約為 5 mg 組的 3[illegible]

10.3 臨床前安全性資料

非臨床毒物學

10.3.1 致癌性、致突變性、生育力受損

GLYXAMBI

尚未有針對 empagliflozin 及 linagliptin 複合劑進行之致癌性、致突變性、生育力受損的研究。已針對個別成分，在大鼠中進行最長 13 週的一般毒性研究，這些試驗的結果顯示，empagliflozin 與 linagliptin 併用並不會導致毒性加成。

Empagliflozin

已於 CD-1 小鼠及 Wistar 大鼠中進行 2 年的致癌性試驗，投予 empagliflozin 100、300、700 mg/kg/天 (最多達最高臨床劑量 25 mg 的 72 倍)，並未增加雄性大鼠的腫瘤發生率。在雄性大鼠方面，劑量達 700 mg/kg/天 (約為臨床劑量 25 mg 的 42 倍) 時，腎盂腺瘤良性與惡性總合的發生頻率增加。投予 empagl.flozin 100、300、1000 mg/kg/天 (最多達最高臨床劑量 25 mg 的 62 倍)，並未增加雌性小鼠的腫瘤發生率。在劑量 1000 mg/kg/天 (約為最高臨床劑量 25 mg 的 45 倍) 時，觀察到雌性小鼠發生腎小管腺瘤和腎小管癌，這些腫瘤可能與主要存在於雌性小鼠腎臟的一種代謝路徑有關。

體外 Ames 細菌致突變分析、體外 L5178Y tk+/- 鼠淋巴瘤細胞分析，以及大鼠的體內微核分析皆顯示，不論是否經過代謝活化，empagliflozin 都不具致突變性，也不會造成染色體斷裂。

在 empagliflozin 最高 700 mg/kg/天的劑量下 (約為臨床劑量 25 mg 的 155 倍)，對雄性或雌性大鼠的交配、生殖力或早期胚胎發育皆無影響。

Linagliptin

在一項為期 2 年的試驗中，以 linagliptin 每天劑量 6、18、60 mg/ kg 施用予大鼠，並未增加雄性及雌性大鼠的腫瘤發生率，根據 AUC 暴露量，此最高劑量 60 mg/ kg 約為臨床劑量 (5 mg/天) 的 418 倍。在一項為期 2 年的試驗中，以 linagliptin 最高 80 mg/ kg (雄性) 和 25 mg/ kg (雌性) 的劑量施用予小鼠，根據 AUC 暴露量，此劑量約為臨床劑量的 35 倍和 270 倍，結果並未增加小鼠的腫瘤發生率。更高劑量的 linagliptin (80 mg/ kg，根據 AUC 暴露量，約為臨床劑量的 215 倍)，可導致雌性小鼠的淋巴瘤發生率增加。

在 Ames 細菌突變性檢測、人類淋巴球染色體畸變檢測、體內微核檢測中，不論有無代謝活化作用，linagliptin 皆不具致突變性，也不會造成染色體斷裂。

在大鼠的生殖力研究中，在 linagliptin 最高 240 mg/ kg 劑量下 (根據 AUC 暴露量，約為臨床劑量的 943 倍)，對於早期胚胎發育、交配、生殖力或活產率皆無不良影響。

11. 藥物動力學特性

GLYXAMBI

與食物一起服用固定劑量複合劑，不會改變 empagliflozin 或 linagliptin 的整體暴露量；但是，empagliflozin 和 linagliptin 的 C_{max} 分別減少 39%和 32%。這些變化不具臨床重要性。

Empagliflozin

[illegible]健康自願受試者與第二型糖尿病病人進行 Empagliflozin 的藥物動力學研究，兩個族群間並未發現具臨床[illegible]的差異[illegible]後，在 1.5 小時達到最高血漿濃度，之後血漿濃度下降可分為兩個階段，在分

終期快速下降。對終止期對相對暴露。穩定狀態平均血漿曲線下面積 (AUC) 和最高血漿濃度 (C_{max})，在 empagliflozin 每日一次 10 mg 組分別為 1870 nmol·h/L 和 259 nmol/L，每日一次 25 mg 組為 4740 nmol·h/L 和 687 nmol/L。在治療劑量範圍內，empagliflozin 的全身暴露量隨劑量等比例增加。empagliflozin 單劑與穩定狀態藥物動力學參數相似，顯示具線性藥物動力學與時間有關。

攝取高脂及高熱量飲食後服用 empagliflozin 25 mg，會使其暴露量略為降低；相較於空腹服用，AUC 減少約 16%，C_{max} 減少約 37%，顯示食物對於 empagliflozin 的藥物動力學不存在具臨床重要性的影響，empagliflozin 可以隨餐或空腹服用。

Linagliptin
Linagliptin 的絕對生體可用率約為 30%。高脂飲食可使 C_{max} 降低 15%，AUC 增加 4%；此影響不具臨床重要性。Linagliptin 可以隨餐或空腹服用。

分佈

Empagliflozin
群體藥物動力學分析結果顯示，穩定狀態的擬似分佈體積預估為 73.8 升。健康受試者口服 [^{14}C]-empagliflozin 溶液後，紅血球分配率(partitioning)約為 36.8%，血漿蛋白結合率為 86.2%。

Linagliptin
健康受試者接受靜脈注射單劑 linagliptin 5 mg 後，穩定狀態的擬似分佈體積平均約為 1110 升，顯示 linagliptin 廣泛分佈於各組織。Linagliptin 與血漿中蛋白質的結合具濃度相關性，濃度 1 nmol/L 時約為 99%，≥30 nmol/L 時下降至 75%-89%，顯示隨著 linagliptin 濃度增加時，與 DPP-4 的結合逐漸飽和。在高濃度下，DPP-4 會完全飽和，因此有 70%至 80%的 linagliptin 為結合狀態，20%至 30%則在血漿中呈未結合狀態。在腎功能或肝功能不全的病人，此藥物在血漿中的結合狀況並未改變。

排除

Empagliflozin: 依據族群藥物動力學分析估計，empagliflozin 的顯末端排除半衰期 (apparent terminal elimination half-life) 為 12.4 小時，擬口服清除率 (apparent oral clearance) 則為 10.6L/小時；每日服一次後，在此第 AUC 方面，穩定期的蓄積率 22%，與 empagliflozin 的半衰期一致。

Linagliptin: Linagliptin 的末端排除半衰期在穩定狀態時約為 200 小時，其累積半衰期約為 11 小時。穩定狀態時的腎臟清除率約為 70 mL/min。

代謝

Empagliflozin
人體血漿中並未測得 empagliflozin 的主要代謝物，含量最多的代謝物為三種葡萄糖醛酸共軛物 (2-O-、3-O-、6-O-glucuronide)，每種代謝物的全身暴露量小於總藥物相關成分的 10%。體外試驗顯示，在人體中 empagliflozin 的主要代謝途徑為經由尿苷 5' 二磷酸葡萄糖醛酸轉移酶 (uridine 5'-diphospho-glucuronosyltransferases) UGT2B7、UGT1A3、UGT1A8、UGT1A9 進行的葡萄糖醛酸化作用。

Linagliptin
linagliptin 口服之後，大部分 (約 90%) 皆以原型藥排出，顯示經代謝清除的路徑僅佔小部分。僅極小部分已吸收的 linagliptin 會代謝為不具藥理活性的代謝物，穩定狀態時的暴露量為 linagliptin 的 13.3%。

排泄

Empagliflozin
健康受試者使用口服 [^{14}C]-empagliflozin 溶液後，約 95.6% 的藥物相關放射活性經由糞便 (41.2%) 或尿液 (54.4%) 排除。大部分糞便中測得的藥物相關放射活性為未發生變化的原型藥，約半數尿液排出的藥物相關放射活性物為未發生變化的原型藥。

Linagliptin
健康受試者使用口服一劑 [^{14}C]-linagliptin 後，藥物相關放射活性約有 85%於 4 天內經由腸肝系統 (80%) 或尿液 (5%) 排除。

特定族群

腎功能不全
*GLYXAMBI：*尚未針對腎功能不全病人進行使用 GLYXAMBI 後的 empagliflozin 及 linagliptin 藥物動力學研究。

*Empagliflozin：*用於治療輕度 (eGFR：60 至 90 mL/min/1.73 m^2)、中度 (eGFR：30 至 60 mL/min/1.73 m^2)、重度 (eGFR 低於 30 mL/min/1.73 m^2) 腎功能不全的病人，以及腎臟疾病末期腎臟病 (ESRD) 病人時，empagliflozin 的 AUC 分別較腎功能正常的受試者高約 18%、20%、66%、48%。相較於腎功能正常的受試者，中度腎功能不全及腎臟疾病末期腎臟病病人的 empagliflozin 最高血漿濃度相近。輕度及重度腎功能不全病人的 empagliflozin 最高血漿濃度，較腎功能正常的受試者高約 20%。群體藥物動力學分析顯示 empagliflozin 的擬似口服清除率隨著 eGFR 下降，因而造成藥物暴露量增加。然而，在尿中以原型態排出的微部分 empagliflozin 以及葡萄糖排泄量，都會隨著 eGFR 下降而減少。

*Linagliptin：*一項開放標示的藥物動力學研究，針對各種程度之慢性腎功能不全的男性與女性病人，進行 linagliptin 5 mg 的藥物動力學評估。此項試驗共收錄 6 名腎功能正常的健康受試者 (肌酸酐清除率 [CrCl] ≥80 mL/min)、6 名輕度腎功能不全病人 (CrCl 50 至 <80 mL/min)、6 名中度腎功能不全病人 (CrCl 30 至 <50 mL/min)、10 名重度腎功能不全的第二型糖尿病病人 (CrCl <30 mL/min)，以及 11 名腎功能正常的第二型糖尿病病人。肌酸酐清除率係由 24 小時尿中肌酸酐清除量計算。或根據 Cockcroft-Gault 公式從血清肌酸酐估計。

在穩定狀態下，輕度腎功能不全病人與健康受試者的 linagliptin 暴露量相近。

相較於健康受試者、中度腎功能不全病人的穩定狀態平均 linagliptin 暴露量增加 (AUC_{tau} 為 71%、C_{max} 為 46%)。此暴露量增加與蓄積半衰期延長、終端排除半衰期或蓄積參數增加皆無關聯性。Linagliptin 由腎臟排除的藥物量低於 5%，且不受腎功能降低影響。相較於腎功能正常的第二型糖尿病病人，重度腎功能不全之第二型糖尿病病人的穩定狀態暴露量約增加 40% (AUC_{tau} 增加 42%，C_{max} 增加 35%)。延而組第二型糖尿病病人的腎臟清除量皆低於所用劑量的 7%。

群體藥物動力學分析結果進一步支持上述。

肝功能不全
*GLYXAMBI：*尚未針對肝功能不全病人進行使用 GLYXAMBI 後的 empagliflozin 及 linagliptin 藥物動力學研究。

*Empagliflozin：*相較於肝功能正常的受試者，依採 Child-Pugh 介類為輕度、中度、重度肝功能不全的病人，empagliflozin 的 AUC 分別增加約 23%、47%、75%，C_{max} 增加約 4%、23%、48%。

*Linagliptin：*相較於健康受試者，輕度肝功能不全病人 (Child-Pugh 第 A 級) 的穩定狀態 linagliptin 暴露量 (AUC_{tau}) 大約降低 25%，$C_{max,ss}$ 降低 36%。相較於健康受試者，中度肝功能不全病人 (Child-Pugh 第 B 級) 的 linagliptin AUC_{ss} 大約降低 14%，$C_{max,ss}$ 降低 8%。重度肝功能不全病人 (Child-Pugh 第 C 級) 的 linagliptin AUC_{ss} 暴露量與健康受試者相近，C_{max} 則降低約 23%。在肝功能不全者所觀察到的藥物動力學參數下降情形，並未符低其對於 DPP-4 的抑制作用。

年齡、身體質量指數、性別和人種的影響
*Empagliflozin：*群體藥物動力學分析結果顯示，年齡、身體質量指數 (BMI)、性別及人種 (亞裔和主要為白人) 對於 empagliflozin 的藥物動力學性質不存在具臨床意義的影響 *[詳見特殊族群注意事項 (6.5)]*。

*Linagliptin：*群體藥物動力學分析結果顯示，年齡、身體質量指數 (BMI)、性別及人種 (亞裔和主要為白人) 對於 linagliptin 的藥物動力學性質不存在具臨床意義的影響 *[詳見特殊族群注意事項 (6.5)]*。

藥物交互作用

尚未針對 GLYXAMBI 進行藥物動力學的交互作用試驗；不過已針對 GLYXAMBI 的個別成分 (empagliflozin 和 linagliptin) 進行此方面的研究。

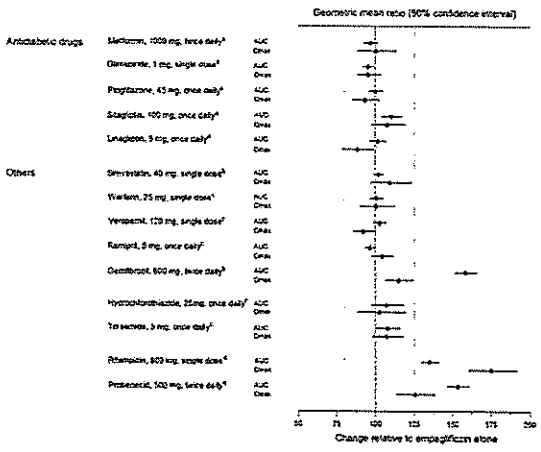
Empagliflozin

體外藥物交互作用評估
Empagliflozin 不會抑制、去活化或誘發 CYP450 同功酶。體外資料顯示，在人體中 empagliflozin 的主要代謝途徑為經由尿苷 5' 二磷酸葡萄糖醛酸轉移酶 (uridine 5'-diphospho-glucuronosyltransferases) UGT1A3、UGT1A8、UGT1A9 和 UGT2B7 進行的葡萄糖醛酸化作用。Empagliflozin 不會抑制 UGT1A1、UGT1A3、UGT1A8、UGT1A9 或 UGT2B7，因此若併用藥物為主要 CYP450 同功酶或 UGT1A1 UGT1A3、UGT1A8、UGT1A9 或 UGT2B7 之受質，則不預期 empagliflozin 會對這等藥物產生影響。誘導 UGT (例如由 rifampicin 或其他 UGT 酵素誘導劑產生誘導作用) 對於 empagliflozin 暴露量所造成的影響仍未曾被受評估。

Empagliflozin 為 P 糖蛋白 (P-gp) 及乳癌抗性蛋白 (BCRP) 之受質，然在治療劑量下不會抑制上述排出運送蛋白。體外藥物交互研究皆顯示，empagliflozin 不太可能與 P-gp 受質藥物產生交互作用。Empagliflozin 為人體吸收轉運蛋白 OAT3、OATP1B1、OATP1B3 之受質，但並非 OAT1 及 OCT2 之受質。Empagliflozin 在具臨床意義的血漿濃度下，不會抑制上述人體吸收轉運蛋白；因此若併用藥物為上述吸收轉運蛋白之受質，則不預期 empagliflozin 會對這等藥物產生影響。

體內藥物交互作用評估
以 empagliflozin 給與健康受試者時，無論有無併用 metformin、glimepiride、pioglitazone、sitagliptin、linagliptin、warfarin、verapamil、ramipril 和 simvastatin，以及用於治療第二型糖尿病病人時，無論有無併用 hydrochlorothiazide 及 torsemide，藥物動力學皆相似 (見圖 1)。在腎臟功能正常的受試者中，以 empagliflozin 併用 probenecid 會使尿中的 empagliflozin 排泄量下降 30%，但不會對 24 小時的尿糖排泄量造成影響。上述相關觀察在腎功能不全病人中尚不清楚。

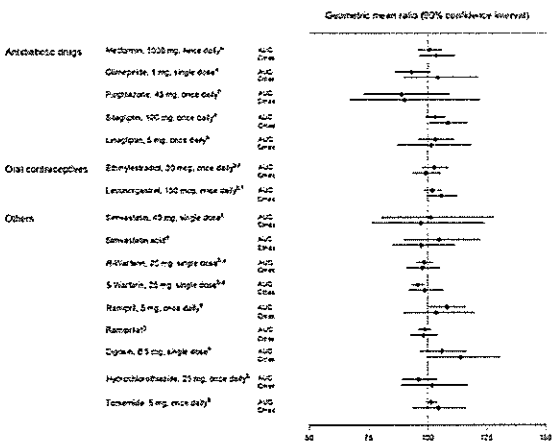
圖 1　各種藥物對 Empagliflozin 藥物動力學的影響，以幾何平均 AUC 與 C_{max} 之比值的 90%信賴區間表示 [參考線代表 100% (80% - 125%)]



[a]empagliflozin 50 mg，每日一次；[b]empagliflozin 25 mg，單劑量；[c]empagliflozin 25 mg，每日一次；[d]empagliflozin 10 mg，單劑量

健康受試者同時併用 empagliflozin 和下列的藥物，對其藥物動力學性質並無具臨床意義的影響：metformin、glimepiride、pioglitazone、sitagliptin、linagliptin、warfarin、digoxin、ramipril、simvastatin、hydrochlorothiazide、torsemide、口服避孕藥 (見圖 2)。

圖 2　Empagliflozin 對各種藥物之藥物動力學的影響，以幾何平均 AUC 與 C_{max} 之比值的 90% 信賴區間表示 [參考線代表 100% (80%、125%)]



[a]empagliflozin 50 mg，每日一次；[b]empagliflozin 25 mg，每日一次；[c]empagliflozin 25 mg，單劑量；[d]給藥方式與 simvastatin 相同；[e]給藥方式與 warfarin 消旋混合物相同；[f]給藥方式與 Microgynon® 相同；[g]給藥方式與 ramipril 相同

Linagliptin

藥物藥物交互作用評估

Linagliptin 為 CYP 同功酶 CYP3A4 的弱至中度抑制劑，但對其他 CYP 同功酶則無抑制作用，亦非 CYP 同功酶的誘發劑，包括 CYP1A2、2A6、2B6、2C8、2C9、2C19、2D6、2E1、4A11。

Linagliptin 為 P-醣蛋白 (P-gp) 受質，在高濃度下可抑制 P-gp 所媒介的 digoxin 運送，這些結果及體內藥物交互作用研究皆顯示，治療濃度的 linagliptin 不太可能與其他 P-gp 受質藥物產生交互作用。

藥內藥物交互作用評估

CYP3A4 或 P-gp 之強效誘發劑 (例如 rifampin) 可能導致 linagliptin 的暴露量降低，甚至低於療效濃度而不具療效。*[詳見交互作用(7)]* 體內研究顯示，linagliptin 與 CYP3A4、CYP2C9、CYP2C8、P-gp 及有機陽離子轉運蛋白 (OCT) 受質產生藥物交互作用的可能性低。

表 4　併用藥物對 Linagliptin 之全身暴露量的影響

併用藥物	併用藥物的用法用量[a]	Linagliptin 的用法用量[a]	幾何平均比值 (有/無併用藥物的比值) 無影響=1.0	
			AUC[c]	C_{max}
Metformin	850 mg TID	10 mg QD	1.20	1.03
Glyburide	1.75 mg[d]	5 mg QD	1.02	1.01
Pioglitazone	45 mg QD	10 mg QD	1.13	1.07
Ritonavir	200 mg BID	5 mg[d]	2.01	2.96
Rifampin[b]	600 mg QD	5 mg QD	0.60	0.56

[a]多劑量 (穩定狀態)，除非另有註明

[b]有關臨床建議資訊*[詳見交互作用(7)]*

[c]單劑量

[d]單劑量治療 AUC = AUC(0 至 24 小時)；多劑量治療 AUC = AUC(TAU)

QD = 每日一次

BID = 每日兩次

TID = 每日三次

表 5　Linagliptin 對併用藥物之全身暴露量的影響

併用藥物	併用藥物的用法用量[a]	Linagliptin 的用法用量[a]	幾何平均比值 (有/無併用藥物的比值) 無影響=1.0		
				AUC[c]	Cmax
Metformin	850 mg TID	10 mg QD	Metformin	1.01	0.89
Glyburide	1.75 mg[b]	5 mg QD	Glyburide	0.86	0.86
Pioglitazone	45 mg QD	10 mg QD	Pioglitazone 代謝物 M-III 代謝物 M-IV	0.94 0.98 1.04	0.86 0.96 1.05
Digoxin	0.25 mg QD	5 mg QD	Digoxin	1.02	0.94
Simvastatin	40 mg QD	10 mg QD	Simvastatin simvastatin acid	1.34 1.33	1.10 1.21

Warfarin	10 mg[b]	5 mg QD	R-warfarin S-warfarin INR PT	0.99 1.03 0.93[d] 1.03[d]	1.00 1.01 1.04[d] 1.15[d]
Ethinylestradiol 及 levonorgestrel	ethinylestradiol 0.03 mg 及 levonorgestrel 0.150 mg QD	5 mg QD	ethinylestradiol levonorgestrel	1.01 1.09	1.08 1.13

[a]多劑量 (穩定狀態)，除非另有註明

[b]單劑量

[c]單劑量治療 AUC = AUC(INF)；多劑量治療 AUC = AUC(TAU)

[d]最小幾何平均比值 AUC-AUC(0-168)，Cmax-Cmax

INR = 國際標準凝血時間比

PT = 凝血酶原時間

QD = 每日一次

TID = 每日三次

12. 臨床試驗資料

GLYXAMBI 之血糖控制試驗

GLYXAMBI 治療於 Metformin 無法

在一項雙盲、有效藥物對照試驗中，總計收錄 686 名第二型糖尿病病人，評估 empagliflozin 10 mg 或 25 mg 併用 linagliptin 5 mg 相較於個別成分的療效及安全性。

經每日劑量 1500 mg 以上的 metformin 治療後，仍然控制不佳的第二型糖尿病病人，進入單盲安慰劑導入期治療 2 週，導入期結束時，血糖控制仍不佳、HbA1c 介於 7% 至 10.5% 的病人，按 1:1:1:1:1 比例隨機分配至 5 個活性治療組，亦即 empagliflozin 10 mg 或 25 mg、linagliptin 5 mg，或 linagliptin 5 mg 併用 empagliflozin 10 mg 或 25 mg 的固定劑量複合錠劑。

第 24 週時，相較於個別成分治療組中曾接受 metformin 而控制不佳的病人，empagliflozin 10 mg 或 25 mg 併用 linagliptin 5 mg 治療組，在 HbA1c (p 值 <0.0001) 和 FPG (p 值 <0.001) 方面達到統計顯著的改善 (見表 6、圖 3)。相較於 linagliptin 5 mg 治療組，每日接受 GLYXAMBI 25 mg/5 mg 或 GLYXAMBI 10 mg/5 mg 的病人在[illegible]方面也達到統計顯著差異 (p 值 <0.0001)。相較於 empagliflozin 單一治療組，沒有統計顯著[illegible]

表 6　針對無法以 Metformin 有效控制血糖者比較添加 GLYXAMBI 與個別成分的試驗中第 24 週的血糖參數

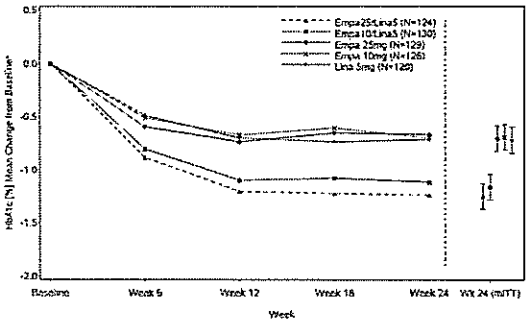
	GLYXAMBI 10 mg/5 mg	GLYXAMBI 25 mg/5 mg	Empagliflozin 10 mg	Empagliflozin 25 mg	Linagliptin 5 mg
HbA1c (%)					
病人數	n=135	n=133	n=137	n=139	n=128
基準點 (平均值)	8.0	7.9	8.0	8.0	8.0
自基準點的變化 (調整後平均值)	-1.1	-1.2	-0.7	-0.6	-0.7
相較於 empagliflozin 25 mg 或 10 mg (調整後平均值) (95% CI)[a]	-0.4 (-0.6, -0.2)[b]	-0.6 (-0.7, -0.4)[b]	--	--	--
相較於 linagliptin 5 mg (調整後平均值) (95% CI)[a]	-0.4 (-0.6, -0.2)[b]	-0.5 (-0.7, -0.3)[b]	--	--	--
達成 HbA1c <7% 之病人數 (%)[b]	74 (58)	76 (62)	35 (28)	43 (33)	43 (36)
FPG (mg/dL)					
病人數	n=133	n=131	n=136	n=137	n=125
基準點 (平均值)	157	155	162	160	156
自基準點的變化 (調整後平均值)	-33	-36	-21	-21	-13
相較於 empagliflozin 25 mg 或 10 mg (調整後平均值) (95% CI)[a]	-12 (-18, -5)[b]	-15 (-22, -9)[b]	--	--	--
相較於 linagliptin 5 mg (調整後平均值) (95% CI)[a]	-20 (-27, -13)[b]	-23 (-29, -16)[b]	--	--	--
體重					
病人數	n=135	n=134	n=137	n=140	n=128
基準點 (平均)，公斤	87	85	86	88	85
自基準點的變化 % (調整後平均值)	-3.1	-3.4	-3.0	-3.5	-0.7
相較於 empagliflozin 25 mg 或 10 mg (調整後平均值) (95% CI)[a]	0.0 (-0.9, 0.8)	0.1 (-0.9, 0.9)	--	--	--
相較於 linagliptin 5 mg (調整後平均值) (95% CI)[a]	-2.4 (-3.3, -1.5)[b]	-2.7 (-3.6, -1.8)[b]	--	--	--

[a]完整分析族群 (觀察資例) 採用重複測量適用的複合對應模型 (MMRM)。MMRM 模型包含治療、腎功能、地區、門診、門診和治療的交互作用、基準點 HbA1c。

[b]基準點 HbA1c 高於 7% 的病人：GLYXAMBI 25 mg/5 mg，n=123；GLYXAMBI 10 mg/5 mg，n=128；empagliflozin 25 mg，n=132；empagliflozin 10 mg，n=125；linagliptin 5 mg，n=119，未完成者視為失敗 (NCF)。[c]合併族群使用最後觀察值推估。共變數分析 (ANCOVA) 模型包含治療、腎功能、地區、基準點體重、基[illegible]HbA1c。

[illegible]001for FPG;HbA1c[illegible]<0.0001

圖 3　每個時間點(完成者)及第 24 週(改良式意圖治療 [mITT] 族群)的調整後平均 HbA1c 變化



*Mean change from baseline adjusted for baseline HbA1c, geographical region, and eGFR at baseline.

Empagliflozin 用於治療無法以 metformin 與 linagliptin 有效控制血糖的病人

對無法以最大耐受劑量之 metformin 有效控制血糖的病人，添加開放標示之 linagliptin 5 mg 治療 16 週，在此 16 週治療後仍無法有效控制血糖者，即接受 empagliflozin 10 mg、empagliflozin 25 mg 或安慰劑雙盲治療 24 週。在此雙盲治療期之後，與安慰劑相較，empagliflozin 10 mg 與 empagliflozin 25 mg 治療皆可顯著改善 HbA_{1c}、FPG 與體重（具統計顯著性）。在此試驗期間所有病人皆繼續接受 metformin 與 linagliptin 5 mg 治療。對基期的 HbA_{1c} ≥7.0 %的病人，與安慰劑相較，接受這兩種劑量的 empagliflozin 治療後達到 HbA_{1c} <7 %目標的病人皆顯著較多（具統計顯著性）（請見表 7），以 empagliflozin 治療 24 週後，收縮壓與舒張壓皆降低：empagliflozin 25 mg 組-2.6/-1.1 mmHg（與安慰劑組的收縮壓與舒張壓相較差異不顯著），empagliflozin 10 mg 組-1.3/-0.1 mmHg（與安慰劑組的收縮壓與舒張壓相較差異不顯著）。

治療 24 週後，救援治療(rescue therapy)開於 4 位(3.6%)empagliflozin 25mg 受試者及 2 位(1.8%)empagliflozin 10mg 受試者，相較於 13 位(12.0%)安慰劑受試者(全部受試者皆有服用 metformin 及 linagliptin 5 mg)。

表 7　在針對無法以 metformin 與 linagliptin 5 mg 有效控制血糖的病人，比較 empagliflozin 與安慰劑做為治加療法的臨床試驗中之療效參數

	Metformin + linagliptin 5 mg		
	Empagliflozin 10 mg[1]	Empagliflozin 25 mg[1]	安慰劑[2]
HbA_{1c} (%) – 24 週[3]			
N	109	110	106
基期（平均值）	7.97	7.97	7.96

相較於基期之變化（校正後之平均值）	-0.65	-0.56	0.14
與安慰劑相較（校正後之平均值）（95 %信賴區間）[2]	-0.79 (-1.02, -0.55) p<0.0001	-0.70 (-0.93, -0.46) p<0.0001	
體重 – 24 週[3]			
N	109	110	106
基期（平均值）（公斤）	88.4	84.4	82.3
相較於基期之變化（校正後之平均值）	-3.1	-2.5	-0.3
與安慰劑相較（校正後之平均值）（95 %信賴區間）[4]	-2.8 (-3.5, -2.1) p<0.0001	-2.2 (-2.9, -1.5) p<0.0001	
基期 HbA_{1c} ≥7 %之病人達成 HbA_{1c} <7 %目標的比例（%）– 24 週[5]			
N	100	107	100
達到 HbA_{1c} <7 %的病人（%）	37.0	32.7	17.0
與安慰劑相較（勝算比）（95 %信賴區間）[6]	4.0 (1.9, 8.7)	2.9 (1.4, 6.1)	

[1] 隨機分派至 empagliflozin 10 mg 或 25 mg 治療組的病人接受 Glyxambi 10 mg/5 mg 或 25 mg/5 mg 加上背景療法 metformin。

[2] 隨機分派至安慰劑組的病人接受安慰劑加上 linagliptin 5 mg 與背景療法 metformin。

[3] 針對全分析集受試者（FAS）（OC）所進行之重複測量的混合效應模型（Mixed-effects models for repeated measurements，MMRM）納入基期 HbA1c、基期 eGFR（MDRD）、地理區域、日餘、治療、以及治療-日餘交互作用，針對 FPG 之分析亦納入基期 FPG，針對體重之分析亦納入基期體重。

[4] 非用於評估統計顯著性：非針對次要指標所進行之依序測試程序的一部分。

[5] 針對全分析受試者（FAS）（NCF）所進行之羅吉斯迴歸分析納入基期 HbA1c、基期 eGFR（MDRD）、地理區域及治療：根據基期 HbA_{1c} ≥7 %的病人。

在一個預先指明之基期 HbA_{1c} ≥8.5%的病人子群，接受 empagliflozin 25 mg/linagliptin 5 mg 治療者第 24 週時 HbA_{1c} 較基期降低-1.3 %（相較於安慰劑與 linagliptin 5 mg 的 p<0.0001），接受 empagliflozin 10 mg/linagliptin 5 mg 治療者亦為-1.3 %（相較於安慰劑與 linagliptin 5 mg 的 p<0.0001）。

Linagliptin 5 mg 用於治療無法以 metformin 與 empagliflozin 10 mg 或 empagliflozin 25 mg 有效控制血糖的病人

對無法以最大耐受劑量之 metformin 有效控制血糖的病人，添加開放標示之 empagliflozin 10 mg 或 empagliflozin 25 mg 治療 16 週，在此 16 週治療後仍無法有效控制血糖者，即接受 linagliptin 5 mg 或安慰劑雙盲治療 24 週。在此雙盲治療期之後，在兩組族群（metformin + empagliflozin 10 mg 與 metformin + empagliflozin 25 mg）的治療，與安慰劑相較，linagliptin 5 mg 皆可顯著改善 HbA_{1c}（具統計顯著性）。在此試驗期間所有病人皆繼續接受 metformin 與 empagliflozin 治療。對基期時 HbA_{1c} ≥7.0 %的病人，與安慰劑相較，接受 linagliptin 治療後達到 HbA_{1c} <7 %目標的病人皆顯著較多（具統計顯著性）（請見表 8）。

表 8　在針對無法以 empagliflozin 10 mg/25 mg 與 metformin 有效控制血糖的病人，比較 Glyxambi 10 mg/5 mg 與 empagliflozin 10 mg 及 Glyxambi 25 mg/5 mg 與 empagliflozin 25 mg 做為治加療法的臨床試驗中之療效參數

	Metformin + empagliflozin 10 mg		Metformin + empagliflozin 25 mg	
	Linagliptin 5 mg	安慰劑	Linagliptin 5 mg	安慰劑
HbA_{1c} (%) – 24 週[1]				
N	122	125	109	108
基期（平均值）	8.04	8.03	7.82	7.88
相較於基期之變化（校正後之平均值）	-0.53	-0.21	-0.58	-0.10
與安慰劑相較（校正後之平均值）（95 %信賴區間）	-0.32 (-0.52, -0.13) p<0.0013		-0.47 (-0.66, -0.28) p<0.0001	
基期 HbA_{1c} ≥7 %之病人達成 HbA_{1c} <7 %目標的比例（%）– 24 週[2]				
N	116	119	100	107
達到 HbA_{1c} <7 %的病人（%）	25.9	10.9	36.0	15.0
與安慰劑相較（勝算比）（95 %信賴區間）[3]	3.965 (1.771, 8.876) P=0.0008		4.429 (2.097, 9.353) P<0.0001	

隨機分派至 linagliptin 5 mg 治療組的病人接受固定劑量複合劑 Glyxambi 10 mg/5 mg 加上 metformin，或固定劑量複合劑 Glyxambi 25 mg/5 mg 加上 metformin。隨機分派至安慰劑組的病人接受安慰劑加上 empagliflozin 10 mg 與 metformin，或安慰劑加上 empagliflozin 25 mg 與 metformin。

[1] 針對全分析集受試者（FAS）（OC）所進行之重複測量的混合效應模型（MMRM）納入基期 HbA1c、基期 eGFR（MDRD）、地理區域、日餘、治療、以及治療-日餘交互作用。針對 FPG 之分析亦納入基期 FPG。

[2] 非用於評估統計顯著性：非針對次要指標所進行之依序測試程序的一部分。

[3] 針對全分析受試者（FAS）（NCF）進行之羅吉斯迴歸分析納入基期 HbA1c、基期 eGFR（MDRD）、地理區域及治療：根據基期 HbA_{1c} ≥7 %的病人。

針對有動脈粥樣硬化性心血管疾病之第二型糖尿病病人的 Empagliflozin 心血管結果試驗

Empagliflozin 適用於經確認有心血管疾病的第二型糖尿病成人病人，用以降低其心血管原因的死亡風險。對於經確認有穩定性動脈粥樣硬化性心血管疾病的第二型糖尿病成人病人，empagliflozin 對其心血管風險的影響如下述。

EMPA-REG OUTCOME 試驗為多中心、多國、隨機分組、雙盲、平行組別試驗，旨在針對其動脈粥樣硬化性心血管疾病的第二型糖尿病病人，比較當 empagliflozin 與安慰劑添加於糖尿病及動脈粥樣硬化性心血管疾病的標準照護療法做主要大不良心血管事件(MACE)的風險。在試驗前前 12 週期間，併用的抗糖尿病藥物應維持穩定。之後，即可依試驗主持人的判斷，對於抗糖尿病及抗動脈粥樣硬化的療法進行調整，以確保能夠依照這些疾病的標準照護療法來治療受試者。

總共有 7020 位病人接受治療(empagliflozin 10 mg = 2345；empagliflozin 25 mg = 2342；安慰劑= 2333)，並接受中位數 3.1 年的追蹤。大約 72%的受試族群為白種人，22%為亞洲人，5%為黑人。平均年齡為 63 歲，男性約佔 72%。

在此項試驗中，基準點時所有受試者的第二型糖尿病皆未獲有效控制(HbA1c≥7%)。基準點時的 HbA1c 平均值為 8.1%，而且 57%的受試者已確患糖尿病超過 10 年。分別有大約 31%、22%與 20%的受試者的試驗主持人報告曾有神經病變、視網膜病變與腎病變病史。eGFR 平均值為 74 mL/min/1.73 m^2。基準點時，病人接受一種(~30%)或更多種(~70%)抗糖尿病藥物治療，包括 metformin (74%)、胰島素(48%)、磺醯尿素類藥物(43%)和二肽基胜酶-4 (dipeptidyl peptidase-4)抑制劑 (11%)。

基準點時所有的病人皆有確診的動脈粥樣硬化性心血管疾病，包括一種(82%)或更多種(18%)以下疾病：經理實的冠狀動脈疾病(76%)、中風(23%)或腦血動脈疾病(21%)。基準點時，收縮壓平均值為 136 mmHg，舒張壓平均值為 76 mmHg，LDL 平均值為 86 mg/dL，HDL 平均值為 44 mg/dL，尿液中白蛋白對肌酸酐比值(UACR)平均值為 175 mg/g。基準點時，約有 81%的病人接受腎素血管收縮素系統抑制劑，65%接受乙型阻斷劑，43%接受利尿劑，77%接受 statin 類藥物，86%接受抗血小板劑(大部分為阿斯匹靈)治療。

EMPA-REG OUTCOME 試驗的主要評估指標為至首次發生重大不良心臟事件(MACE)的時間，重大不良心臟事件的定義為發生心血管原因死亡或發生非致命性心肌梗塞(MI)或非致命性中風。統計分析計畫已預先指明將 10 與 25 mg 劑量合併分析。針對預先指明的風險邊際值 1.3，使用 Cox 比例風險模型來檢定在重大不良心臟事件之風險比(hazard ratio)上的不劣性，以及劣證明不劣性，對檢定在重大不良心臟事件上的優越性，使用分層檢定策略來控制多重檢定的第一型錯誤。

Empagliflozin 可顯著減少發生心血管死亡、非致命性心肌梗塞或非致命性中風之主要綜合指標的風險(HR：0.86；95%信賴區間 0.74, 0.99)，此治療效果係由隨機分配至 empagliflozin 組之受試者的心血管原因死亡風險顯著降低所致(HR：0.62；95%信賴區間 0.49, 0.77)。非致命性心肌梗塞或非致命性中風的風險則未改變(請見表 9 以及圖 4 和 5)。10 mg 和 25 mg empagliflozin 劑量組個別的結果與兩劑量組合併的結果一致。

表 9　在主要綜合指標與個別成分指標方面的治療效果[a]

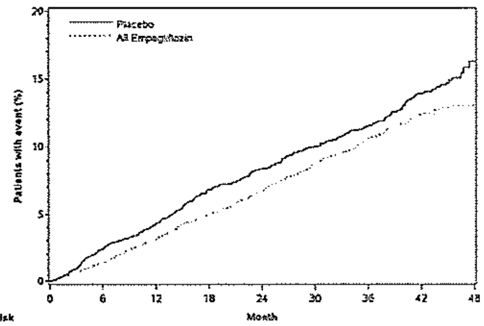
	安慰劑 N=2333	Empagliflozin N=4687	相較於安慰劑之風險比 (95% CI)
心血管原因死亡、非致命性心肌梗塞或非致命性中風的綜合指標（至首次發生的時間）[b]	282 (12.1%)	490 (10.5%)	0.86 (0.74, 0.99)
非致命性心肌梗塞[c]	121 (5.2%)	213 (4.5%)	0.87 (0.70, 1.09)
非致命性中風[c]	60 (2.6%)	150 (3.2%)	1.24 (0.92, 1.67)
心血管原因死亡[c]	137 (5.9%)	172 (3.7%)	0.62 (0.49, 0.77)

[a] 接受治療者資料集(接受至少一劑試驗藥物的受試者)

[b] 經越柱檢定之 p-值(雙尾)為 0.04

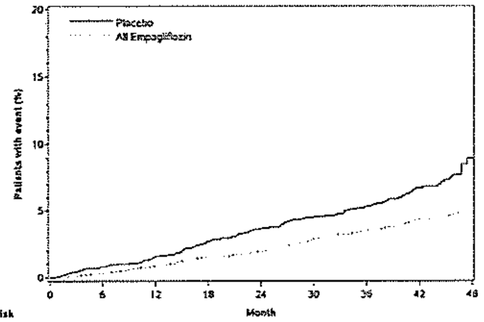
[c] 事件總數

圖 4 首次重大不良心臟事件的累積發生率估計值



Subjects at risk	0	6	12	18	24	30	36	42	48
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166
All Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370

圖 5 心血管原因死亡的累積發生率估計值



Subjects at risk	0	6	12	18	24	30	36	42	48
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177
All Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414

就心血管原因死亡而言，empagliflozin 對於各個主要人口與疾病子群的療效一致，包含 eGFR 為 30 到低於 45mL/min/1.73m² 的病人(Jardiance 治療組 381 名，安慰劑組 189 名)。

在此項試驗中，99.2%的受試者皆有存活狀態資料。在 EMPA-REG OUTCOME 試驗期間，總共記錄 463 例死亡。這些死亡案例大部分歸因於心血管原因死亡，非心血管原因死亡僅佔少部分，且兩治療組之間相近(接受 empagliflozin 者為 2.1%，接受安慰劑者為 2.4%)。

Linagliptin 心血管安全性試驗

CARMELINA

CARMELINA 試驗，針對第二型糖尿病成人病人且具有大血管或腎臟疾病病史之病人族群，評估 linagliptin 對心血管風險的影響，此試驗為多中心、多國、隨機分組、雙盲，以 linagliptin 治療組(N＝3494)及安慰劑組(N=3485)作為平行組別的臨床試驗。此項試驗將 linagliptin 與安慰劑併加至標準病及其他心血管危險因子的標準療法中與其併用，比較兩組出現之重大不良心血管事件（MACE）的風險。此試驗追蹤時間中位數為 2.2 年，取得 99.7%受試者的存活狀態資料。納入此臨床試驗之標準為：患有第二型糖尿病，其基期的 HbA1c 為 6.5%~10%且具白蛋白尿及先前患有大血管疾病(占 39%的受試者族群)或腎功能不全(以 eGFR 及 UACR 標準判定)(占 42%的受試者族群)或兩者皆具(占 18%的受試者族群)

基期時，平均受試者年齡為 66 歲，受試者族群 63%為男性，80%為白種人，9%為亞洲人，6%為黑人。HbA1c 平均值為 8.0%，罹患第二型糖尿病的持續時間平均約為 15 年。試驗族群包括≥75 歲的病人，占 17%，腎功能不全病人 eGFR <60 mL／min／1.73 m²，占 62%。平均 eGFR 為 55 mL／min／1.73 m²，27%受試者為輕度腎功能不全(eGFR 60-90 mL／min／1.73 m²)，47%受試者為中度腎功能不全(eGFR 30 至<60 mL／min／1.73 m²)及 15%為重度腎功能不全(eGFR <30 mL／min／1.73 m2)。97%的受試者服用至少一種抗糖尿病藥物，分別為胰島素及其類似物占 57%，metformin 占 54%，磺醯尿素類占 32%。96%的受試者服用抗血壓藥物，76%受試者服用降血脂藥物，其中 72%為司他汀類藥物及阿斯匹靈 62%。CARMELINA 試驗的主要評估指標為：首次出現重大心臟血管綜合不良事件（MACE）三者之任一項的時間。重大心臟不良事件的定義為心血管原因死亡或非致命性心肌梗塞（MI）或非致命性中風。此為不劣性試驗設計，預先設定風險比值之臨界點為 1.3。

總共 434 位病人使用 linagliptin 及 420 位病人使用安慰劑發生重大心臟血管綜合不良事件。重大心臟血管綜合不良事件發生率於兩個治療組別：安慰劑組每 1000 病人年發生 56.3 次事件相較於 linagliptin 治療組每 1000 病人年發生 57.7 次事件。Linagliptin 相較於安慰劑的 MACE 風險比值為 1.02（95%信賴區間：0.89, 1.17）。此信賴區間的上限值為 1.17，低於預先界定的風險比值 1.3。

CAROLINA

CAROLINA 試驗，針對第二型糖尿病成人病人且過去有心血管病史和/或多種心血管風險因素，評估 linagliptin 對心血管風險的影響：此試驗為多中心、多國、隨機分組、雙盲，以 linagliptin(N=3023)和 glimepiride (N=3010)作為平行組別的臨床試驗。此項試驗將 linagliptin 與 glimepiride 合併糖尿病及其他心血管危險因子的標準療法，比較兩組出現之重大不良心血管事件(MACE)的風險。此試驗追蹤時間中位數 6.23 年，取得 99.3%受試者的存活狀態資料。

納入此臨床試驗之標準為:患有第二型糖尿病之成人且血糖控制不佳(定義為糖化血色素為 6.5%~8.5%，或 6.5%~7.5%取決於未治療、單方治療或合併治療)，且高心血管風險如先前有心血管疾病、有末端器官損傷實證，年齡≥70 歲和/或 2 個心血管風險因素(糖尿病史>10 年、收縮壓> 140mmHg、正在抽菸者、低密度膽固醇≥135 mg/dL)

基期時，平均受試者年齡為 64 歲，受試者族群 60%為男性，73%為白種人，18%為亞洲人，5%為黑人。HbA1c 平均值為 7.15%，罹患第二型糖尿病的持續時間平均約為 7.6 年。試驗族群包括≥70 歲的病人占 34%，腎功能不全病人定義為 eGFR <60 mL/min/1.73 m² 占 19%，平均 eGFR 為 77 mL/min/1.73 m²。91%的受試者服用至少一種

抗糖尿病藥物，最常見為 metformin 占 83%，磺醯尿素類占 28%。89%的受試者服用抗血壓藥物，70%受試者服用降血脂藥物，其中 65%受試者為司他汀類藥物及 47%的受試者服用阿斯匹靈。

試驗的主要評估指標為：首次出現重大心臟血管綜合不良事件（MACE）三者之任一項的時間。重大心臟血管不良事件的定義為心血管原因死亡或非致命性心肌梗塞（MI）或非致命性中風。此為不劣性試驗設計，預先設定風險比值之臨界點為 1.3。總共 356 位病人使用 linagliptin 及 362 位病人使用 glimperide 發生重大心臟血管綜合不良事件。重大心臟血管綜合不良事件發生率於兩個治療組別: linagliptin 治療組每 1000 病人年發生 20.7 次事件相較於 glimperide 治療組每 1000 病人年發生 21.2 次事件。Linagliptin 相較於 glimperide 的 MACE 風險比值為 0.98(95%信賴區間:0.84,1.14)。此信賴區間的上限值為 1.14，低於預先界定的風險比值 1.3。

13. 包裝及儲存

13.1 包裝

GLYXAMBI (empagliflozin 及 linagliptin) 錠劑：

10 mg/5 mg 錠劑：淡黃色、圓弧三角形、平面、邊緣斜切的膜衣錠，一面壓印百靈佳殷格翰公司標誌，另一面壓印數字「10/5」。2-1000 錠鋁箔盒裝。

25 mg/5 mg 錠劑：淡粉紅色、圓弧三角形、平面、邊緣斜切的膜衣錠，一面壓印百靈佳殷格翰公司標誌，另一面壓印數字「25/5」。2-1000 錠鋁箔盒裝。

13.2 效期

如包裝所示。

13.3 儲存條件

請儲存於 30°C 以下。

13.4 儲存注意事項

請存放於兒童無法取得的安全處所。

14. 病人使用須知

<u>胰臟炎</u>
請告知病人，linagliptin 上市後，曾在使用期間通報發生急性胰臟炎的案例，並告知病人持續性嚴重腹痛 (有時會牽引至背部，且可能會發生嘔吐，也可能不會發生嘔吐) 為急性胰臟炎的典型症狀。指示病人若有持續嚴重的腹痛，請立即停用 GLYXAMBI 並就醫 *[詳見警語及注意事項 (5.1.1)]*。

<u>酮酸中毒</u>
請告知病人酮酸中毒是可能危及生命的嚴重狀況。曾有使用 empagliflozin 時，通報出現酮酸中毒的案例，有時與疾病或手術相關的其他風險因子有關。請指示病人如果出現符合酮酸中毒的症狀時，即使血糖並未上升，應立即就醫。請指示病人如果出現酮酸中毒的症狀（包括噁心、嘔吐、腹痛、疲累及呼吸困難），應停用 GLYXAMBI 並立即就醫 *[詳見警語及注意事項 (5.1.2)]*。

<u>體液容量減少</u>
告知病人服用 Glyxambi 可能會發生帶有症狀的低血壓，若病人出現上述症狀，請與開立處方之醫師聯絡 *[詳見警語及注意事項 (5.1.3)]*。告知病人脫水可能會增加發生低血壓的風險，請維持足夠的水分攝取。

<u>嚴重泌尿道感染</u>
請告知病人泌尿道感染的可能性（可能為嚴重感染），以及泌尿道感染的相關症狀。請建議病人於出現泌尿道症狀時就醫 *[詳見警語及注意事項 (5.1.4)]*。

<u>併用胰島素與胰島素促泌劑時發生的低血糖</u>
請告知病人 GLYXAMBI 與胰島素促泌劑(例如磺醯尿素類藥物)或胰島素併用時，會增加低血糖症的發生風險，因此可能須降低胰島素促泌劑或胰島素的劑量，以減少低血糖症的風險 *[請參閱警語及注意事項(5.1.5)]*。

<u>會陰部壞死性筋膜炎(弗尼爾氏壞疽)</u>
請告知病人，曾有使用 empagliflozin(糖順平的成分)時出現會陰壞死性感染(弗尼爾氏壞疽)的病例，建議病人，如果生殖器或其後至直腸區域出現疼痛或壓痛，伴紅或腫脹並伴隨發燒超過 38°C 或身體不適，應立即就醫 *[請參閱警語及注意事項 5.1.6)]*。

<u>女性的生殖器黴菌感染 (如外陰陰道炎)</u>
請告知女性病人可能發生陰道的真菌感染，並針對陰道真菌感染的症狀和徵象提供相關資訊。請告知病人可能的治療選擇，以及何時應尋求醫療建議 *[詳見警語及注意事項 (5.1.7)]*。

<u>男性的生殖器黴菌感染 (如龜頭炎或龜頭包皮炎)</u>
請告知男性病人可能發生陰莖的真菌感染 (如龜頭炎或龜頭包皮炎)，尤其是未割包皮的男性以及慢性和反覆感染者。請針對龜頭炎和龜頭包皮炎的徵象和症狀 (陰莖的龜頭或包皮發紅或出現皮疹) 向病人提供相關資訊。請告知病人可能的治療選擇，以及何時應尋求醫療建議 *[詳見警語及注意事項 (5.1.7)]*。

<u>過敏反應</u>
請告知病人 empagliflozin 或 linagliptin (GLYXAMBI 的成分之一) 上市後，曾有案例報告嚴重過敏反應，例如急性過敏、血管性水腫和剝脫性皮膚炎。如果發生過敏反應症狀 (例如皮疹、皮膚剝落或脫皮、蕁麻疹、皮膚腫脹；或臉部、嘴唇、舌頭和喉嚨腫脹，可能造成呼吸或吞嚥困難)，必須停用 GLYXAMBI 並立即就醫 *[詳見警語及注意事項 (5.1.8)]*。

<u>嚴重和行動不便之關節疼痛</u>
請告知病人使用 DPP4 抑制劑這類藥可能發生嚴重和行動不便之關節疼痛，有可能在用藥後第 1 天或幾年後發生。請告知病人如果發生嚴重關節疼痛症狀，必須立即就醫 *[詳見警語及注意事項(5.1.10)]*。

<u>大皰性類天皰瘡</u>
請告知病人，使用此類藥物時可能發生大皰性類天皰瘡。請告知病人，出現水泡或糜爛時應就醫 *[詳見警語及注意事項（5.1.11）]*。

<u>實驗室檢測</u>
請提醒病人，服用 GLYXAMBI 時尿液分析中的尿糖升高為正常現象。

<u>懷孕</u>
請告知懷孕病人和具有生育能力的病人，以 GLYXAMBI 治療可能對胎兒造成風險 *[詳見特殊族群注意事項 (6.1)]*。請指示具有生育能力的病人，應在懷孕時儘快告知醫師。

<u>哺乳</u>
請告知病人，不建議在接受 GLYXAMBI 治療期間餵哺母乳 *[詳見特殊族群注意事項 (6.2)]*。

<u>漏服藥物</u>
請指示病人務必依照處方服用 GLYXAMBI。應提醒病人，若錯過一劑藥物，請儘速於記起時立刻服用，請勿於下一劑時服用雙倍劑量。

15. 其他

共用仿單產品:

格喘平妥脈衣錠 10/5 毫克 Glyxambi® 10/5mg Film-Coated Tablets (衛部藥輸字第 027074 號)

格喘平妥脈衣錠 25/5 毫克 Glyxambi® 25/5mg Film-Coated Tablets (衛部藥輸字第 027073 號)

修訂日期 2022 年 5 月
核定日期 2022 年 9 月

製造廠

Rottendorf Pharma GmbH
Ostenfelder Straße 51-61 59320 Ennigerloh, Germany

分包裝廠

Rottendorf Pharma GmbH
Am Fleigendahl 3, 59320 Ennigerloh, Germany

國外許可證持有者
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Germany

藥商
台灣百靈佳殷格翰股份有限公司
台北市民生東路三段 2 號 12 樓

Glyxambi® 10/5 mg Film-Coated Tablets
Glyxambi® 25/5 mg Film-Coated Tablets
The product should be used by physician prescription.

1. DESCRIPTION

1.1 Active Ingredients and Strengths

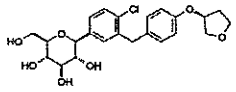
GLYXAMBI tablets for oral use contain: empagliflozin and linagliptin.

Empagliflozin

Empagliflozin is an inhibitor of the sodium-glucose co-transporter 2 (SGLT2).

The chemical name of empagliflozin is D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S).

The molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91. The structural formula is:



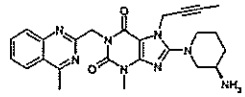
Empagliflozin is a white to yellowish, non-hygroscopic powder. It is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol and acetonitrile, soluble in 50% acetonitrile/water, and practically insoluble in toluene.

Linagliptin

Linagliptin is an inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme.

The chemical name of linagliptin is 1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]-

The molecular formula is $C_{25}H_{28}N_8O_2$ and the molecular weight is 472.54. The structural formula is:



Linagliptin is a white to yellowish, not or only slightly hygroscopic solid substance. It is very slightly soluble in water. Linagliptin is soluble in methanol, sparingly soluble in ethanol, very slightly soluble in isopropanol, and very slightly soluble in acetone.

GLYXAMBI

GLYXAMBI tablets are available in two dosage strengths containing 10 mg or 25 mg empagliflozin in combination with 5 mg linagliptin.

1.2 Excipients

The inactive ingredients of GLYXAMBI are the following: Tablet Core: mannitol, pregelatinized starch, corn starch, copovidone, crospovidone, talc and magnesium stearate. Coating: hypromellose, mannitol, talc, titanium dioxide, polyethylene glycol and ferric oxide, yellow (10 mg/5 mg) or ferric oxide, red (25 mg/5 mg).

1.3 Dosage Form

film-coated tablets.

1.4 Appearance

GLYXAMBI tablets are a combination of empagliflozin and linagliptin available as

- 10 mg empagliflozin/5 mg linagliptin are pale yellow, are triangular, flat-faced, bevel-edged, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol; the other side is debossed with "10/5".
- 25 mg empagliflozin/5 mg linagliptin are pale pink, are triangular, flat-faced, bevel-edged, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol; the other side is debossed with "25/5".

2. INDICATION

GLYXAMBI tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when metformin and one of the monocomponents of Glyxambi do not provide adequate glycaemic control; or when already being treated with both empagliflozin and linagliptin is appropriate.

Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease However, the effectiveness of GLYXAMBI on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease has not been established.

Limitations of Use
GLYXAMBI is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients *[see Warnings and Precautions (5.1.2)]*.

GLYXAMBI has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using GLYXAMBI *[see Warnings and Precautions (5.1.1)]*.

3. DOSAGE AND ADMINISTRATION

3.1 Dosage and Administration

3.1.1 Prior to Initiation of GLYXAMBI

- Assess renal function before initiating GLYXAMBI and as clinically indicated *[see Warnings and Precautions (5.1.3)]*.

- In patients with volume depletion, correct this condition before initiating GLYXAMBI *[see Warnings and Precautions (5.1.3) and Warnings in Special Populations (6.3, 6.7)]*.

3.1.2 Recommended Dosage
The recommended dose of GLYXAMBI is 10 mg empagliflozin/5 mg linagliptin once daily in the morning, taken with or without food. GLYXAMBI may be increased to 25 mg empagliflozin/5 mg linagliptin once daily for additional glycemic control.

3.3 Specific Populations Dosage and Administration
Dosage Recommendations in Patients with Renal Impairment
GLYXAMBI should not be initiated in patients with an eGFR less than 30 mL/min/1.73 m^2.

No dose adjustment is needed in patients with an eGFR greater than or equal to 30 mL/min/1.73 m^2.

GLYXAMBI should be discontinued if eGFR is persistently less than 30 mL/min/1.73 m^2 *[see Warnings and Precautions (5.1.3, 5.1.5) and Warnings in Special Populations (6.7)]*.

4. CONTRAINDICATIONS

GLYXAMBI is contraindicated in patients with:

- Severe renal impairment, end-stage renal disease, or dialysis *[see Warnings in Special Populations (6.7)]*.
- Hypersensitivity to empagliflozin, linagliptin, or any of the excipients in GLYXAMBI, reactions such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity have occurred *[see Warnings and Precautions (5.1.6) and Adverse Reactions (6)]*.

5. WARNINGS AND PRECAUTIONS

5.1 Warnings / Precautions

5.1.1 Pancreatitis
Acute pancreatitis, including fatal pancreatitis, has been reported in patients treated with linagliptin. In the CARMELINA trial *[see Clinical Studies (12)]*, acute pancreatitis was reported in 9 (0.3%) patients treated with linagliptin and in 5 (0.1%) patients treated with placebo. Two patients treated with linagliptin in the CARMELINA trial had acute pancreatitis with a fatal outcome. There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients treated with linagliptin.

Take careful notice of potential signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue GLYXAMBI and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using GLYXAMBI.

5.1.2 Ketoacidosis
Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in clinical trials and postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including empagliflozin. Fatal cases of ketoacidosis have been reported in patients taking empagliflozin. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. GLYXAMBI is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (2)]*.

Patients treated with GLYXAMBI who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with GLYXAMBI may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, GLYXAMBI should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating GLYXAMBI, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing GLYXAMBI for at least 3 days prior to surgery [*see Clinical Pharmacology (10.2) and Pharmacokinetics (11)*].

Consider monitoring for ketoacidosis and temporarily discontinuing GLYXAMBI in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting GLYXAMBI.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue GLYXAMBI and seek medical attention immediately if signs and symptoms occur.

5.1.3 Volume Depletion
Empagliflozin can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine *[see Clinical Trial Experience (8.2)]*. There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating GLYXAMBI in patients with one or more of these characteristics, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating GLYXAMBI. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.

5.1.4 Urosepsis and Pyelonephritis
There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including empagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated *[see Adverse Reactions (8)]*.

5.1.5 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
Insulin and insulin secretagogues are known to cause hypoglycemia. The use of empagliflozin or linagliptin in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin was associated with a higher rate of

hypoglycemia compared with placebo in a clinical trial. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with GLYXAMBI.

5.1.6 Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
Reports of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with GLYXAMBI presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue GLYXAMBI, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

5.1.7 Genital Mycotic Infections
Empagliflozin increases the risk for genital mycotic infections *[see Clinical Trial Experience (8.2)]*. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat as appropriate.

5.1.8 Hypersensitivity Reactions
There have been postmarketing reports of serious hypersensitivity reactions in patients treated with linagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred predominantly within the first 3 months after initiation of treatment with linagliptin, with some reports occurring after the first dose.

Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema to another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with GLYXAMBI.

There have been postmarketing reports of serious hypersensitivity reactions, (e.g., angioedema) in patients treated with empagliflozin.

If a hypersensitivity reaction occurs, discontinue GLYXAMBI, treat promptly per standard of care, and monitor until signs and symptoms resolve. GLYXAMBI is contraindicated in patients with hypersensitivity to linagliptin empagliflozin or any of the excipients in GLYXAMBI *[see Contraindications (4)]*.

5.1.9 Increased Low-Density Lipoprotein Cholesterol (LDL-C)
Increases in LDL-C can occur with empagliflozin *[see Clinical Trial Experience (8.2)]*. Monitor and treat as appropriate.

5.1.10 Severe and Disabling Arthralgia
There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider as a possible cause for severe joint pain and discontinue drug if appropriate.

5.1.11 Bullous Pemphigoid

Bullous pemphigoid was reported in 7 (0.2%) patients treated with linagliptin compared to none in patients treated with placebo in the CARMELINA trial *[see Clinical Studies (12)]*, and 3 of these patients were hospitalized due to bullous pemphigoid. Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving GLYXAMBI. If bullous pemphigoid is suspected, GLYXAMBI should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

6. WARNINGS IN SPECIAL POPULATIONS

6.1 Pregnancy

Risk Summary
Based on animal data showing adverse renal effects from empagliflozin, GLYXAMBI is not recommended during the second and third trimesters of pregnancy.

The limited available data with GLYXAMBI, linagliptin, or empagliflozin in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations)*.

In animal studies, empagliflozin, a component of GLYXAMBI, resulted in adverse renal changes in rats when administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 13-times the maximum clinical dose caused renal pelvic and tubule dilatations that were reversible. No adverse developmental effects were observed when the combination of linagliptin and empagliflozin was administered to pregnant rats *(see Data)*.

The estimated background risk of major birth defects is 6% to 10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20% to 25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations
Disease-associated maternal and/or embryo/fetal risk: Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data
Animal Data
The combined components administered during the period of organogenesis were not teratogenic in rats up to and including a combined dose of 700 mg/kg/day empagliflozin and 140 mg/kg/day linagliptin, which is 253- and 353-times the clinical exposure. A pre- and postnatal development study was not conducted with the combined components of GLYXAMBI.

Empagliflozin: Empagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND [illegible] doses of 1, 10, 30, and 100 mg/kg/day caused increased kidney weights and renal tubular and pelvic dilatation at 100 mg/kg/day, which approximates 13-times the maximum clinical dose of 25 mg, based on AUC [illegible] findings were not observed after a 13-week drug-free recovery period. These outcomes occurred with [illegible]

exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development.

In embryo-fetal development studies in rats and rabbits, empagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. Doses up to 300 mg/kg/day, which approximates 48-times (rats) and 128-times (rabbits) the maximum clinical dose of 25 mg (based on AUC), did not result in adverse developmental effects. In rats, at higher doses of empagliflozin causing maternal toxicity, malformations of limb bones increased in fetuses at 700 mg/kg/day or 154-times the 25 mg maximum clinical dose. Empagliflozin crosses the placenta and reaches fetal tissues in rats. In the rabbit, higher doses of empagliflozin resulted in maternal and fetal toxicity at 700 mg/kg/day, or 139-times the 25 mg maximum clinical dose.

In pre- and postnatal development studies in pregnant rats, empagliflozin was administered from gestation day 6 through to lactation day 20 (weaning) at up to 100 mg/kg/day (approximately 16-times the 25 mg maximum clinical dose) without maternal toxicity. Reduced body weight was observed in the offspring at greater than or equal to 30 mg/kg/day (approximately 4-times the 25 mg maximum clinical dose).

Linagliptin: No adverse developmental outcome was observed when linagliptin was administered to pregnant Wistar Han rats and Himalayan rabbits during the period of organogenesis at doses up to 240 mg/kg/day and 150 mg/kg/day, respectively. These doses represent approximately 943-times (rats) and 1943-times (rabbits) the 5 mg maximum clinical dose, based on exposure. No adverse functional, behavioral, or reproductive outcome was observed in offspring following administration of linagliptin to Wistar Han rats from gestation day 6 to lactation day 21 at a dose 49-times the maximum recommended human dose, based on exposure.

Linagliptin crosses the placenta into the fetus following oral dosing in pregnant rats and rabbits.

6.2 Lactation

Risk Summary
There is no information regarding the presence of GLYXAMBI, or its individual components in human milk, the effects on the breastfed infant, or the effects on milk production. Empagliflozin and linagliptin are present in rat milk *(see Data)*. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in a breastfed infant, including the potential for empagliflozin to affect postnatal renal development, advise patients that use of GLYXAMBI is not recommended while breastfeeding.

Data
Empagliflozin was present at a low level in rat fetal tissues after a single oral dose to the dams at gestation day 18. In rat milk, the mean milk to plasma ratio ranged from 0.634 to 5, and was greater than one from 2 to 24 hours post-dose. The mean maximal milk to plasma ratio of 5 occurred at 8 hours post-dose, suggesting accumulation of empagliflozin in the milk. Juvenile rats directly exposed to empagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

[illegible]diatric use
[illegible] and effectiveness of GLYXAMBI have not been established in pediatric patients.

6.5 Geriatric use

GLYXAMBI

Empagliflozin is associated with osmotic diuresis, which could affect hydration status of patients age 75 years and older *[see Warnings and Precautions (5.1.3)]*.

Empagliflozin

In empagliflozin type 2 diabetes studies, 2721 empagliflozin-treated patients were 65 years of age and older and 491 patients were 75 years of age and older. In these studies, volume depletion-related adverse reactions occurred in 2.1%, 2.3%, and 4.4% of patients 75 years of age and older in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg once daily groups, respectively; and urinary tract infections occurred in 10.5%, 15.7%, and 15.1% of patients 75 years of age and older in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg once daily groups, respectively.

Linagliptin

In linagliptin studies, 1085 linagliptin-treated patients were 65 years of age and older and 131 patients were 75 years of age and older. In these linagliptin studies, no overall differences in safety or effectiveness of linagliptin were observed between geriatric patients and younger adult patients.

6.6 Hepatic Impairment

GLYXAMBI may be used in patients with hepatic impairment *[see Pharmacokinetics (12)]*.

6.7 Renal Impairment

Empagliflozin

The glucose lowering benefit of empagliflozin 25 mg decreased in patients with worsening renal function. The risks of renal impairment *[see Warnings and Precautions (5.1.3)]*, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function.

Efficacy and safety studies with empagliflozin did not enroll patients with ESRD on dialysis or patients with an eGFR less than 30 mL/min/1.73 m^2. Empagliflozin is contraindicated in patients on dialysis *[see Indications and Usage (2) and Contraindications (4)]*.

7. INTERACTIONS

Table 1 Clinically Relevant Interactions with GLYXAMBI

Diuretics	
Clinical Impact	Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.
Intervention	Before initiating GLYXAMBI, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating GLYXAMBI. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.
Insulin or Insulin Secretagogues	
Clinical Impact	Empagliflozin or linagliptin in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial.
Intervention	Coadministration of GLYXAMBI with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.
Positive Urine Glucose Test	
Clinical Impact	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
Intervention	Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay	
Clinical Impact	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.
Intervention	Monitoring glycemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycemic control.
Inducers of P-glycoprotein or CYP3A4 Enzymes	
Clinical Impact	Rifampin decreased linagliptin exposure, suggesting that the efficacy of linagliptin may be reduced when administered in combination with a strong P-gp or CYP3A4 inducer.
Intervention	Use of alternative treatments is strongly recommended when linagliptin is to be administered with a strong P-gp or CYP3A4 inducer.

8. ADVERSE REACTIONS

8.1 Clinically Significant Adverse Reactions

The following important adverse reactions are described below and elsewhere in the labeling:

- Pancreatitis *[see Warnings and Precautions (5.1.1)]*
- Ketoacidosis *[see Warnings and Precautions (5.1.2)]*
- Volume Depletion *[see Warnings and Precautions (5.1.3)]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (5.1.4)]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.1.5)]*
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) *[see Warnings and Precautions (5.1.6)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.1.7)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.1.8)]*
- Increased Low-Density Lipoprotein Cholesterol (LDL-C) *[see Warnings and Precautions (5.1.9)]*
- Severe and Disabling Arthralgia *[see Warnings and Precautions (5.1.10)]*
- Bullous Pemphigoid *[see Warnings and Precautions (5.1.11)]*

8.2 Clinical Trial Experience

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.

Empagliflozin and Linagliptin

The safety of concomitantly administered empagliflozin (daily dose 10 mg or 25 mg) and linagliptin (daily dose 5 mg) has been evaluated in a total of 1363 patients with type 2 diabetes treated for up to 52 weeks in active-controlled clinical trials. The most common adverse reactions with concomitant administration of empagliflozin and linagliptin based on a pooled analyses of these studies are shown in Table 2.

Table 2 Adverse Reactions Reported in ≥5% of Patients Treated with Empagliflozin and Linagliptin

Adverse Reactions	GLYXAMBI (%) 10 mg/5 mg n=272	GLYXAMBI (%) 25 mg/5 mg n=273
Urinary tract infection[a]	12.5	11.4
Nasopharyngitis	5.9	6.6
Upper respiratory tract infection	7.0	7.0

[a]Predefined adverse event grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis

Empagliflozin

Adverse reactions that occurred in ≥2% of patients receiving empagliflozin and more commonly than in patients given placebo included (10 mg, 25 mg, and placebo): urinary tract infection (9.3%, 7.6%, and 7.6%), female genital mycotic infections (5.4%, 6.4%, and 1.5%), upper respiratory tract infection (3.1%, 4.0%, and 3.8%), increased urination (3.4%, 3.2%, and 1.0%), dyslipidemia (3.9%, 2.9%, and 3.4%), arthralgia (2.4%, 2.3%, and 2.2%), male genital mycotic infections (3.1%, 1.6%, and 0.4%), and nausea (2.3%, 1.1%, and 1.4%).

Thirst (including polydipsia) was reported in 0%, 1.7%, and 1.5% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Empagliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. Events related to volume depletion (hypotension and syncope) were reported in 3 patients (1.1%) treated with GLYXAMBI plus metformin.

Linagliptin

Adverse reactions reported in ≥2% of patients treated with linagliptin 5 mg and more commonly than in patients treated with placebo included: nasopharyngitis (7.0% and 6.1%), diarrhea (3.3% and 3.0%), and cough (2.1% and 1.4%).

Other adverse reactions reported in clinical studies with treatment of linagliptin monotherapy were hypersensitivity (e.g., urticaria, angioedema, localized skin exfoliation, or bronchial hyperreactivity) and myalgia.

In the clinical trial program, pancreatitis was reported in 15.2 cases per 10,000 patient year exposure while being treated with linagliptin compared with 3.7 cases per 10,000 patient year exposure while being treated

with comparator (placebo and active comparator, sulfonylurea). Three additional cases of pancreatitis were reported following the last administered dose of linagliptin.

Hypoglycemia

Table 3 summarizes the reports of hypoglycemia with empagliflozin and linagliptin over a treatment period of 52 weeks.

Table 3 Incidence of Overall[a] and Severe[b] Hypoglycemic Adverse Reactions

Add-on to Metformin (52 weeks)	GLYXAMBI (%) 10 mg/5 mg (n=136)	GLYXAMBI (%) 25 mg/5 mg (n=137)
Overall	2.2	3.6
Severe	0	0

[a]Overall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL or requiring assistance

[b]Severe hypoglycemic events: requiring assistance regardless of blood glucose

Laboratory Tests

Empagliflozin and Linagliptin

Changes in laboratory findings in patients treated with the combination of empagliflozin and linagliptin included increases in cholesterol and hematocrit compared to baseline.

Empagliflozin

Increases in Serum Creatinine and Decreases in eGFR: Initiation of empagliflozin causes an increase in serum creatinine and decrease in eGFR within weeks of starting therapy and then these changes stabilize. In a study of patients with moderate renal impairment, larger mean changes were observed. In a long-term cardiovascular outcomes trial, the increase in serum creatinine and decrease in eGFR generally did not exceed 0.1 mg/dL and -9.0 mL/min/1.73 m^2, respectively, at Week 4, and reversed after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with empagliflozin.

Increase in Low-Density Lipoprotein Cholesterol (LDL-C): Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in patients treated with empagliflozin. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively *[see Warnings and Precautions (5.1.9)]*. The range of mean baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups.

Increase in Hematocrit: Median hematocrit decreased by 1.3% in placebo and increased by 2.8% in empagliflozin 10 mg and 2.8% in empagliflozin 25 mg treated patients. At the end of treatment, 0.6%, 2.7%, and 3.5% of patients with hematocrits initially within the reference range had values above the upper limit of the reference range with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Linagliptin

Increase in Uric Acid: Changes in laboratory values that occurred more frequently in the linagliptin group and ≥1% more than in the placebo group were increases in uric acid (1.3% in the placebo group, 2.7% in the linagliptin group).

Increase in Lipase: In a placebo-controlled clinical trial with linagliptin in type 2 diabetes mellitus patients with micro- or macroalbuminuria, a mean increase of 30% in lipase concentrations from baseline to 24 weeks was observed in the linagliptin arm compared to a mean decrease of 2% in the placebo arm. Lipase levels above 3 times upper limit of normal were seen in 8.2% compared to 1.7% patients in the linagliptin and placebo arms, respectively.

Increase in Amylase: In a cardiovascular safety study comparing linagliptin versus glimepiride in patients with type 2 diabetes mellitus, amylase levels above 3 times upper limit of normal were seen in 1.0% compared to 0.5% of patients in the linagliptin and glimepiride arms, respectively.

The clinical significance of elevations in lipase and amylase with linagliptin is unknown in the absence of other signs and symptoms of pancreatitis.

8.3 Post-marketing Experience

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

- *Gastrointestinal Disorders:* Acute pancreatitis, including fatal pancreatitis *[see Indications and Usage (2)]*, constipation, mouth ulceration, stomatitis
- *Immune System Disorders:* Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions
- *Infections:* Necrotizing fasciitis of the perineum (Fournier's gangrene), urosepsis and pyelonephritis
- *Metabolism and Nutrition Disorders:* Ketoacidosis
- *Musculoskeletal and Connective Tissue Disorders:* Severe and disabling arthralgia
- *Renal and Urinary Disorders:* Acute kidney injury
- *Skin and Subcutaneous Tissue Disorders:* Bullous pemphigoid, skin reactions (e.g., rash, urticaria)

9. OVERDOSE

In the event of an overdose with GLYXAMBI, contact the physician immediately. Removal of empagliflozin by hemodialysis has not been studied, and removal of linagliptin by hemodialysis or peritoneal dialysis is unlikely.

10. CLINICAL PHARMACOLOGY

10.1 Mechanism of action

GLYXAMBI

GLYXAMBI contains: empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor.

Empagliflozin

Sodium-glucose co-transporter 2 (SGLT2) is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Empagliflozin is an inhibitor of SGLT2. By

inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

Linagliptin

Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Thus, linagliptin increases the concentrations of active incretin hormones, stimulating the release of insulin in a glucose-dependent manner and decreasing the levels of glucagon in the circulation. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretin hormones are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. Furthermore, GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in hepatic glucose output.

10.2 Pharmacodynamics

Empagliflozin

Urinary Glucose Excretion

In patients with type 2 diabetes, urinary glucose excretion increased immediately following a dose of empagliflozin and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78 grams per day with 25 mg empagliflozin once daily. Data from single oral doses of empagliflozin in healthy subjects indicate that, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg and 25 mg doses.

Urinary Volume

In a 5-day study, mean 24-hour urine volume increase from baseline was 341 mL on Day 1 and 135 mL on Day 5 of empagliflozin 25 mg once daily treatment.

Cardiac Electrophysiology

In a randomized, placebo-controlled, active-comparator, crossover study, 30 healthy subjects were administered a single oral dose of empagliflozin 25 mg, empagliflozin 200 mg (8 times the maximum recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

Linagliptin

Linagliptin binds to DPP-4 in a reversible manner and increases the concentrations of incretin hormones. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion, thus resulting in a better regulation of the glucose homeostasis. Linagliptin binds selectively to DPP-4 and selectively inhibits DPP-4, but not DPP-8 or DPP-9 activity *in vitro* at concentrations approximating therapeutic exposures.

Cardiac Electrophysiology

In a randomized, placebo-controlled, active-comparator, 4-way crossover study, 36 healthy subjects were administered a single oral dose of linagliptin 5 mg, linagliptin 100 mg (20 times the recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either the recommended dose of 5 mg or the 100-mg dose. At the 100-mg dose, peak linagliptin plasma concentrations were approximately 38-fold higher than the peak concentrations following a 5-mg dose.

10.3 Preclinical safety data

Nonclinical Toxicology

10.3.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

GLYXAMBI

No carcinogenicity, mutagenicity, or impairment of fertility studies have been conducted with the combination of empagliflozin and linagliptin. General toxicity studies in rats up to 13 weeks were performed with the combined components. These studies indicated that no additive toxicity is caused by the combination of empagliflozin and linagliptin.

Empagliflozin

Carcinogenesis was evaluated in 2-year studies conducted in CD-1 mice and Wistar rats. Empagliflozin did not increase the incidence of tumors in female rats dosed at 100, 300, or 700 mg/kg/day (up to 72 times the exposure from the maximum clinical dose of 25 mg). In male rats, hemangiomas of the mesenteric lymph node were increased significantly at 700 mg/kg/day or approximately 42 times the exposure from a 25 mg clinical dose. Empagliflozin did not increase the incidence of tumors in female mice dosed at 100, 300, or 1000 mg/kg/day (up to 62 times the exposure from a 25 mg clinical dose). Renal tubule adenomas and carcinomas were observed in male mice at 1000 mg/kg/day, which is approximately 45 times the exposure of the maximum clinical dose of 25 mg. These tumors may be associated with a metabolic pathway predominantly present in the male mouse kidney.

Empagliflozin was not mutagenic or clastogenic with or without metabolic activation in the *in vitro* Ames bacterial mutagenicity assay, the *in vitro* L5178Y $tk^{+/-}$ mouse lymphoma cell assay, and an *in vivo* micronucleus assay in rats.

Empagliflozin had no effects on mating, fertility or early embryonic development in treated male or female rats up to the high dose of 700 mg/kg/day (approximately 155 times the 25 mg clinical dose in males and females, respectively).

Linagliptin

Linagliptin did not increase the incidence of tumors in male and female rats in a 2-year study at doses of 6, 18, and 60 mg/kg. The highest dose of 60 mg/kg is approximately 418 times the clinical dose of 5 mg/day based on AUC exposure. Linagliptin did not increase the incidence of tumors in mice in a 2-year study at doses up to 80 mg/kg (males) and 25 mg/kg (females), or approximately 35- and 270-times the clinical dose based on AUC exposure. Higher doses of linagliptin in female mice (80 mg/kg) increased the incidence of lymphoma at approximately 215-times the clinical dose based on AUC exposure.

Linagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a chromosomal aberration test in human lymphocytes, and an *in vivo* micronucleus assay.

In fertility studies in rats, linagliptin had no adverse effects on early embryonic development, mating, fertility, or bearing live young up to the highest dose of 240 mg/kg (approximately 943-times the clinical dose based on AUC exposure).

11. PHARMACOKINETICS

GLYXAMBI

Administration of the fixed-dose combination with food resulted in no change in overall exposure of empagliflozin or linagliptin; however, the peak exposure was decreased 59% and 32% for empagliflozin and linagliptin, respectively. These changes are not likely to be clinically significant.

Absorption

Empagliflozin

The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes and no clinically relevant differences were noted between the two populations. After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady-state mean plasma AUC and C_{max} were 1870 nmol·h/L and 259 nmol/L, respectively, with 10 mg empagliflozin once daily treatment, and 4740 nmol·h/L and 687 nmol/L, respectively, with 25 mg empagliflozin once daily treatment. Systemic exposure of empagliflozin increased in a dose-proportional manner in the therapeutic dose range. The single-dose and steady-state pharmacokinetic parameters of empagliflozin were similar, suggesting linear pharmacokinetics with respect to time.

Administration of 25 mg empagliflozin after intake of a high-fat and high-caloric meal resulted in slightly lower exposure: AUC decreased by approximately 16% and C_{max} decreased by approximately 37%, compared to fasted condition. The observed effect of food on empagliflozin pharmacokinetics was not considered clinically relevant and empagliflozin may be administered with or without food.

Linagliptin

The absolute bioavailability of linagliptin is approximately 30%. High-fat meal reduced C_{max} by 15% and increased AUC by 4%; this effect is not clinically relevant. Linagliptin may be administered with or without food.

Distribution

Empagliflozin

The apparent steady-state volume of distribution was estimated to be 73.8 L based on a population pharmacokinetic analysis. Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

Linagliptin

The mean apparent volume of distribution at steady-state following a single intravenous dose of linagliptin 5 mg to healthy subjects is approximately 1110 L, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent, decreasing from about 99% at 1 nmol/L to 75% to 89% at ≥30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations, where DPP-4 is fully saturated, 70% to 80% of linagliptin remains bound to plasma proteins and 20% to 30% is unbound in plasma. Plasma binding is not altered in patients with renal or hepatic impairment.

Elimination

Empagliflozin: The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state, which was consistent with empagliflozin half-life.

Linagliptin: Linagliptin has a terminal half-life of about 200 hours at steady-state, though the accumulation half-life is about 11 hours. Renal clearance at steady-state was approximately 70 mL/min.

Metabolism

Empagliflozin: No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide). Systemic exposure of each metabolite was less than 10% of total drug-related material. *In vitro* studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Linagliptin: Following oral administration, the majority (about 90%) of linagliptin is excreted unchanged, indicating that metabolism represents a minor elimination pathway. A small fraction of absorbed linagliptin is metabolized to a pharmacologically inactive metabolite, which shows a steady-state exposure of 13.3% relative to linagliptin.

Excretion

Empagliflozin: Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug-related radioactivity was eliminated in feces (41.2%) or urine (54.4%). The majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

Linagliptin: Following administration of an oral [^{14}C]-linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated via the enterohepatic system (80%) or urine (5%) within 4 days of dosing.

Specific Populations

Renal Impairment

GLYXAMBI: Studies characterizing the pharmacokinetics of empagliflozin and linagliptin after administration of GLYXAMBI in renally impaired patients have not been performed.

Empagliflozin: In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m^2), moderate (eGFR: 30 to less than 60 mL/min/1.73 m^2), and severe (eGFR: less than 30 mL/min/1.73 m^2) renal impairment and patients with kidney failure/end stage renal disease (ESRD), AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in patients with moderate renal impairment and kidney failure/ESRD compared to subjects with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in patients with mild and severe renal impairment as compared to subjects with normal renal function. Population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased, with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR.

Linagliptin: An open-label pharmacokinetic study evaluated the pharmacokinetics of linagliptin 5 mg in male and female patients with varying degrees of chronic renal impairment. The study included 6 healthy subjects with normal renal function (creatinine clearance [CrCl] ≥80 mL/min), 6 patients with mild renal impairment (CrCl 50 to <80 mL/min), 6 patients with moderate renal impairment (CrCl 30 to <50 mL/min), 10 patients with type 2 diabetes and severe renal impairment (CrCl <30 mL/min), and 11 patients with type 2 diabetes and normal renal function. Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula.

Under steady-state conditions, linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects.

In patients with moderate renal impairment under steady-state conditions, mean exposure of linagliptin increased ($AUC_{\tau,ss}$ by 71% and C_{max} by 46%) compared with healthy subjects. This increase was not associated with a prolonged accumulation half-life, terminal half-life, or an increased accumulation factor. Renal excretion of linagliptin was below 5% of the administered dose and was not affected by decreased renal function. Patients with type 2 diabetes and severe renal impairment showed steady-state exposure approximately 40% higher than that of patients with type 2 diabetes and normal renal function (increase in $AUC_{\tau,ss}$ by 42% and C_{max} by 35%). For both type 2 diabetes groups, renal excretion was below 7% of the administered dose.

These findings were further supported by the results of population pharmacokinetic analyses.

Hepatic Impairment

GLYXAMBI: Studies characterizing the pharmacokinetics of empagliflozin and linagliptin after administration of GLYXAMBI in hepatically impaired patients have not been performed.

Empagliflozin: In patients with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased by approximately 23%, 47%, and 75% and C_{max} increased by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

Linagliptin: In patients with mild hepatic impairment (Child-Pugh class A) steady-state exposure ($AUC_{\tau,ss}$) of linagliptin was approximately 25% lower and $C_{max,ss}$ was approximately 36% lower than in healthy subjects. In patients with moderate hepatic impairment (Child-Pugh class B), AUC_{ss} of linagliptin was about 14% lower and $C_{max,ss}$ was approximately 8% lower than in healthy subjects. Patients with severe hepatic impairment (Child-Pugh class C) had comparable exposure of linagliptin in terms of AUC_{0-24} and approximately 23% lower C_{max} compared with healthy subjects. Reductions in the pharmacokinetic parameters seen in patients with hepatic impairment did not result in reductions in DPP-4 inhibition.

Effects of Age, Body Mass Index, Gender, and Race

Empagliflozin: Based on the population PK analysis, age, body mass index (BMI), gender and race (Asians versus primarily Whites) do not have a clinically meaningful effect on pharmacokinetics of empagliflozin *[see Warnings in Special Populations (6.5)]*.

Linagliptin: Based on the population PK analysis, age, body mass index (BMI), gender and race do not have a clinically meaningful effect on pharmacokinetics of linagliptin *[see Warnings in Special Populations (6.5)]*.

Drug Interactions

Pharmacokinetic drug interaction studies with GLYXAMBI have not been performed; however, such studies have been conducted with the individual components of GLYXAMBI (empagliflozin and linagliptin).

Empagliflozin

In vitro Assessment of Drug Interactions

Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. *In vitro* data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT1A3, UGT1A8, UGT1A9 and UGT2B7. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. Therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of the major CYP450 isoforms or UGT1A1, UGT1A3,

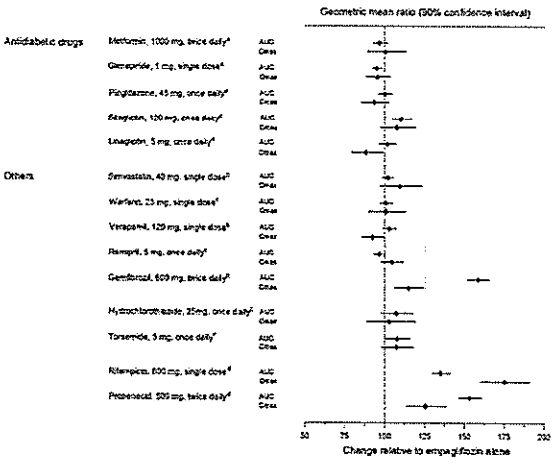
UGT1A8, UGT1A9, or UGT2B7. The effect of UGT induction (e.g., induction by rifampicin or any other UGT enzyme inducer) on empagliflozin exposure has not been evaluated.

Empagliflozin is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but it does not inhibit these efflux transporters at therapeutic doses. Based on *in vitro* studies, empagliflozin is considered unlikely to cause interactions with drugs that are P-gp substrates. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin does not inhibit any of these human uptake transporters at clinically relevant plasma concentrations and, therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of these uptake transporters.

In vivo Assessment of Drug Interactions

Empagliflozin pharmacokinetics were similar with and without coadministration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, and simvastatin in healthy volunteers and with or without coadministration of hydrochlorothiazide and torsemide in patients with type 2 diabetes (see Figure 1). In subjects with normal renal function, coadministration of empagliflozin with probenecid resulted in a 30% decrease in the fraction of empagliflozin excreted in urine without any effect on 24-hour urinary glucose excretion. The relevance of this observation to patients with renal impairment is unknown.

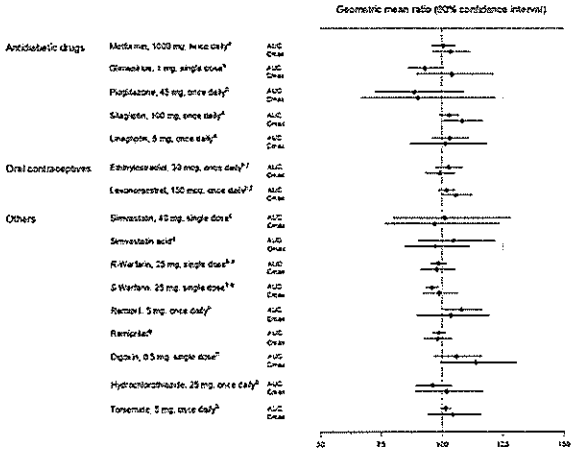
Figure 1 Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



[a]empagliflozin, 50 mg, once daily; [b]empagliflozin, 25 mg, single dose; [c]empagliflozin, 25 mg, once daily; [d]empagliflozin, 10 mg, single dose

Empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torsemide, and oral contraceptives when coadministered in healthy volunteers (see Figure 2).

Figure 2 Effect of Empagliflozin on the Pharmacokinetics of Various Medications as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



[a]empagliflozin, 50 mg, once daily; [b]empagliflozin, 25 mg, once daily; [c]empagliflozin, 25 mg, single dose; [d]administered as simvastatin; [e]administered as warfarin racemic mixture; [f]administered as Microgynon®; [g]administered as ramipril

Linagliptin

In vitro Assessment of Drug Interactions

Linagliptin is a weak to moderate inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes and is not an inducer of CYP isozymes, including CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 4A11.

Linagliptin is a P-glycoprotein (P-gp) substrate, and inhibits P-gp mediated transport of digoxin at high concentrations. Based on these results and *in vivo* drug interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates at therapeutic concentrations.

In vivo Assessment of Drug Interactions

Strong inducers of CYP3A4 or P-gp (e.g., rifampin) decrease exposure to linagliptin to subtherapeutic and likely ineffective concentrations *[see Interactions (7)]*. *In vivo* studies indicated evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-gp and organic cationic transporter (OCT).

Table 4 Effect of Coadministered Drugs on Systemic Exposure of Linagliptin

Coadministered Drug	Dosing of Coadministered Drug[a]	Dosing of Linagliptin[a]	Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.0	
			AUC[d]	C_{max}
Metformin	850 mg TID	10 mg QD	1.20	1.03
Glyburide	1.75 mg[c]	5 mg QD	1.02	1.01
Pioglitazone	45 mg QD	10 mg QD	1.13	1.07
Ritonavir	200 mg BID	5 mg[c]	2.01	2.96
Rifampin[b]	600 mg QD	5 mg QD	0.60	0.56

[a]Multiple dose (steady-state) unless otherwise noted
[b]For information regarding clinical recommendations *[see Interactions (7)]*.
[c]Single dose
[d]AUC = AUC(0 to 24 hours) for single dose treatments and AUC = AUC(TAU) for multiple-dose treatments
QD = once daily
BID = twice daily
TID = three times daily

Table 5 Effect of Linagliptin on Systemic Exposure of Coadministered Drugs

Coadministered Drug	Dosing of Coadministered Drug[a]	Dosing of Linagliptin[a]	Geometric Mean Ratio (ratio with/without coadministered drug) No effect = 1.0		
				AUC[c]	C_{max}
Metformin	850 mg TID	10 mg QD	metformin	1.01	0.89
Glyburide	1.75 mg[b]	5 mg QD	glyburide	0.86	0.86
Pioglitazone	45 mg QD	10 mg QD	pioglitazone metabolite M-III metabolite M-IV	0.94 0.98 1.04	0.86 0.96 1.05
Digoxin	0.25 mg QD	5 mg QD	digoxin	1.02	0.94
Simvastatin	40 mg QD	10 mg QD	simvastatin simvastatin acid	1.34 1.33	1.10 1.21
Warfarin	10 mg[b]	5 mg QD	R-warfarin S-warfarin INR PT	0.99 1.03 0.93[d] 1.03[d]	1.00 1.01 1.04[d] 1.15[d]
Ethinylestradiol and levonorgestrel	ethinylestradiol 0.03 mg and levonorgestrel 0.150 mg QD	5 mg QD	ethinylestradiol levonorgestrel	1.01 1.09	1.08 1.13

[a]Multiple dose (steady-state) unless otherwise noted
[b]Single dose
[c]AUC = AUC(INF) for single dose treatments and AUC = AUC(TAU) for multiple dose treatments
[d]AUC=AUC(0-168) and C_{max} = E_{max} for pharmacodynamic end points
INR = International Normalized Ratio
PT = Prothrombin Time
QD = once daily
TID = three times daily

12. CLINICAL STUDIES

GLYXAMBI Glycemic Control Studies

Add-on Combination Therapy with Metformin

A total of 686 patients with type 2 diabetes participated in a double-blind, active-controlled study to evaluate the efficacy and safety of empagliflozin 10 mg or 25 mg in combination with linagliptin 5 mg compared to the individual components.

Patients with type 2 diabetes inadequately controlled on at least 1500 mg of metformin per day entered a single-blind placebo run-in period for 2 weeks. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7% and 10.5% were randomized 1:1:1:1:1 to one of 5 active-treatment arms of empagliflozin 10 mg or 25 mg, linagliptin 5 mg, or linagliptin 5 mg in combination with 10 mg or 25 mg empagliflozin as a fixed dose combination tablet.

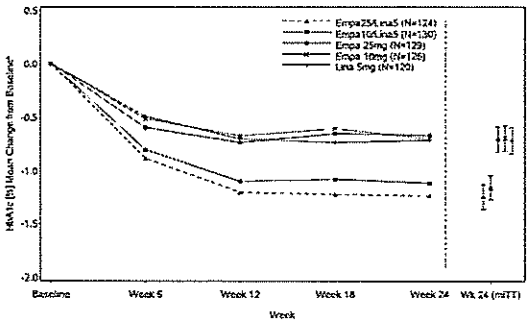
At Week 24, empagliflozin 10 mg or 25 mg used in combination with linagliptin 5 mg provided statistically significant improvement in HbA1c (p-value <0.0001) and FPG (p-value <0.001) compared to the individual components in patients who had been inadequately controlled on metformin (see Table 6, Figure 3). Treatment with GLYXAMBI 25 mg/5 mg or GLYXAMBI 10 mg/5 mg daily also resulted in a statistically significant reduction in body weight compared to linagliptin 5 mg (p-value <0.0001). There was no statistically significant difference compared to empagliflozin alone.

Table 6 Glycemic Parameters at 24 Weeks in a Study Comparing GLYXAMBI to the Individual Components as Add-on Therapy in Patients Inadequately Controlled on Metformin

	GLYXAMBI 10 mg/5 mg	GLYXAMBI 25 mg/5 mg	Empagliflozi n 10 mg	Empagliflozi n 25 mg	Linagliptin 5 mg
HbA1c (%)					
Number of patients	n=135	n=133	n=137	n=139	n=128
Baseline (mean)	8.0	7.9	8.0	8.0	8.0
Change from baseline (adjusted mean)	-1.1	-1.2	-0.7	-0.6	-0.7
Comparison vs empagliflozin 25 mg or 10 mg (adjusted mean) (95% CI)[a]	-0.4 (-0.6, -0.2)[d]	-0.6 (-0.7, -0.4)[d]	--	--	--
Comparison vs linagliptin 5 mg (adjusted mean) (95% CI)[a]	-0.4 (-0.6, -0.2)[d]	-0.5 (-0.7, -0.3)[d]	--	--	--
Patients [n (%)] achieving HbA1c <7%[b]	74 (58)	76 (62)	35 (28)	43 (33)	43 (36)
FPG (mg/dL)					
Number of patients	n=133	n=131	n=136	n=137	n=125
Baseline (mean)	157	155	162	160	156
Change from baseline (adjusted mean)	-33	-36	-21	-21	-13
Comparison vs empagliflozin 25 mg or 10 mg (adjusted mean) (95% CI)[a]	-12 (-16, -5)[d]	-15 (-22, -9)[d]	--	--	--
Comparison vs linagliptin 5 mg (adjusted mean) (95% CI)[a]	-20 (-27, -13)[d]	-23 (-29, -16)[d]	--	--	--
Body Weight					
Number of patients	n=135	n=134	n=137	n=140	n=128
Baseline (mean) in kg	87	85	86	88	85
% change from baseline (adjusted mean)	-3.1	-3.4	-3.0	-3.5	-0.7
Comparison vs empagliflozin 25 mg or 10 mg (adjusted mean) (95% CI)[a]	0.0 (-0.9, 0.8)	0.1 (-0.8, 0.9)	--	--	--
Comparison vs linagliptin 5 mg (adjusted mean) (95% CI)[c]	-2.4 (-3.3, -1.5)[d]	-2.7 (-3.6, -1.8)[d]	--	--	--

[a]Full analysis population (observed case) using MMRM. MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c.
[b]Patients with HbA1c above 7% at baseline: GLYXAMBI 25 mg/5 mg, n=123; GLYXAMBI 10 mg/5 mg, n=128; empagliflozin 25 mg, n=132; empagliflozin 10 mg, n=125; linagliptin 5 mg, n=119. Non-completers were considered failures (NCF).
[c]Full analysis population using last observation carried forward. ANCOVA model included treatment, renal function, region, baseline weight, and baseline HbA1c.
[d]p<0.001 for FPG; p<0.0001 for HbA1c and body weight

Figure 3 Adjusted Mean HbA1c Change at Each Time Point (Completers) and at Week 24 (mITT population)



*Mean change from baseline adjusted for baseline HbA1c, geographical region, and eGFR at baseline.

Empagliflozin in patients inadequately controlled on metformin and linagliptin

In patients inadequately controlled on maximally tolerated doses of metformin, open label linagliptin 5 mg was added for 16 weeks. In patients inadequately controlled after this 16 week period, patients received double-blind treatment with either empagliflozin 10 mg, empagliflozin 25 mg or placebo for 24-weeks. After this double-blind period, treatment with both empagliflozin 10 mg and empagliflozin 25 mg provided statistically significant improvements in HbA_{1c}, FPG and body weight compared to placebo; all patients continued treatment with metformin and linagliptin 5 mg during the study. A statistically significant greater number of patients with a baseline HbA_{1c} ≥7.0 % treated with both doses of empagliflozin achieved a target HbA_{1c} of <7 % compared to placebo (see Table 7). After 24-weeks treatment with empagliflozin, both systolic and diastolic blood pressures were reduced, -2.6/-1.1 mmHg (n.s. versus placebo for SBP and DBP) for empagliflozin 25 mg and -1.3/-0.1 mmHg (n.s. versus placebo for SBP and DBP) for empagliflozin 10 mg.

After 24 weeks, rescue therapy was used in 4 (3.6 %) patients treated with empagliflozin 25 mg and in 2 (1.8 %) patients treated with empagliflozin 10 mg, compared to 13 (12.0 %) patients treated with placebo (all patients on background metformin + linagliptin 5 mg).

Table 7 Efficacy parameters in the clinical study comparing empagliflozin to placebo as add-on therapy in patients inadequately controlled on metformin and linagliptin 5 mg

	Metformin + linagliptin 5 mg		
	Empagliflozin 10 mg[1]	Empagliflozin 25 mg[1]	Placebo[2]
HbA_{1c} (%) – 24 weeks[3]			
N	109	110	106
Baseline (mean)	7.97	7.97	7.96
Change from baseline (adjusted mean)	-0.65	-0.56	0.14
Comparison vs. placebo (adjusted mean) (95 % CI)[2]	-0.79 (-1.02, -0.55) p<0.0001	-0.70 (-0.93, -0.46) p<0.0001	
Body Weight – 24 weeks[3]			
N	109	110	106
Baseline (mean) in kg	88.4	84.4	82.3
Change from baseline (adjusted mean)	-3.1	-2.5	-0.3
Comparison vs. placebo (adjusted mean) (95 % CI)[1]	-2.8 (-3.5, -2.1) p<0.0001	-2.2 (-2.9, -1.5) p<0.0001	
Patients (%) achieving HbA_{1c} <7 % with baseline HbA_{1c} ≥7 % - 24 weeks[4]			
N	100	107	100
Patients (%) achieving HbA_{1c} <7 %	37.0	32.7	17.0
Comparison vs. placebo (odds ratio) (95 % CI)[5]	4.0 (1.9, 8.7)	2.9 (1.4, 6.1)	

[1] Patients randomized to the empagliflozin 10 mg or 25 mg groups were receiving Glyxambi 10 mg/5 mg or 25 mg/5 mg with background metformin

[2] Patients randomized to the placebo group were receiving the placebo plus linagliptin 5 mg with background metformin

[3] Mixed-effects models for repeated measurements (MMRM) on FAS (OC) includes baseline HbA1c, baseline eGFR (MDRD), geographical region, visit treatment,and treatment by visit interaction. For FPG, baseline FPG is also included.
For weight, baseline weight is also included.

[4] Not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints

[5] Logistic regression on FAS (NCF) includes baseline HbA1c, baseline eGFR (MDRD), geographical region, and treatment; based on patients with HbA1c of 7 % and above at baseline

In a pre-specified subgroup of patients with baseline HbA_{1c} greater or equal than 8.5 % the reduction from baseline in HbA_{1c} with empagliflozin 25 mg/linagliptin 5 mg was -1.3 % at 24 weeks (p<0.0001 versus

placebo and linagliptin 5 mg) and with empagliflozin 10 mg/ linagliptin 5 mg -1.3 % at 24 weeks (p<0.0001 versus placebo and linagliptin 5 mg).

Linagliptin 5 mg in patients inadequately controlled on metformin and empagliflozin 10 mg or empagliflozin 25 mg

In patients inadequately controlled on maximally tolerated doses of metformin, open label empagliflozin 10 mg or empagliflozin 25 mg was added for 16 weeks. In patients inadequately controlled after this 16 week period, patients received double-blind treatment with either linagliptin 5 mg or placebo for 24-weeks. After this double-blind period, treatment in both populations (metformin + empagliflozin 10 mg and metformin + empagliflozin 25 mg) linagliptin 5 mg provided statistically significant improvements in HbA_{1c} compared to placebo; all patients continued treatment with metformin and empagliflozin during the study. A statistically significant greater number of patients with a baseline HbA1c ≥7.0 % and treated with linagliptin achieved a target HbA1c of <7 % compared to placebo (see Table 8).

Table 8 Efficacy parameters in clinical studies comparing Glyxambi 10 mg/5 mg to empagliflozin 10 mg as well as Glyxambi 25 mg/5 mg to empagliflozin 25 mg as add-on therapy in patients inadequately controlled on empagliflozin 10 mg/25 mg and metformin

	Metformin + empagliflozin 10 mg		Metformin + empagliflozin 25 mg	
	Linagliptin 5 mg	Placebo	Linagliptin 5 mg	Placebo
HbA_{1c} (%) – 24 weeks[1]				
N	122	125	109	108
Baseline (mean)	8.04	8.03	7.82	7.88
Change from baseline (adjusted mean)	-0.53	-0.21	-0.58	-0.10
Comparison vs. placebo (adjusted mean) (95 % CI)	-0.32 (-0.52, -0.13) p<0.0013		-0.47 (-0.66, -0.28) p<0.0001	
Patients (%) achieving HbA_{1c} <7 % with baseline HbA_{1c} ≥7 % - 24 weeks[2]				
N	116	119	100	107
Patients (%) achieving HbA_{1c} <7 %	25.9	10.9	36.0	15.0
Comparison vs. placebo (odds ratio) (95 % CI)[3]	3.965 (1.771, 8.876) P=0.0008		4.429 (2.097, 9.353) P<0.0001	

Patients randomized to the linagliptin 5 mg group were receiving either fixed dose combination tablets Glyxambi 10 mg/5 mg plus metformin or fixed dose combination tablets Glyxambi 25 mg/5 mg plus

metformin; patients randomized to the placebo group were receiving placebo plus empagliflozin 10 mg plus metformin or placebo plus empagliflozin 25 mg plus metformin

[1] MMRM model on FAS (OC) includes baseline HbA_{1c}, baseline eGFR (MDRD), geographical region, visit, treatment, and treatment by visit interaction. For FPG, baseline FPG is also included.

[2] Not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints

[3] Logistic regression on FAS (NCF) includes baseline HbA1c, baseline eGFR (MDRD), geographical region, and treatment; based on patients with HbA_{1c} of 7 % and above at baseline

Empagliflozin Cardiovascular Outcome Study in Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease

Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. The effect of empagliflozin on cardiovascular risk in adult patients with type 2 diabetes and established, stable, atherosclerotic cardiovascular disease is presented below.

The EMPA-REG OUTCOME study, a multicenter, multi-national, randomized, double-blind parallel group trial compared the risk of experiencing a major adverse cardiovascular event (MACE) between empagliflozin and placebo when these were added to and used concomitantly with standard of care treatments for diabetes and atherosclerotic cardiovascular disease. Coadministered antidiabetic medications were to be kept stable for the first 12 weeks of the trial. Thereafter, antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of investigators, to ensure participants were treated according to the standard care for these diseases.

A total of 7020 patients were treated (empagliflozin 10 mg = 2345; empagliflozin 25 mg = 2342; placebo = 2333) and followed for a median of 3.1 years. Approximately 72% of the study population was Caucasian, 22% was Asian, and 5% was Black. The mean age was 63 years and approximately 72% were male.

All patients in the study had inadequately controlled type 2 diabetes mellitus at baseline (HbA1c greater than or equal to 7%). The mean HbA1c at baseline was 8.1% and 57% of participants had diabetes for more than 10 years. Approximately 31%, 22% and 20% reported a past history of neuropathy, retinopathy and nephropathy to investigators respectively and the mean eGFR was 74 mL/min/1.73 m^2. At baseline, patients were treated with one (~30%) or more (~70%) antidiabetic medications including metformin (74%), insulin (48%), sulfonylurea (43%) and dipeptidyl peptidase-4 inhibitor (11%).

All patients had established atherosclerotic cardiovascular disease at baseline including one (82%) or more (18%) of the following: a documented history of coronary artery disease (76%), stroke (23%) or peripheral artery disease (21%). At baseline, the mean systolic blood pressure was 136 mmHg, the mean diastolic blood pressure was 76 mmHg, the mean LDL was 86 mg/dL, the mean HDL was 44 mg/dL, and the mean urinary albumin to creatinine ratio (UACR) was 175 mg/g. At baseline, approximately 81% of patients were treated with renin angiotensin system inhibitors, 65% with beta-blockers, 43% with diuretics, 77% with statins, and 86% with antiplatelet agents (mostly aspirin).

The primary endpoint in EMPA-REG OUTCOME was the time to first occurrence of a Major Adverse Cardiac Event (MACE). A major adverse cardiac event was defined as occurrence of either a cardiovascular death or a non-fatal myocardial infarction (MI) or a non-fatal stroke. The statistical analysis plan had pre-specified that the 10 and 25 mg doses would be combined. A Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio of MACE and superiority on MACE if non-inferiority was demonstrated. Type-1 error was controlled across multiples tests using a hierarchical testing strategy.

Empagliflozin significantly reduced the risk of first occurrence of primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (HR: 0.86; 95% CI 0.74, 0.99). The treatment effect was due to a significant reduction in the risk of cardiovascular death in subjects randomized to empagliflozin (HR: 0.62; 95% CI 0.49, 0.77), with no change in the risk of non-fatal myocardial infarction or non-fatal stroke (see Table 9 and Figures 4 and 5). Results for the 10 mg and 25 mg empagliflozin doses were consistent with results for the combined dose groups.

Table 9 Treatment Effect for the Primary Composite Endpoint, and its Components[a]

	Placebo N=2333	Empagliflozin N=4687	Hazard ratio vs placebo (95% CI)
Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (time to first occurrence)[b]	282 (12.1%)	490 (10.5%)	0.86 (0.74, 0.99)
Non-fatal myocardial infarction[c]	121 (5.2%)	213 (4.5%)	0.87 (0.70, 1.09)
Non-fatal stroke[c]	60 (2.6%)	150 (3.2%)	1.24 (0.92, 1.67)
Cardiovascular death[c]	137 (5.9%)	172 (3.7%)	0.62 (0.49, 0.77)

[a]Treated set (patients who had received at least one dose of study drug)
[b]p-value for superiority (2-sided) 0.04
[c]Total number of events

Figure 4 Estimated Cumulative Incidence of First MACE

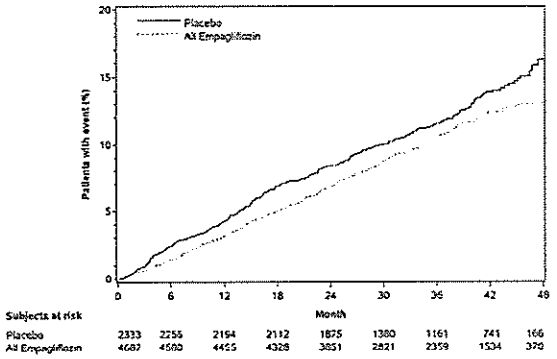
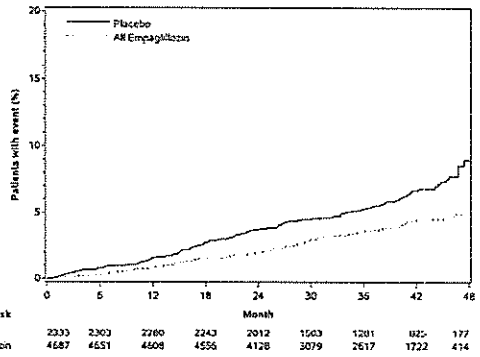


Figure 5 Estimated Cumulative Incidence of Cardiovascular Death



The efficacy of empagliflozin on cardiovascular death was generally consistent across major demographic and disease subgroups , including patients with an eGFR of 30 to <45 ml/min/1.73 m^2 (381 patients treated with JARDIANCE; 189 patients treated with placebo).

Vital status was obtained for 99.2% of subjects in the trial. A total of 463 deaths were recorded during the EMPA-REG OUTCOME trial. Most of these deaths were categorized as cardiovascular deaths. The non-cardiovascular deaths were only a small proportion of deaths, and were balanced between the treatment groups (2.1% in patients treated with empagliflozin, and 2.4% of patients treated with placebo).

Linagliptin Cardiovascular Safety Trials

CARMELINA

The cardiovascular risk of linagliptin was evaluated in CARMELINA, a multi-national, multi-center, placebo-controlled, double-blind, parallel group trial comparing linagliptin (N=3494) to placebo (N=3485) in adult patients with type 2 diabetes mellitus and a history of established macrovascular and/or renal disease. The trial compared the risk of major adverse cardiovascular events (MACE) between linagliptin and placebo when these were added to standard of care treatments for diabetes and other cardiovascular risk factors. The trial was event driven, the median duration of follow-up was 2.2 years and vital status was obtained for 99.7% of patients.

Patients were eligible to enter the trial if they were adults with type 2 diabetes, with HbA1c of 6.5% to 10%, and had either albuminuria and previous macrovascular disease (39% of enrolled population), or evidence of impaired renal function by eGFR and Urinary Albumin Creatinine Ratio (UACR) criteria (42% of enrolled population), or both (18% of enrolled population).

At baseline the mean age was 66 years and the population was 63% male, 80% Caucasian, 9% Asian, and 6% Black. Mean HbA1c was 8.0% and mean duration of type 2 diabetes mellitus was 15 years. The trial population included 17% patients ≥75 years of age and 62% patients with renal impairment defined as eGFR <60 mL/min/1.73 m^2. The mean eGFR was 55 mL/min/1.73 m^2 and 27% of patients had mild renal impairment (eGFR 60 to 90 mL/min/1.73 m^2), 47% of patients had moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m^2) and 15% of patients had severe renal impairment (eGFR <30 mL/min/1.73 m^2). Patients were taking at least one antidiabetic drug (97%), and the most common were insulin and analogues (57%), metformin (54%) and sulfonylurea (32%). Patients were also taking antihypertensives (96%), lipid lowering drugs (76%) with 72% on statin, and aspirin (62%).

The primary endpoint, MACE, was the time to first occurrence of one of three composite outcomes which included cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The study was designed as a non-inferiority trial with a pre-specified risk margin of 1.3 for the hazard ratio of MACE. A total of 434 patients on linagliptin and 420 patients on placebo experienced MACE. The incidence rate of MACE in both treatment arms: 56.3 MACE per 1000 patient-years on placebo vs. 57.7 MACE per 1000 patient-years on linagliptin. The estimated hazard ratio for MACE associated with linagliptin relative to placebo was 1.02 with a 95% confidence interval of (0.89, 1.17). The upper bound of this confidence interval, 1.17, excluded the risk margin of 1.3.

CAROLINA

The cardiovascular risk of linagliptin was evaluated in CAROLINA, a multi-center, multi-national, randomized, double-blind parallel group trial comparing linagliptin (N=3023) to glimepiride (N=3010) in adult patients with type 2 diabetes mellitus and a history of established cardiovascular disease and/or multiple cardiovascular risk factors. The trial compared the risk of major adverse cardiovascular events (MACE) between linagliptin and glimepiride when these were added to standard of care treatments for diabetes and other cardiovascular risk factors. The trial was event driven, the median duration of follow-up was 6.23 years and vital status was obtained for 99.3% of patients.

Patients were eligible to enter the trial if they were adults with type 2 diabetes with insufficient glycemic control (defined as HbA1c of 6.5% to 8.5% or 6.5% to 7.5% depending on treatment-naïve, on monotherapy or on combination therapy), and were defined to be at high cardiovascular risk with previous vascular disease, evidence of vascular related end-organ damage, age ≥70 years, and/or two cardiovascular risk factors (duration of diabetes >10 years, systolic blood pressure >140 mmHg, current smoker, LDL cholesterol ≥135 mg/dL).

At baseline the mean age was 64 years and the population was 60% male, 73% Caucasian, 18% Asian, and 5% Black. The mean HbA1c was 7.15% and mean duration of type 2 diabetes was 7.6 years. The trial population included 34% patients ≥70 years of age and 19% patients with renal impairment defined as eGFR <60 mL/min/1.73 m^2. The mean eGFR was 77 mL/min/1.73 m^2. Patients were taking at least one antidiabetic drug (91%) and the most common were metformin (83%) and sulfonylurea (28%). Patients were also taking antihypertensives (89%), lipid lowering drugs (70%) with 65% on statin, and aspirin (47%).

The primary endpoint, MACE, was the time to first occurrence of one of three composite outcomes which included cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The study was designed as a non-inferiority trial with a pre-specified risk margin of 1.3 for the hazard ratio of MACE. A total of 362 patients on linagliptin and 362 patients on glimepiride experienced MACE. The incidence rate of MACE in both treatment arms: 20.7 MACE per 1000 patient-years on linagliptin vs. 21.2 MACE per 1000 patient-years on glimepiride. The estimated hazard ratio for MACE associated with linagliptin relative to glimepiride was 0.98 with a 95% confidence interval of (0.84, 1.14). The upper bound of this confidence interval, 1.14, excluded the risk margin of 1.3.

13. HOW SUPPLIED/STORAGE AND HANDLING

13.1 How Supplied

GLYXAMBI (empagliflozin and linagliptin) tablets are available as follows:

10 mg/5 mg tablets: pale yellow, are triangular, flat-faced, bevel-edged, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol; the other side is debossed with "10/5".

2-1000 tablets in aluminium blister of paper box.

25 mg/5 mg tablets: pale pink, are triangular, flat-faced, bevel-edged, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol; the other side is debossed with "25/5".

2-1000 tablets in aluminium blister of paper box.

13.2 Shelf Life

See the label on the packaging.

13.3 Storage Condition

Store below 30°C.

13.4 Special precautions for storage

Store in a safe place out of reach of children.

14. PATIENT COUNSELING INFORMATION

Pancreatitis

Inform patients that acute pancreatitis has been reported during use of linagliptin. Inform patients that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue GLYXAMBI promptly and contact their physician if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.1.1)]*.

Ketoacidosis

Inform patients that ketoacidosis is a serious life-threatening condition and that cases of ketoacidosis have been reported during use of empagliflozin, sometimes associated with illness or surgery among other risk factors. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue GLYXAMBI and seek medical attention immediately *[see Warnings and Precautions (5.1.2)]*.

Volume Depletion

Inform patients that symptomatic hypotension may occur with GLYXAMBI and advise them to contact their healthcare provider if they experience such symptoms *[see Warnings and Precautions (5.1.3)]*. Inform patients that dehydration may increase the risk for hypotension, and to maintain adequate fluid intake.

Genital Urinary Tract Infections

Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur *[see Warnings and Precautions (5.1.4)]*.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
Inform patients that the incidence of hypoglycemia is increased when GLYXAMBI is used in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin and that a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.1.5)]*.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
Inform patients that necrotizing infections of the perineum (Fournier's gangrene) have occurred with empagliflozin, a component of GLYXAMBI. Counsel patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4°F or malaise *[see Warnings and Precautions (5.1.6)]*.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis)
Inform female patients that vaginal yeast infections may occur and provide them with information on the signs and symptoms of vaginal yeast infections. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.1.7)]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis)
Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with chronic and recurrent infections. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.1.7)]*.

Hypersensitivity Reactions
Inform patients that serious allergic reactions, such as anaphylaxis, angioedema, and exfoliative skin conditions, have been reported during postmarketing use of linagliptin or empagliflozin, components of GLYXAMBI. If symptoms of allergic reactions (such as rash, skin flaking or peeling, urticaria, swelling of the skin, or swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking GLYXAMBI and seek medical advice promptly *[see Warnings and Precautions (5.1.8)]*.

Severe and Disabling Arthralgia
Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs *[see Warnings and Precautions (5.1.10)]*.

Bullous Pemphigoid
Inform patients that bullous pemphigoid has been reported during use of linagliptin. Instruct patients to seek medical advice if blisters or erosions occur *[see Warnings and Precautions (5.1.11)]*.

Laboratory Tests
Inform patients that elevated glucose in urinalysis is expected when taking GLYXAMBI.

Pregnancy
Advise pregnant patients, and patients of reproductive potential of the potential risk to a fetus with treatment with GLYXAMBI *[see Warnings in Special Populations (6.1)]*. Instruct patients to report pregnancies to their physicians as soon as possible.

Lactation
Advise patients that breastfeeding is not recommended during treatment with GLYXAMBI *[see Warnings in Special Populations (6.2)]*.

Missed Dose
Instruct patients to take GLYXAMBI only as prescribed. If a dose is missed, it should be taken as soon as the patient remembers. Advise patients not to double their next dose.

15. References

Products sharing package inserts:

Glyxambi® 10/5mg Film-Coated Tablets (registration number: 027074)

Glyxambi® 25/5mg Film-Coated Tablets (registration number: 027073)

USPI March 2022

Manufactured by

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Packaging site

Rottendorf Pharma GmbH

Am Fleigendahl 3, 59320 Ennigerloh, Germany

LICENSE HOLDER

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Ingelheim am Rhein, Germany

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受文者：台灣百靈佳殷格翰股份有限公司

發文日期：中華民國111年11月28日
發文字號：衛授食字第1119024353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「糖順平膜衣錠10/5毫克 (Glyxambi Film-Coated Tablets 10/5 mg)」（衛部藥輸字第027074號）仿單變更一案（案號：1119024353），本部同意，請查照。

說明：

一、復貴公司111年5月6日(111)百登字第136號藥品變更登記申請書。

二、核准變更項目：仿單變更，詳如「藥品電子結構化仿單平台」之仿單核定本。

三、有關仿單規定如下：市售藥品得僅放置經審查核定之中文仿單。但如市售藥品同時放置中、外文仿單者，外文仿單內容須與核定本之中文仿單內容相符，廠商得依核定之中文仿單自行修正其外文仿單內容。

四、對上述內容如有疑義，請與承辦人許弼凱聯絡，電話：(02)8170-6000轉525，Email: bkhsu820@cde.org.tw。

正本：台灣百靈佳殷格翰股份有限公司
副本：

部長 薛瑞元

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正本：台灣百靈佳殷格翰股份有限公司
副本：

部長 薛瑞元

裝 訂 線