

恩美糖®膜衣錠 5/500 毫克
恩美糖®膜衣錠 5/850 毫克
恩美糖®膜衣錠 5/1000 毫克
恩美糖®膜衣錠 12.5/500 毫克
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JARDIANCE DUO® 5/500mg Film-Coated Tablets
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完整處方資訊

警語：乳酸中毒

與 metformin 有關之乳酸中毒的上市後病例曾造成死亡、體溫過低、低血壓與頑固性緩脈心律不整。與 metformin 有關之乳酸中毒開始發病時往往不易察覺，僅會伴隨不具專一性的一些症狀，例如倦怠(malaise)、肌肉疼痛、呼吸不順、嗜睡與腹痛。與 metformin 有關之乳酸中毒的特徵為血中乳酸濃度升高(>5 mmol/Liter)、陰離子間隙酸中毒(無酮尿或酮血症證據)、乳酸／丙酮酸比值增高，且血漿中 metformin 濃度往往>5 mcg/mL [請參閱警語及注意事項(5.1)]。與 metformin 有關之乳酸中毒的危險因子包括腎功能不全、併用某些藥物(例如，碳酸酐酶[carbonic anhydrase]抑制劑，例如 topiramate)、年滿 65 歲、接受使用顯影劑之放射檢查、手術及其他程序、缺氧狀態(例如急性充血性心臟衰竭)、飲酒過量及肝功能不全。對於這些高危險群，如何降低與 metformin 有關之乳酸中毒的風險及其治療步驟，於完整的處方資訊中提供[請參閱用法用量(2.1)、禁忌症(4)、警語及注意事項(5.1)、藥物交互作用(7)與在特殊族群的使用(8.6, 8.7)]。若懷疑發生與 metformin 有關之乳酸中毒，應立即停止使用恩美糖，並住院接受一般的支持性措施。建議立即進行血液透析。[請參閱警語及注意事項(5.1)]

1 適應症與用法

適用於單用 metformin 或 empagliflozin 時血糖控制不佳，或早已同時接受 metformin 及 empagliflozin 合併治療而狀況穩定者的第二型糖尿病成人病人，在飲食與運動外，做為改善血糖之輔助治療。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[請參閱臨床試驗(14.2)]。然而，本品恩美糖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

恩美糖不建議用於第一型糖尿病病人，其可能會增加這類病人酮酸中毒的風險。[請參閱警語及注意事項(5.2)]。

2 用法用量

本藥須由醫師處方使用。

2.1 開始使用恩美糖前

- 開始使用恩美糖前請先評估腎功能，並遵照臨床指示[請參閱警語及注意事項(5.1, 5.3)]。
- 針對體液容量減少的病人，建議在開始服用恩美糖前先矯正此一狀況[請參閱警語及注意事項(5.3)及在特定族群的使用(8.5, 8.6)]。

2.2 建議的用法用量

- 請根據病人治療現況調整恩美糖的初始劑量：

- 對於正在接受 metformin 治療的病人，請換成內含 empagliflozin 5 mg 及與近似之 metformin HCl 每日總劑量的恩美糖；
- 對於正在接受 empagliflozin 治療的病人，請換成內含 metformin HCl 500 mg 及近似之 empagliflozin 每日總劑量的恩美糖；
- 對於已同時接受 empagliflozin 和 metformin HCl 治療的病人，請換成各成分所含每日總劑量皆與原來相同的恩美糖。
- 監控有效性及耐受性並適度調整劑量，不可超過最高建議每日劑量（empagliflozin 為 25 mg，metformin HCl 為 2000 mg）。
- 請一天兩次隨餐服用恩美糖；劑量調升應逐步以減少 metformin 引起的腸胃副作用 [請參閱劑型與藥物含量 (3)]。

2.3 腎功能不全病人的建議劑量

- 恩美糖禁用於腎絲球過濾率估計值低於 30 mL/min/1.73 m² 的病人。[請參閱禁忌症 (4)，警語及注意事項 (5.1 及在特定族群的使用(8.6))]。

3 劑型與藥物含量

恩美糖膜衣錠：

Empagliflozin 含量	Metformin HCl 含量	顏色/形狀	錠劑壓印字樣
5 mg	500 mg	橘黃色、橢圓形、兩面中央凸起的膜衣錠	一面壓印百靈佳般格翰公司標誌與「S5」字樣，另一面則壓印「500」
5mg	850mg	米黃色、橢圓形、兩面中央凸起的膜衣錠	一面壓印百靈佳般格翰公司標誌與「S5」字樣，另一面則壓印「850」
5 mg	1000 mg	棕黃色、橢圓形、兩面中央凸起的膜衣錠	一面壓印百靈佳般格翰公司標誌與「S5」字樣，另一面則壓印「1000」
12.5 mg	500 mg	淺棕紫色、橢圓形、兩面中央凸起的膜衣錠	一面壓印百靈佳般格翰公司標誌與「S12」字樣，另一面則壓印「500」
12.5 mg	850mg	淺粉紅色、橢圓形、兩面中央凸起的膜衣錠	一面壓印百靈佳般格翰公司標誌與「S12」字樣，另一面則壓印「850」
12.5 mg	1000 mg	深棕紫色、橢圓形、兩面中央凸起的膜衣錠	一面壓印百靈佳般格翰公司標誌與「S12」字樣，另一面則壓印「1000」

4 禁忌症

恩美糖禁用於有下列狀況的病人：

- 重度腎功能不全（腎絲球過濾率估計值低於 30 mL/min/1.73 m²）、末期腎病 (ESRD) 或透析病人 [請參閱警語及注意事項 (5.1) 以及在特定族群的使用 (8.6)]。
- 急性或慢性代謝性酸中毒，包括糖尿病酮酸中毒。[請參閱警語及注意事項 (5.1)]。
- 對 empagliflozin、metformin 或恩美糖任何賦形劑產生過敏反應，例如曾發生血管性水腫反應。[請參閱警語及注意事項 (5.8)]。

5 警語及注意事項

5.1 乳酸中毒

曾有與 metformin 有關之乳酸中毒的上市後病例，包括導致死亡的病例。這些病例開始發病時往往不易察覺，僅會伴隨不具專一性的一些症狀，例如倦怠、肌肉疼痛、腹痛、呼吸不順或嗜睡，不過，在重度酸中毒病例曾發生體溫過低、低血壓與頑固性緩脈心律不整。與 metformin 有關之乳酸

中毒的特徵為血中乳酸濃度升高 (>5 mmol/Liter)、陰離子間隙酸中毒 (無酮尿或酮血症證據)、乳酸／丙酮酸比值增高，與血漿中 metformin 濃度往往 >5 mcg/mL。Metformin 會降低肝臟的乳酸吸收，升高血中乳酸濃度，因而增高乳酸中毒的風險。

若懷疑發生與 metformin 有關之乳酸中毒，應立即停止使用恩美糖，並儘速住院接受一般的支持性措施治療。在接受恩美糖治療且經確診或強烈懷疑有乳酸中毒的病人，建議應立即進行血液透析，以矯正酸中毒與移除蓄積的 metformin (metformin hydrochloride 可被透析清除，在血行動力學狀況良好時的清除率為 170 mL/min)。血液透析通常可使症狀逆轉與恢復正常。

應教導病人及其家屬如何辨識乳酸中毒的症狀，並請他們在出現這些症狀時，應停止使用恩美糖，並向醫護人員通報這些症狀。

針對與 metformin 有關之乳酸中毒的所有已知與可能的危險因子，茲提供以下可降低與 metformin 有關之乳酸中毒的風險及其處置的建議：

腎功能不全：上市後發生與 metformin 有關之乳酸中毒的病例，主要發生在有嚴重腎功能不全的病人。Metformin 蓄積以及與 metformin 有關之乳酸中毒的風險會隨腎功能不全的嚴重程度增高，因為很大部分的 metformin 經由腎臟排除。根據病人腎功能狀況，臨床建議包括 [詳見用法用量 (2.3) 及，臨床藥理學 (12.3)]。

- 在開始恩美糖治療之前，應先取得腎絲球濾過率估計值 (eGFR)。
- 恩美糖不可用於 eGFR 低於 30 mL/min/1.73 m² 的病人。[詳見禁忌症 (4)]
- 對於所有使用恩美糖的病人，皆應至少每年評估一次 eGFR。對於腎功能不全之風險增高的病人 (例如老年人)，應更頻繁地進行腎功能評估。

藥物交互作用：恩美糖與特定藥物併用可能使與 metformin 有關之乳酸中毒的風險增高：會降低腎功能、會導致血行動力學顯著改變、干擾酸鹼平衡或增加 metformin 蓄積的藥物 [詳見藥物交互作用 (7.2)]。因此，應考慮更頻繁地進行病人監測。

年滿 65 歲或更年長者：與 metformin 有關之乳酸中毒的風險會隨病人的年齡增高，因為老年病人出現肝臟、腎臟或心臟功能不全的可能性高於較年輕者。應更頻繁對老年病人進行腎功能評估 [詳見在特殊族群的使用 (8.5)]。

使用顯影劑之放射檢查：靜脈注射顯影劑有導致急性腎功能下降之危險，因此醫師為病人注射顯影劑應先停止 Metformin。應於造影程序後 48 小時重新評估 eGFR，需確認病人術後之腎功能恢復穩定，才能再開始使用該藥品。醫師為病人處方含 Metformin 成分之藥品時，需定期監測其腎功能。

手術與其他程序：在進行手術或其他程序期間須限制飲食時，可能使血容量不足、低血壓與腎功能不全的風險增加。當病人須限制飲食時，應暫時停用恩美糖。

缺氧狀態：有數例與 metformin 有關之乳酸中毒的上市後病例是發生在急性充血性心臟衰竭的狀況 (尤其是伴隨血流灌注過低與血氧過低時)。循環衰竭 (休克)、急性心肌梗塞、敗血症以及其他血氧過低狀況皆可能引發乳酸中毒，亦可能造成前腎因性氮血症 (prerenal azotemia)。發生這類事件時，應停止使用恩美糖。

飲酒過量：酒精可加劇 metformin 對乳酸代謝的作用，這可能導致與 metformin 有關之乳酸中毒的風險增高，因此，應警告病人勿於服用恩美糖期間飲酒過量。

肝功能不全：曾有一些肝功能不全病人在 metformin 治療時出現乳酸中毒，這可能是因乳酸清除功能下降導致血中乳酸濃度增高，因此恩美糖通常應避免用於有臨床或實驗檢測證據的肝臟疾病病人。

5.2 酮酸中毒

過去在對使用第二型鈉-葡萄糖轉運通道 (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；這是一種嚴重、威脅生命且必須緊急住院治療的疾病。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。恩美糖不建議用於治療第一型糖尿病病人 [請參閱適應症與用法 (1)]。

接受恩美糖治療的病人如果有出現重度代謝性酸中毒的徵象和症狀，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，仍可能發生恩美糖相關酮酸中毒。如果懷疑酮酸中毒，應停用恩美糖、評估病人，並立即開始施行治療。治療酮酸中毒時，可能需要給予胰島素、水分並補充碳水化合物。

多份上市後報告顯示，尤其是在第一型糖尿病病人中，酮酸中毒的出現並未立即被發現，即刻的治療也被延遲進行，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）。病人就診時的徵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，以及呼吸急促。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、急性發燒性疾病、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。

開始使用恩美糖前，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、熱量攝取限制，以及酗酒。病人進行預定手術時，考慮於術前至少三天暫時停用恩美糖。[請參閱藥效學 (12.2, 12.3)]。請在已知較可能發生酮酸中毒的其他臨床情境下（例如因急性疾病或術後而長時間禁食時）考慮監測酮酸中毒，並暫時停用恩美糖。再開始使用恩美糖前須確認發生酮酸中毒的危險因素已解決。應教導病人辨識酮酸中毒的徵象與症狀，並請病人在出現這些症狀時，應停止使用恩美糖並就醫。

5.3 體液容量減少

Empagliflozin 可引發血管內容積減少，有時進而發生帶有症狀的低血壓或血清肌酸酐急性瞬間的變化 [請參閱不良反應 (6.1)]。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，在開始恩美糖治療之前，請評估體液狀態及腎功能。體液容量減少的病人，開始恩美糖治療之前，請先矯正此情形。開始恩美糖治療之後，請監測體液容量減少之徵象和症狀以及腎功能。

5.4 尿路敗血症與腎盂腎炎

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。請評估病人身上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 [請參閱不良反應 (6)]。

5.5 併用胰島素與胰島素促分泌物質時發生的低血糖

胰島素與胰島素促分泌物質已知都可能引發低血糖。Empagliflozin 與胰島素促泌劑 (例如，磺醯尿素類藥物) 或胰島素併用時，低血糖的發生風險較高 [請參閱不良反應 (6.1)]。Metformin 與胰島素及/或胰島素促泌劑併用時，可能增加低血糖發生的風險。因此，與恩美糖併用時，可能須調降胰島素促泌劑或胰島素的劑量，以減少發生低血糖的風險。

5.6 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。

對於接受恩美糖治療如有出現生殖器或會陰區域疼痛或壓痛、紅斑或腫脹並伴隨發燒或身體不適的病人，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，停用恩美糖，密切監測血糖濃度，並提供適當的血糖控制替代療法。

5.7 生殖器黴菌感染

Empagliflozin 在少數病人會提高生殖器黴菌感染的發生風險 [請參閱不良反應 (6.1)]。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。請視情況進行監測及治療。

5.8 過敏反應

曾有上市後的報告指出，接受 empagliflozin 治療的病人出現嚴重的過敏反應(如血管性水腫)。如果發生過敏反應，應即停用恩美糖，按照標準照護程序給予及時治療，並進行監測，直至病徵與症狀消失。

對 empagliflozin 或恩美糖的任何賦形劑有過敏反應的病人不可使用恩美糖 [請參閱禁忌症(4)]。

5.9 維生素 B₁₂ 缺乏

在為期 29 週的 metformin 臨床試驗中，metformin 治療組約有 7% 受試者其先前正常的血清維生素 B₁₂ 降至正常濃度以下。此濃度降低的現象，可能因 B₁₂-內生性因子複合物吸收 B₁₂ 的程序受干擾所致，可能與貧血有關。然而，停用 metformin 或補充維生素 B₁₂ 之後，此現象似乎可迅速恢復正常。某些人（維生素 B₁₂ 或鈣之攝取或吸收不足者）似乎較易出現維生素 B₁₂ 濃度低於正常值的狀況。對使用恩美糖的病人，每年進行一次血液學參數測量及每二至三年進行維生素 B₁₂ 檢測，並處置異常狀況 [請參閱不良反應 (6.1)]。

6 不良反應

下文及仿單內其他部分將針對下列重要不良反應提出說明：

- 乳酸中毒 [請參閱黑框警語和警語及注意事項 (5.1)]
- 酮酸中毒 [請參閱警語及注意事項 (5.2)]
- 體液容量減少 [請參閱警語及注意事項 (5.3)]
- 尿路敗血症與腎盂腎炎 [請參閱警語及注意事項 (5.4)]
- 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 (5.5)]
- 會陰部壞死性筋膜炎(弗尼爾氏壞疽) [請參閱警語及注意事項 (5.6)]
- 生殖器黴菌感染 [請參閱警語及注意事項 (5.7)]
- 過敏反應 [請參閱警語及注意事項 (5.8)]
- 維生素 B₁₂ 缺乏 [請參閱警語及注意事項 (5.9)]

6.1 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。

併用 empagliflozin（每日劑量 10 mg 和 25 mg）和 metformin hydrochloride（平均每日劑量約為 1800 mg）的安全性，曾於 3456 名接受 16 到 24 週治療的第二型糖尿病病人中進行評估；其中使用安慰劑者有 926 人，每日使用 empagliflozin 10 mg 者有 1271 人，每日使用 empagliflozin 25 mg 者有 1259 人。在安慰劑、empagliflozin 10 mg 和 empagliflozin 25 mg 等治療組內，因不良事件而停止治療的比例分別為 3.0%、2.8% 和 2.9%。

以 Empagliflozin 輔助既有 Metformin 的合併療法

在一項以 empagliflozin 10 mg 和 25 mg 每日一次輔助既有 metformin 療法的 24 週安慰劑對照試驗

中，並未發生在受試者中發生率 $\geq 5\%$ 且比在安慰劑組中常見的不良反應（無論試驗主持人對因果關係的評估結果為何）。

以 *Empagliflozin* 輔助既有 *Metformin* 和磺醯尿素類藥物的合併療法

在一項以 *empagliflozin* 10 mg 和 25 mg 每日一次輔助既有 *metformin* 和磺醯尿素類藥物療法的 24 週安慰劑對照試驗中，在受試者中發生率 $\geq 5\%$ 且比在安慰劑組中常見的不良反應（無論試驗主持人對因果關係的評估結果為何）列於表 1（亦請見表 4）。

表 1 在一項 24 週的安慰劑對照臨床試驗中，在 *Empagliflozin* 併用 *Metformin* + 磺醯尿素類藥物組內發生率 $\geq 5\%$ 且高於安慰劑組的不良反應

不良反應	安慰劑 (%) n=225	<i>Empagliflozin</i> 10 mg (%) n=224	<i>Empagliflozin</i> 25 mg (%) n=217
低血糖	9.8	15.6	12.9
泌尿道感染	6.7	9.4	6.9
鼻咽炎	4.9	8.0	6.0

Empagliflozin

表 2 的數據是由 4 項 24 週安慰劑對照試驗，以及 1 項使用基礎胰島素的安慰劑對照試驗之 18 週數據統整而來。*Empagliflozin* 在其中 1 項試驗乃為單獨療法使用，在另外 4 項試驗則為合併療法使用 [請參閱臨床試驗 (14)]。

這些數據反映出 1976 名病人對 *empagliflozin* 的暴露經驗，平均暴露時間為大約 23 週。病人接受安慰劑 (N=995)、*empagliflozin* 10 mg (N=999) 或 *empagliflozin* 25 mg (N=977) 每日一次的治療。該族群的平均年齡為 56 歲，且有 3% 超過 75 歲。族群內超過半數 (55%) 為男性；46% 為白人、50% 為亞洲人，3% 為黑人或非裔美國人。族群內有 57% 具有超過 5 年的糖尿病病史，在基準點時族群的平均糖化血色素 (HbA1c) 為 8%。經確認為糖尿病之小血管併發症的事件包括糖尿病腎病變 (7%)、視網膜病變 (8%) 或神經病變 (16%)。有 91% 的病人為腎功能正常或輕度腎功能不全，9% 的病人為中度腎功能不全（平均腎絲球過濾率估計值為 86.8 mL/min/1.73 m²）。

表 2 顯示使用 *empagliflozin* 時伴隨出現的常見不良反應（不包括低血糖）。這些不良反應在基準點時並不存在、在 *empagliflozin* 組內的發生率高於安慰劑組，而且在 *empagliflozin* 10 mg 或 25 mg 組內的發生率高於或等於 2%。

表 2 在以安慰劑對照的 *empagliflozin* 單獨療法或合併療法臨床試驗群中，在 *empagliflozin* 組發生率 $\geq 2\%$ ，且高於安慰劑組的不良反應

不良反應	安慰劑 (%) N=995	<i>Empagliflozin</i> 10 mg (%) N=999	<i>Empagliflozin</i> 25 mg (%) N=977
泌尿道感染 ^a	7.6	9.3	7.6
女性生殖器黴菌感染 ^b	1.5	5.4	6.4
上呼吸道感染	3.8	3.1	4.0
排尿增加 ^c	1.0	3.4	3.2
血脂異常	3.4	3.9	2.9
關節痛	2.2	2.4	2.3
男性生殖器黴菌感染 ^d	0.4	3.1	1.6
噁心	1.4	2.3	1.1

^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。

^b 女性生殖器黴菌感染包括下列不良反應：外陰陰道黴菌感染、陰道感染、外陰炎、外陰陰道念珠菌病、生殖器感染、生殖器念珠菌病、生殖器真菌感染、生殖泌尿道感染、外陰陰道炎、子宮頸炎、泌尿生殖道真菌感染、細菌性陰道炎。計算百分比時，均以各組內的女性受試者人數作為分母：安慰劑 (N=481)、*empagliflozin* 10 mg (N=443)、*empagliflozin* 25 mg (N=420)。

^c 試驗預設之不良反應類別，包括（但不限於）：多尿、頻尿和夜尿。

^d 男性生殖器黴菌感染包括下列不良反應：龜頭包皮質炎、龜頭炎、生殖器真菌感染、生殖泌尿道感染、念珠菌龜頭炎、陰囊膿瘍、陰莖感染。計算百分比時，均以各組內的男性受試者人數作為分母：安慰劑 (N=514)、*empagliflozin* 10 mg

(N=556)、empagliflozin 25 mg (N=557)。

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%。

體液容量減少

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。涵蓋五項安慰劑對照臨床試驗的統整數據顯示，體液容量減少相關不良反應（如〔居家〕血壓下降、收縮壓下降、脫水、低血壓、低血容、姿勢性低血壓及昏厥）在安慰劑、empagliflozin 10 mg 和 empagliflozin 25 mg 組內的通報比例分別為 0.3%、0.5%和 0.3%。在具有血管內容量減少風險的病人中，empagliflozin 可使其低血壓發生風險上升 [請參閱在特定族群的使用 (8.5、8.6)]。

排尿增加

涵蓋五項安慰劑對照臨床試驗的統整數據顯示，排尿增加（如多尿、頻尿及夜尿）不良反應的發生率是以 empagliflozin 組高於安慰劑組（見表 3）。具體而言，夜尿在安慰劑、empagliflozin 10 mg 和 empagliflozin 25 mg 組內的通報比例分別為 0.4%、0.3%和 0.8%。

低血糖

低血糖的發生率（按照試驗區分）已列於表 3。Empagliflozin 與胰島素或磺醯尿素類藥物併用時，低血糖的發生率會上升。

表 3 安慰劑對照臨床試驗^c中，總體^a和嚴重^b低血糖事件的發生率

單獨療法 (24 週)	安慰劑 (n=229)	Empagliflozin 10 mg (n=224)	Empagliflozin 25 mg (n=223)
總體 (%)	0.4	0.4	0.4
嚴重 (%)	0	0	0
與 Metformin 併用 (24 週)	安慰劑 + Metformin (n=206)	Empagliflozin 10 mg + Metformin (n=217)	Empagliflozin 25 mg + Metformin (n=214)
總體 (%)	0.5	1.8	1.4
嚴重 (%)	0	0	0
與 Metformin + 磺醯尿素類藥物併用 (24 週)	安慰劑 (n=225)	Empagliflozin 10 mg + Metformin + 磺醯尿素類藥物 (n=224)	Empagliflozin 25 mg + Metformin + 磺醯尿素類藥物 (n=217)
總體 (%)	8.4	16.1	11.5
嚴重 (%)	0	0	0
與 Pioglitazone +/- Metformin 併用 (24 週)	安慰劑 (n=165)	Empagliflozin 10 mg + Pioglitazone +/- Metformin (n=165)	Empagliflozin 25 mg + Pioglitazone +/- Metformin (n=168)
總體 (%)	1.8	1.2	2.4
嚴重 (%)	0	0	0
與基礎胰島素併用 +/-Metformin 併用 (18 週 ^d)	安慰劑 (n=170)	Empagliflozin 10 mg (n=169)	Empagliflozin 25 mg (n=155)
總體 (%)	20.6	19.5	28.4
嚴重 (%)	0	0	1.3
與 MDI 胰島素 +/-Metformin 併用 (18 週 ^d)	安慰劑 (n=188)	Empagliflozin 10 mg (n=186)	Empagliflozin 25 mg (n=189)
總體 (%)	37.2	39.8	41.3
嚴重 (%)	0.5	0.5	0.5

^a總體低血糖事件：血漿或微血管葡萄糖值低於或等於 70 mg/dL

^b嚴重低血糖事件：需要協助（無論血糖值為何）

^c接受治療者資料集(接受至少一劑試驗藥物的受試者)

^d最初的 18 週治療期內不得調整胰島素的劑量

生殖器黴菌感染

在涵蓋五項安慰劑對照臨床試驗的統整數據中，生殖器黴菌感染（如陰道黴菌感染、陰道感染、生殖器真菌感染、外陰陰道念珠菌病，以及外陰炎）的發生率是以 empagliflozin 治療組高於安慰劑治療組，在隨機分配至安慰劑、empagliflozin 10 mg 和 empagliflozin 25 mg 組的發生率分別為 0.9%、4.1%和 3.7%。因生殖器感染而退出試驗的比例，在安慰劑治療組為 0%，在接受 empagliflozin 10 或 25 mg 治療組為 0.2%。

生殖器黴菌感染在女性病人的發生率高於男性（見表 2）。

包莖的發生率在接受 empagliflozin 10 mg（低於 0.1%）和 empagliflozin 25 mg（0.1%）治療的男性病人高於接受安慰劑治療者（0%）。

泌尿道感染

涵蓋五項安慰劑對照臨床試驗的統整數據顯示：在接受 empagliflozin 治療的病人中，泌尿道感染（如泌尿道感染、無症狀之菌尿症以及膀胱炎）的發生率高於安慰劑組（見表 2）。有慢性或復發性泌尿道感染病史的病人，會有較高的機率發生泌尿道感染。因泌尿道感染而中斷治療的比例，在安慰劑、empagliflozin 10 mg 和 empagliflozin 25 mg 組分別為 0.1%、0.2%和 0.1%。

泌尿道感染在女性病人的發生率較高。被隨機分配至安慰劑、empagliflozin 10 mg 和 empagliflozin 25 mg 組的女性病人，泌尿道感染的發生率分別為 16.6%、18.4%和 17.0%。被隨機分配至安慰劑、empagliflozin 10 mg 和 empagliflozin 25 mg 組的男性病人，泌尿道感染的發生率分別為 3.2%、3.6%和 4.1% [請參閱在特定族群的使用 (8.5)]。

Metformin

開始 metformin 治療後最常見（>5%）的不良反應為腹瀉、噁心／嘔吐、脹氣、腹部不適、消化不良、無力及頭痛。

實驗室檢測

Empagliflozin

血清肌酸酐升高及 eGFR 降低：開始以 empagliflozin 治療的幾週內，會誘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，推測使用 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 和 empagliflozin 25 mg 治療的病人中，LDL-C 分別上升 2.3%、4.6%和 6.5%。平均基準點 LDL-C 濃度在各治療組的範圍為 90.3 到 90.6 mg/dL。

血比容上升：四項安慰劑對照試驗的統整數據顯示，安慰劑組的血比容中位數下降 1.3%，而 empagliflozin 10 mg 組和 25 mg 組均上升 2.8%。安慰劑、empagliflozin 10 mg 和 empagliflozin 25 mg 組在治療起始時的血比容均落在參考範圍內，治療結束時分別有 0.6%、2.7%和 3.5%的比例病人的血比容數值超過參考範圍的上限。

Metformin

維生素 B₁₂ 濃度降低：

在為期 29 週的 metformin 臨床試驗中，約有 7%受試者其先前正常的血清維生素 B₁₂ 降至正常濃度以下。

6.2 上市後使用經驗

在上市後使用經驗中還曾發現其它的不良反應。由於這些反應是由人數未定的族群自主通報而得，因此一般而言無法可靠估計其發生率，或確立其與藥物暴露之間的因果關係。

Empagliflozin

- 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)
- 血管性水腫
- 急性腎損傷
- 皮膚反應(例如皮疹、蕁麻疹)

Metformin hydrochloride

- 膽汁淤積、肝細胞損傷與混合型肝細胞肝臟損傷

7 藥物交互作用藥

表 4 與 Jardiance Duo 臨床上相關的交互作用

碳酸酐酶 (Carbonic Anhydrase) 抑制劑	
臨床上的影響	Topiramate 或其他碳酸酐酶抑制劑（例如，zonisamide、acetazolamide 或 dichlorphenamide）常會降低血清中的重碳酸鹽 (bicarbonate) 濃度，並誘發非陰離子間隙、高氯血症性代謝性酸中毒 (hyperchloremic metabolic acidosis)。
處置	併用這些藥物與恩美糖，可能誘發代謝性酸中毒。考量對這些病人實施更頻繁的監測。
可降低 Metformin 清除率的藥物	
臨床上的影響	合併使用這些藥物會干擾參與腎臟之 metformin 清除的總腎小管轉運系統（例如有機陽離子轉運蛋白-2 [OCT2] / 多重藥物及毒素排除系統[MATE]抑制劑，例如 ranolazine、vandetanib、dolutegravir 及 cimetidine）併用，可能使全身性的 metformin 暴露量增高，因而增加乳酸中毒的風險[詳見臨床藥理學（12.3）]。
處置	應考量併用時的益處與風險。
酒精	
臨床上的影響	已知酒精可加劇 metformin 對乳酸代謝的作用，
處置	警告病人勿於服用恩美糖期間飲酒過量。
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	在開始恩美糖治療之前，請評估體溶液狀態及腎功能。體溶液減少的病人，開始恩美糖治療之前，請先矯正此情形。開始恩美糖治療之後，監測體溶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	Empagliflozin 與胰島素或胰島素促泌劑(例如:sulfonylurea)併用，會增加低血糖的發生風險。Metformin 與胰島素或胰島素促泌劑併用，可能會增加低血糖發生的風險。
處置	恩美糖與胰島素促泌劑(例如:sulfonylurea)或胰島素併用時，可能須調降胰島素促泌劑或胰島素的劑量，以減少發生低血糖的風險。
影響血糖控制的藥物	
臨床上的影響	某些藥物具有引發高血糖的傾向，可能導致血糖失去控制。這些藥物包括 thiazide 類藥物及其他利尿劑、皮質類固醇、phenothiazine 類藥物、甲狀腺產

	物、雌激素、口服避孕藥、phenytoin、菸鹼酸 (nicotinic acid)、擬交感神經作用劑 (sympathomimetics)、鈣離子通道阻斷劑及 isoniazid。
處置	將這類藥物用於服用恩美糖的病人時，應密切監測病人的血糖，以維持適當的血糖控制。將這類藥物從服用恩美糖的病人移除時，應密切監測病人是否出現低血糖的狀況。
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	不建議以尿中葡萄糖檢測來監測血糖的控制，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	1,5-AG 的測量值對使用 SGLT2 抑制劑的病人，其血糖控制的評估並不可靠。
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。

8 在特定族群的使用

8.1 懷孕

風險摘要

由於從 empagliflozin 的動物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恩美糖。

在懷孕婦女使用恩美糖或 empagliflozin 的現有資料極少，因此無法據以判定藥物與重大先天缺陷和流產風險之間是否具有相關性。在懷孕期間使用 metformin 的已發表之試驗中，未報告 metformin 與重大先天缺陷和流產風險之間具有明確的相關性(請參閱「資料」一節)。懷孕期間糖尿病控制不佳可能對母體和胎兒造成風險(請參閱「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施用 empagliflozin 時，empagliflozin (恩美糖的成分之一)會導致大鼠有不良腎臟變化。約為最大臨床劑量 13 倍的劑量引發可復原的腎盂和腎小管擴張。當 metformin 施用於懷孕的大鼠和兔子，未觀察到對發育有不良影響(請參閱「資料」一節)。

在有孕前糖尿病且 HbA1c >7 的女性，其小孩出現重大先天缺陷的背景風險估計值為 6% 至 10%，在 HbA1c >10 的女性則高達 20% 至 25%，但不知道此族群的流產背景風險估計值。。在美國一般人群中，臨床確認的產婦發生重大出生缺陷和流產的估計背景風險分別為 2% 至 4% 和 15% 至 20%。

臨床考量

疾病相關的母體和/或胚胎/胎兒風險：懷孕期間若患有控制狀況不佳的糖尿病，會提高母體發生糖尿病酮酸血症、子癲前症(pre-eclampsia)、自發性流產、早產和生產併發症的風險。控制狀況不佳的糖尿病也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

人體資料

已發表的上市後研究資料中並未報告在懷孕期間使用 metformin 時，metformin 與重大先天缺陷、流產或不良母體或胎兒結果之間具有明確的相關性。不過，因為方法上的限制(包括樣本數小和比較組不一致)，這些研究無法證明確實無任何 metformin 相關風險存在。

動物資料

Empagliflozin：在從出生後第 21 天 (PND 21) 開始，以 1、10、30 和 100 mg/kg 之每日劑量對年幼大鼠直接施用 empagliflozin 至 PND 90 為止，在 100 mg/kg 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，這些現象在停止藥物的 13 周恢復期後便未發現。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

三孕期) 暴露於藥物時發生。

在大鼠和兔子的胚胎胎兒發育試驗中，empagliflozin 是在相當於人類器官形成期(第一孕期)的時期施用。在最高 300 mg/kg 的每日劑量（根據 AUC 計算，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案例會增加。Empagliflozin 會穿過胎盤並到達大鼠的胎兒組織。於兔子使用較高的 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）會引發母體及胎兒毒性。

在懷孕大鼠的產前和產後發育試驗中，empagliflozin 係以最高 100 mg/kg 的每日劑量（約相當於最大臨床劑量 25 mg 的 16 倍），自妊娠第 6 天開始施用至泌乳第 20 天（斷奶）為止，期間未產生母體毒性。在大於或等於 30 mg/kg/日的劑量下（約相當於最大臨床劑量 25 mg 的 4 倍），可以觀察到子代的體重降低。

Metformin hydrochloride：懷孕的 Sprague Dawley 大鼠和兔子在器官形成期期間使用最高 600 mg/kg 每日劑量的 metformin hydrochloride 時，未對發育造成不良影響。根據大鼠與兔子的體表面積 (mg/m²) 計算，此暴露量分別為臨床劑量 2000 mg 的大約 2 與 6 倍。

Empagliflozin 與 Metformin hydrochloride：於懷孕大鼠的器官形成期期間併用 empagliflozin 和 metformin hydrochloride 時，使其暴露量分別為 10 mg 和 25 mg 劑量所產生之 empagliflozin 臨床 AUC 暴露量的大約 35 和 14 倍，及 2000 mg 劑量所產生之 metformin 臨床 AUC 暴露量的 4 倍時，未觀察到對發育有不良影響。

8.2 授乳

風險摘要

目前僅有限的資料可說明，關於恩美糖或其成分(empagliflozin 或 metformin)是否會進入人乳以及其對哺乳嬰兒或乳汁生成有何影響。有極少數已發表的試驗報告指出，metformin 會出現在人乳中(請參閱「資料」一節)。Empagliflozin 會進入泌乳大鼠的乳汁中(請參閱「資料」一節)。由於人類腎臟的成熟發生自母體內至可能接觸乳汁的 2 歲前階段，故此藥可能對發育中的人類腎臟帶來風險。

因為恩美糖可能對哺乳嬰兒造成嚴重的不良反應，包含 empagliflozin 可能影響胎兒出生後的腎臟發育，應告知病人，不建議在哺乳期間使用。

資料

已發表的臨床泌乳研究報告指出，metformin 會進入人乳中，所造成的嬰兒劑量約為對體重進行校正後之母體劑量的 0.11%至 1%，且乳汁／血漿中藥物濃度比在 0.13 至 1 之間。不過，這些研究並非設計用於確認於授乳期間使用 metformin 的風險，因為樣本數小且針對嬰兒收集的不良事件資料極少。

在懷孕第 18 天的母大鼠施用單劑口服藥物之後，大鼠胎兒組織中存在低濃度的 empagliflozin。在大鼠乳汁中，乳汁對血漿中藥物濃度比平均值在 0.634 至 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 會蓄積在乳汁內。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)。

8.3 具有生育能力的女性和男性

請與停經前的婦女討論意外懷孕的可能性，因為 metformin 治療可能造成某些無排卵的婦女開始排卵。

8.4 兒童使用

恩美糖的安全性與有效性於兒童病人，尚未獲得確立。

8.5 老年人使用

由於開始使用 empagliflozin 後可能發生腎功能異常、相當大量的 metformin 是由腎臟排除，且腎功能可隨老化下降，因此應更頻繁監測老年人的腎功能[請參閱用法用量(2.1) 以及警語及注意事項(5.1, 5.3)]。

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%。

Metformin hydrochloride

在 Metformin 臨床試驗中所納入的老年病人數不夠多，因此無法判定其反應是否與年輕病人有差異。。

8.6 腎功能不全

恩美糖禁用於重度腎功能不全病人（腎絲球過濾率估計值小於 30 mL/min/1.73 m²）。

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 [請參閱警語及注意事項(5.2)]、體液容量減少不良反應，以及泌尿道感染相關不良反應的發生風險，都會隨著腎功能的惡化上升。

Metformin hydrochloride

相當大量的 metformin 是由腎臟排除，而且 metformin 蓄積及乳酸中毒的風險，會隨腎功能不全嚴重度而增加。[請參閱警語及注意事項(5.1)]。

8.7 肝功能不全

由於曾有一些肝功能不全病人在 metformin hydrochloride 治療時出現乳酸中毒，因此不建議恩美糖用於肝功能不全的病人 [請參閱警語及注意事項(5.1)]。

10 用藥過量

若發生恩美糖用藥過量的情形，請立即就診。

曾有 metformin HCl 用藥過量的報告，包括食入超過 50 公克的量。Metformin 用藥過量的病例約有 32%發生乳酸中毒 [請參閱黑框警語以及警語與注意事項(5.1)]。在良好的血行動力學狀況下，metformin 能以最高 170 mL/分鐘的速度經由透析移除。因此，對於疑似服用過量恩美糖的病人，血液透析可能有助移除蓄積的 metformin。

目前尚未有相關研究，以血液透析清除 empagliflozin。

11 性質說明

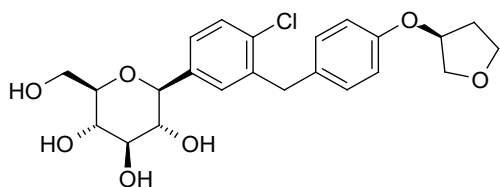
恩美糖錠劑為口服藥物含：empagliflozin 及 metformin hydrochloride。

Empagliflozin

Empagliflozin 為第二型鈉-葡萄糖轉運通道 (sodium-glucose co-transporter 2, SGLT2) 抑制劑。

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

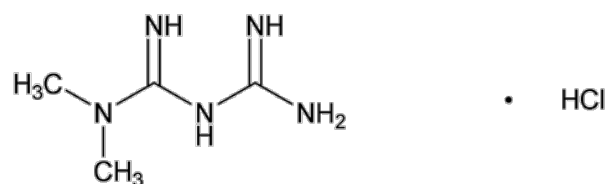
其分子式為 C₂₃H₂₇ClO₇，分子量為 450.91，結構式為：



Empagliflozin 為白色至淡黃色、不具吸濕性的固態粉末，其水溶性極低、略溶於甲醇、幾乎不溶於乙醇和乙腈、可溶於 50% 的乙腈水溶液，但完全不溶於甲苯。

Metformin hydrochloride

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) 是雙胍類藥物，為白色至灰白色結晶化合物；分子式為 $C_4H_{11}N_5 \cdot HCl$ ，而分子量為 165.63。Metformin hydrochloride 可溶於水，幾乎不溶於丙酮、乙醚及氯仿；metformin 的 pK_a 值為 12.4；1% 的 metformin hydrochloride 水溶液 pH 值為 6.68。其結構式如下：



恩美糖

恩美糖口服錠劑有下列六種劑量：5 mg empagliflozin 加上 500 mg metformin hydrochloride、5 mg empagliflozin 加上 850 mg metformin hydrochloride、5 mg empagliflozin 加上 1000 mg metformin hydrochloride、12.5 mg empagliflozin 加上 500 mg metformin hydrochloride、12.5 mg empagliflozin 加上 850 mg metformin hydrochloride，或 12.5 mg empagliflozin 加上 1000 mg metformin hydrochloride。每顆恩美糖膜衣錠含有以下非活性成分：copovidone、玉米澱粉、膠態二氧化矽 (colloidal silicon dioxide)、硬脂酸鎂 (magnesium stearate)。膜衣成分：羥丙甲纖維素 (hypromellose)、二氧化鈦、滑石、聚乙二醇 400，以及黃氧化鐵 (5 mg/500 mg、5 mg/850 mg、5 mg/1000 mg) 或紅氧化鐵和黑氧化鐵 (12.5 mg/500 mg、12.5 mg/850 mg、12.5 mg/1000 mg)。

12 臨床藥理學

12.1 作用機轉

恩美糖

恩美糖含 empagliflozin，是第二型鈉-葡萄糖轉運通道 (SGLT2) 抑制劑；含 metformin，是雙胍類 (biguanide) 藥物。

Empagliflozin

第二型鈉-葡萄糖轉運通道 (SGLT2) 係負責重吸收由腎絲球過濾回體循環之葡萄糖的主要轉運通道。Empagliflozin 係一種 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，並降低腎臟對葡萄糖的閾值，藉此提升尿糖排泄量。

Metformin HCl

Metformin 是一種降血糖藥物，能改善第二型糖尿病病人的葡萄糖耐受性，降低基礎及飯後血中葡萄糖。其在化學結構上或藥理學上，與任何其他種類的口服降血糖藥物均無關聯性。Metformin 能減少肝臟葡萄糖的生成、降低腸道對葡萄糖的吸收，並可藉由增加周邊組織對葡萄糖的吸收和利用而改善胰島素敏感性。不同於磺醯尿素類藥物，metformin 對於第二型糖尿病病人或正常人（除非在特殊的狀況下）都不會造成低血糖 [請參閱警語及注意事項 (5.5)]，也不會引發高胰島素血症。以 metformin 治療時，胰島素的分泌仍維持不變，而空腹胰島素濃度及全天的血中胰島素反應實際上可能減少。

12.2 藥效學

Empagliflozin

尿糖排泄

治療第二型糖尿病病人時，服用一劑 empagliflozin 後尿糖排泄量會立刻增加，在四週每日服用一次 25 mg empagliflozin 的治療期，效果可維持至 4 週。治療期結束時，平均尿糖排泄量約為 78g/日；若每日服用一次 10 mg empagliflozin，則平均排泄量約為 64 g/日 [請參閱臨床試驗 (14)]。從健康受試者口服單劑 empagliflozin 10mg、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。

尿量

在一項為期 5 日的試驗中，以 empagliflozin 25 mg 每日一次進行治療時，平均 24 小時尿量相較於基準點所增加的容積於第 1 天時為 341 mL，而第 5 天時則為 135 mL。

心臟電生理學

在一項隨機分組、以安慰劑及活性對照劑為對照的交叉試驗中，共有 30 名健康受試者接受單一劑口服 empagliflozin 25 mg、empagliflozin 200 mg（最大劑量的 8 倍）、moxifloxacin 以及安慰劑治療，無論使用 25 mg 或 200 mg 的 empagliflozin，QTc 皆未延長。

12.3 藥物動力學

恩美糖

飽食狀態下服用 empagliflozin 12.5 mg/metformin hydrochloride 1000 mg 複合劑時，empagliflozin 的曲線下面積 (AUC) 比起空腹狀態下降 9%，最大濃度 (C_{max}) 則下降 28%。在 metformin 方面，AUC 相較於空腹狀態下降 12%，而 C_{max} 下降 26%。食物對 empagliflozin 和 metformin 的影響經認定並無臨床重要性。

Empagliflozin

吸收

已針對健康受試者與第二型糖尿病病人進行研究討論 empagliflozin 的藥物動力學，結果並未觀察到兩族群之間存在任何具有臨床意義的差異。在口服後，empagliflozin 會在服藥後 1.5 小時達到最高血漿濃度，之後血漿濃度下降可分為兩階段，其一為迅速分佈期 (distribution phase)，其二為相對緩慢的終止期 (terminal phase)。使用 10 mg empagliflozin 每日一次的治療時，穩定狀態平均血漿曲線下面積 (AUC) 和 C_{max} 分別為 1870 nmol·h/L 和 259 nmol/L，而使用 25 mg empagliflozin 每日一次的治療時，則分別為 4740 nmol·h/L 和 687 nmol/L；在治療劑量範圍內，empagliflozin 的全身暴露量增幅與劑量成正比，empagliflozin 的單劑治療與穩定狀態藥物動力學參數相似，顯示其線性藥物動力學與時間相關。

相較於空腹服藥，攝取高脂肪及高熱量膳食後服用 25 mg empagliflozin 會使其暴露量略微降低：AUC 降低約 16%，而 C_{max} 降低約 37%，此膳食對 empagliflozin 藥物動力學的影響未被認為具有臨床意義，empagliflozin 可與食物一起服用，亦可空腹服用。

分佈

依據族群藥物動力學分析估計，穩定狀態的擬分佈體積 (apparent steady-state volume of distribution) 為 73.8L，健康受試者口服 [14 C]-empagliflozin 溶液後，紅血球分配率 (partitioning) 約為 36.8%，血漿結合蛋白分配率 (plasma protein binding) 為 86.2%。

排除

依據族群藥物動力學分析估計，empagliflozin 的擬末端排除半衰期 (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；每日用藥一次後，在血漿 AUC 方面，穩定期的蓄積率 22%，與 empagliflozin 的半衰期一致。

代謝

人類血漿中無法測得 empagliflozin 的主要代謝物，含量最多的代謝物為三種葡萄糖醛酸

(glucuronide)共軛物 (2-O-, 3-O 以及 6-O-葡萄糖醛酸) 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 UGT2B7、UGT1A3、UGT1A8 以及 UGT1A9 等尿嘧啶 5'-二磷酸-葡萄糖醛酸基轉移酶 (uridine 5'-diphospho-glucuronosyltransferase) 的葡萄糖醛酸化作用。

排泄

健康受試者口服 [¹⁴C]-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性活性為未發生變化的原形藥 (unchanged parent drug)，而且約半數尿液排泄出的藥物相關放射活性為未發生變化的原形藥。

Metformin

吸收

在空腹狀況下服用 500 mg metformin hydrochloride 錠劑的絕對生體可用率約為 50 至 60%。單次口服 metformin hydrochloride 錠 500 mg 至 1500 mg，及 850 mg 至 2550 mg 的研究顯示，劑量增加時生體可用率並未隨劑量等比例增加；這是由於吸收減少而非排除作用的改變。

食物會降低 metformin 的吸收量並稍微延後其吸收作用，證據如下：相較於空腹下使用藥物含量相同之藥錠的情況，搭配食物施用單劑 metformin 850 mg 藥錠後 C_{max} 約下降 40%、AUC 下降 25%，而達到最高血漿濃度前所經時間 (T_{max}) 則延長 35 分鐘。上述現象的臨床重要性不明。

分佈

單次口服 850 mg 即釋型 metformin hydrochloride 錠劑後的擬分布體積 (V/F) 平均為 654 ± 358 公升。Metformin 幾乎不會與血漿蛋白質結合。Metformin 會分布至紅血球內，且分布狀況很可能與時間具相關性。

排除

metformin 血漿排除半衰期約為 6.2 小時。在血液中的排除半衰期約為 17.6 小時，這顯示紅血球可能為藥物分佈的所在之一。

代謝

針對正常受試者進行的單劑靜脈投藥研究顯示，metformin 未進行肝臟代謝（人體中未找到其代謝產物），亦不經膽汁排泄。

排泄

口服之後，所吸收的藥物約有 90% 在最初的 24 小時內經由腎臟途徑排泄。腎臟清除率約為肌酸酐清除率的 3.5 倍，這顯示腎小管分泌是 metformin 主要的排除途徑。

特定族群

腎功能不全

恩美糖：尚未針對腎功能不全病人使用恩美糖後的 empagliflozin 與 metformin 藥物動力學特性進行研究。

Empagliflozin：用於治療輕度 (eGFR: 60 到小於 90 mL/min/1.73 m²)、中度 (eGFR: 30 到小於 60 mL/min/1.73 m²)、重度 (eGFR: 小於 30 mL/min/1.73 m²) 腎功能不全的病人以及腎衰竭／末期腎臟病 (ESRD) 病人時，empagliflozin 的 AUC 分別較腎功能正常的病人高約 18%、20%、66% 以及 48%；相較於腎功能正常的病人，中度腎功能不全受試者與腎衰竭／ESRD 病人的 empagliflozin 最高血漿濃度相近，輕與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%。族群藥物動力學分析顯示 empagliflozin 的擬口服清除率隨著 eGFR 下降，因而造成藥物暴露量增加。然而，在尿中以原始型態排出的該部分 empagliflozin 以及尿糖排泄量，都會隨著 eGFR 下降而減少。

Metformin hydrochloride：在腎臟功能降低的病人，metformin 的血漿及血液半衰期會延長，且腎臟清除率是降低的[請見禁忌症 (4)與警語及注意事項 (5.1)]。

肝功能不全

恩美糖：尚未針對肝功能不全病人使用恩美糖後的 empagliflozin 與 metformin 藥物動力學特性進行研究。[請參閱警語及注意事項 (5.1)]。

Empagliflozin：用於治療輕度、中度與重度肝功能不全（依據 Child-Pugh 分級法判定）的病人時，empagliflozin 的 AUC 分別較肝功能正常的受試者高約 23%、47%以及 75%，C_{max} 分別較肝功能正常的受試者高約 4%、23%以及 48%。

Metformin hydrochloride：尚無針對肝功能不全病人進行的 metformin 藥物動力學研究。

年齡、身體質量指數、性別和人種的影響

Empagliflozin：族群藥物動力學分析結果顯示，年齡、身體質量指數 (BMI)、性別以及人種（區分亞洲人和主要為白人）對於 empagliflozin 的藥物動力學性質不存在具有臨床意義的影響[請參閱在特定族群的使用 (8.5)]。

Metformin hydrochloride：依據性別進行分析時，metformin hydrochloride 的藥物動力學參數在正常受試者與第二型糖尿病病人之間並無顯著差異。同樣地，針對第二型糖尿病病人進行的有對照組臨床試驗顯示，metformin 的降血糖作用在男性和女性中相當。

尚未根據人種進行 metformin 藥物動力學參數的研究。在針對第二型糖尿病病人的有對照組臨床試驗中，Metformin HCl 用於白人 (n = 249)、黑人 (n = 51) 及拉丁美洲裔 (n = 24) 時的降血糖效果相當。

老年人

恩美糖：尚未針對老年病人使用恩美糖後的 empagliflozin 與 metformin 藥物動力學特性進行研究[請參閱警語及注意事項 (5.2)與在特定族群的使用 (8.5)]。

Empagliflozin：一項族群藥物動力學分析顯示，年齡對於 empagliflozin 的藥物動力學特性並無臨床上有意義的影響[請參閱在特定族群的使用 (8.5)]。

Metformin hydrochloride：針對健康老年受試者的 metformin 有對照組藥物動力學研究的有限資料顯示，相較於年輕的健康受試者，老年人的 metformin 總血漿清除率降低、半衰期延長，且 C_{max} 增高。這些資料顯示，metformin 隨著年齡改變的藥物動力學性質主要由腎臟功能的變化所造成。

藥物交互作用

尚未針對恩美糖進行藥物動力學的藥物交互作用研究；不過，已針對恩美糖的個別成分 (empagliflozin 與 metformin HCl) 進行此方面的研究。

Empagliflozin

體外藥物交互作用評估：

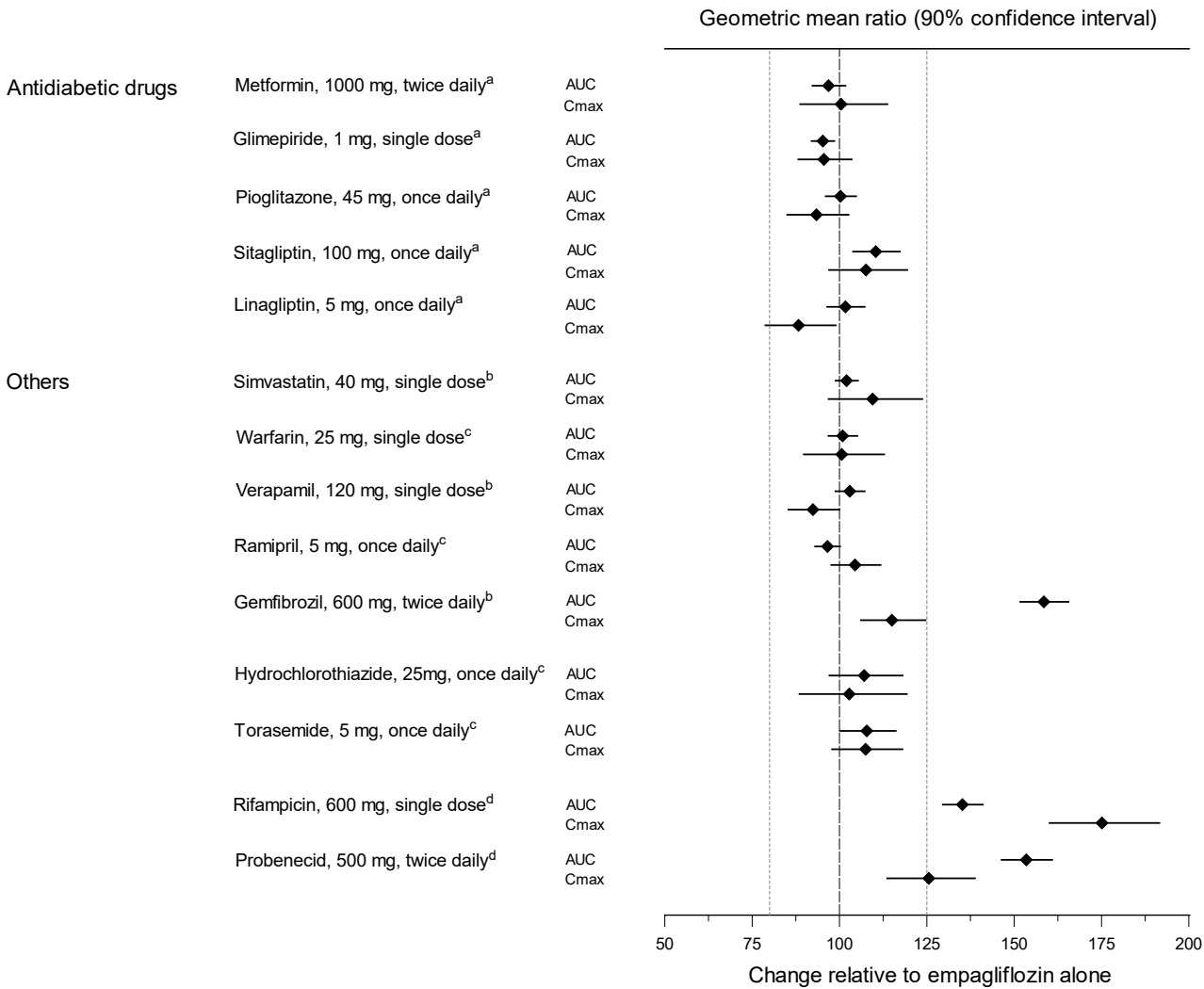
Empagliflozin 不會抑制、去活化或誘發 CYP450 同功酶。體外試驗資料顯示，在人體中 empagliflozin 的主要代謝途徑為經由 UGT1A3、UGT1A8、UGT1A9 及 UGT2B7 等尿嘧啶 5'-二磷酸-葡萄糖醛酸基轉移酶的葡萄糖醛酸化作用。Empagliflozin 不會抑制 UGT1A1、UGT1A3、UGT1A8、UGT1A9 或 UGT2B7。因此，若併用藥物為主要 CYP450 同功酶或 UGT1A1、UGT1A3、UGT1A8、UGT1A9 或 UGT2B7 之受質，則不預期 empagliflozin 會對該等藥物產生影響。誘導 UGT（例如由 rifampicin 或任何其他 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

曾接受評估。

Empagliflozin 為 P-glycoprotein (P-gp) 以及乳癌抗性蛋白 (BCRP) 之受質，然在治療劑量下不會抑制上述排出轉運蛋白 (efflux transporter)，體外藥物交互研究皆顯示，empagliflozin 不太可能與 P-gp 受質類藥物產生交互作用；Empagliflozin 為人體吸收轉運蛋白 (uptake transporter) OAT3、OATP1B1 以及 OATP1B3 之受質（不含 OAT1 與 OCT2），臨床相關血漿濃度之 empagliflozin 不會抑制任何上述人體吸收轉運蛋白，因此，併用的藥物如果是上述吸收轉運蛋白之受質，則不預期 empagliflozin 會對這類藥物造成任何影響。

體內藥物交互作用評估：治療健康受試者時，無論有無併用 metformin hydrochloride、glimepiride、pioglitazone、sitagliptin、linagliptin、warfarin、verapamil、ramipril 與 simvastatin，以及用於治療第二型糖尿病病人時，無論有無併用 hydrochlorothiazide 與 torsemide，empagliflozin 的藥物動力學皆相似（見圖 1）。在腎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任何影響。對於腎功能不全病人而言，此觀察結果的相關性仍不明。

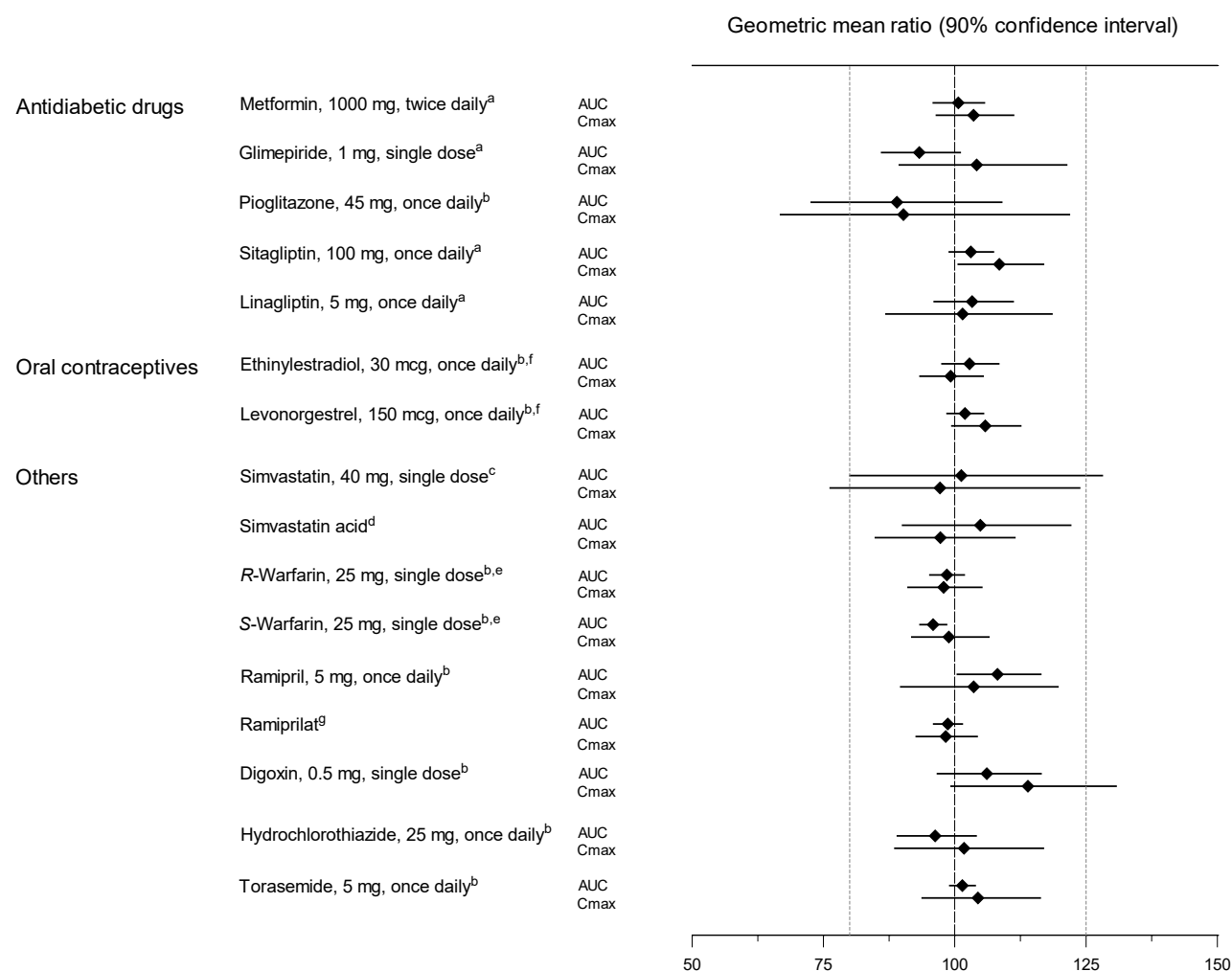
圖 1 各種藥物對 Empagliflozin 藥物動力學的影響，以幾何平均 AUC 與 C_{max} 之比值的 90%信賴區間表式[參考線代表 100% (80% - 125%)]



^aempagliflozin, 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

與 empagliflozin 併用時，empagliflozin 對 metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torsemide 以及口服避孕藥之藥物動力學並無具有臨床相關性的影響 (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 Cmax 之比值的 90%信賴區間表式 [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 給予 simvastatin; ^e 給予 warfarin 消旋混合物 (racemic mixture); ^f 給予 Microgynon®; ^g 給予 ramipril

表 5 併用藥物對血漿中 Metformin 全身性暴露量的影響

併用的藥物	併用藥物的劑量*	Metformin hydrochloride 的劑量*	幾何平均比值 (有／無併用藥物的比值) 無影響 = 1.0		
				AUC [†]	C _{max}
Glyburide	5 mg	850 mg	metformin	0.91 _‡	0.93 _‡
Furosemide	40 mg	850 mg	metformin	1.09 _‡	1.22 _‡
Nifedipine	10 mg	850 mg	metformin	1.16	1.21
Propranolol	40 mg	850 mg	metformin	0.90	0.94
Ibuprofen	400 mg	850 mg	metformin	1.05 _‡	1.07 _‡
陽離子藥物經由腎小管分泌作用排除的藥物可能會減少 metformin 的排除[請參閱藥物交互作用 (7)]。					
Cimetidine	400 mg	850 mg	metformin	1.40	1.61
碳酸酐酶抑制劑可能引發代謝性酸中毒[請參閱警語及注意事項 (5.1) 與藥物交互作用 (7.1)]。					
Topiramate**	100 mg	500 mg	metformin	1.25	1.17

* 所有的 metformin 與併用藥物皆為單劑給藥。

[†] AUC = AUC(INF)

_‡ 算術平均比值

**每 12 小時服用一次 topiramate 100 mg 與每 12 小時服用一次 metformin 500 mg 的穩定狀態；AUC = AUC (0-12 hours)。

表 6 Metformin 對於併用藥物全身性暴露量的影響

併用的藥物	併用藥物的劑量*	Metformin hydrochloride 的劑量*	幾何平均比值 (有／無 metformin 的比值) 無影響 = 1.0		
				AUC [†]	C _{max}
Glyburide	5 mg	500 mg§	glyburide	0.78 _‡	0.63 _‡
Furosemide	40 mg	850 mg	furosemide	0.87 _‡	0.69 _‡
Nifedipine	10 mg	850 mg	nifedipine	1.10§	1.08
Propranolol	40 mg	850 mg	propranolol	1.01§	0.94
Ibuprofen	400 mg	850 mg	ibuprofen	0.97¶	1.01¶
Cimetidine	400 mg	850 mg	cimetidine	0.95§	1.01

* 所有的 metformin 與併用藥物皆為單劑給藥。

[†] AUC = AUC(INF)，除非另外註明。

_‡ 算術平均比值，差異的 p 值<0.05。

§ 所報告的 AUC(0-24 小時)。

¶ 算術平均比值

13 非臨床毒物學

13.1 致癌性、致突變性、生育力受損

恩美糖

尚未有針對 empagliflozin 和 metformin hydrochloride 併用之致癌性、致突變性或生育力受損的研究。已針對這兩種成分在大鼠中進行最長 13 週的一般毒性研究。這些研究顯示 empagliflozin 與 metformin 的併用不會帶來加成性毒性。

Empagliflozin

於 CD-1 小鼠和 Wistar 大鼠中進行的 2 年試驗曾經評估本藥的致癌性，結果 Empagliflozin 在 100、300 或 700 mg/kg/日（約為最大臨床劑量 25 mg 所產生之暴露量的 72 倍）的劑量下不會增加雌性大鼠的腫瘤發生率；在雄性大鼠方面，於 700 mg/kg/日（約為最大臨床劑量 25 mg 所產生之暴露量的 42 倍）的劑量下，腸系膜淋巴結血管瘤的案例會顯著增加。Empagliflozin 在 100、300 或 1000 mg/kg/日（約相當於最大臨床劑量 25 mg 暴露量的 62 倍）的劑量下不會增加雌性小鼠的腫瘤發生率。在 1000 mg/kg/日（約相當於最大臨床劑量 25 mg 暴露量的 45 倍）的劑量下，曾在雄性小鼠中觀察到腎小管腺瘤和腎臟癌的案例。這些腫瘤可能與主要存在於雄性小鼠腎臟內的代謝路徑有關。

體外 Ames 細菌致突變分析、體外 L5178Y tk⁺/– 小鼠淋巴瘤細胞分析以及大鼠中的體內微核分析皆顯示，無論經過代謝活化與否，empagliflozin 均不具有致突變性及誘變性 (clastogenic)。

在最高 700 mg/kg/日的劑量下（在雄鼠和雌鼠中約相當於最大臨床劑量 25 mg 的 155 倍），empagliflozin 對投藥的雄性或雌性大鼠中於交配、生殖力或早期胚胎發育皆無影響。

Metformin hydrochloride

已經有針對大鼠（給藥時間 104 週）及小鼠（給藥時間 91 週）進行的長期致癌性研究，使用的最高劑量分別達到 900 mg/kg/天及 1500 mg/kg/天。根據體表面積計算，這兩個劑量皆約為人體每日最大建議劑量 2000 mg/kg/天的 4 倍。在雄性小鼠及雌性小鼠中，皆未發現 metformin 具致癌性的證據。同樣地，在雄性大鼠身上亦未觀察到 metformin 具有致腫瘤的可能。然而，在雌性大鼠使用 900 mg/kg/天的劑量時，良性基質子宮息肉的發生率增高。

在下列體外檢測中並未找到 metformin 具有致突變性的證據：Ames 檢測 (*S. typhimurium*)、基因突變檢測（小鼠淋巴瘤細胞）或染色體異常檢測（人類淋巴球）。小鼠的活體內微核檢測結果亦顯示 metformin 不具致突變性。

在高達 600 mg/kg/天的劑量下，metformin 不會影響雄性小鼠及雌性小鼠的生殖力；根據體表面積計算，此劑量約為人體每日最大建議劑量的 2 倍。

14 臨床試驗

恩美糖之血糖控制研究

對於第二型糖尿病病人，與安慰劑相較，接受 empagliflozin 和 metformin 治療後，糖化血色素 (HbA1c) 出現臨床上和統計上顯著的改善現象。在按照年齡、性別、人種及基準點身體質量指數 (BMI) 所區分的不同子群中，都可以觀察得到糖化血色素下降的現象。

以 *Empagliflozin* 輔助既有 *Metformin* 的合併療法

總計有 637 名第二型糖尿病病人參與一項評估 empagliflozin 併用 metformin 時之療效與安全性的雙盲安慰劑對照試驗。

經每日劑量 1500 mg 以上的 metformin hydrochloride 治療後，仍無法妥善控制病情的第二型糖尿病病人先進入開放標示的安慰劑導入期治療 2 週。導入期結束時，血糖控制仍不佳且 HbA1c 介於 7 和 10% 之間的病人會隨機分入安慰劑組、empagliflozin 10 mg 組或 empagliflozin 25 mg 組進行治療。

第 24 週時，相較於安慰劑，每日 empagliflozin 10 mg 或 25 mg 之治療可使 HbA1c ($p < 0.0001$)、空腹血糖值 (FPG) 與體重產生統計上顯著的下降（見表 7）。

表 7 Empagliflozin 併用 Metformin 之安慰劑對照試驗於第 24 週時的結果

	Empagliflozin 10 mg + Metformin N=217	Empagliflozin 25 mg + Metformin N=213	安慰劑 + Metformin N=207
HbA1c (%)^a			
基準點（平均值）	7.9	7.9	7.9
自基準點起之變化（校正後平均值）	-0.7	-0.8	-0.1
與安慰劑 + metformin 之差異（校正後平均值）(95% CI)	-0.6 ^b (-0.7, -0.4)	-0.6 ^b (-0.8, -0.5)	--
達成 HbA1c <7% 之病人人數 (%)	75 (38%)	74 (39%)	23 (13%)
FPG (mg/dL)^c			
基準點（平均值）	155	149	156
自基準點起之變化（校正後平均值）	-20	-22	6
與安慰劑之差異 + metformin（校正後平均值）	-26	-29	--
體重			
基準點平均值 (kg)	82	82	80
自基準點起之變化百分比（校正後平均值）	-2.5	-2.9	-0.5
與安慰劑之差異（校正後平均值）(95%CI)	-2.0 ^b (-2.6, -1.4)	-2.5 ^b (-3.1, -1.9)	--

^a修訂版意圖治療族群。插補第 24 週時缺失的數據時，係採用試驗期間的最後觀察值（LOCF 法）。第 24 週時，被隨機分配至 empagliflozin 10 mg、empagliflozin 25 mg 和安慰劑組的病人中，分別有 9.7%、14.1% 和 24.6% 的數據是以推估而得。

^b由 ANCOVA 法得到的 p 值 < 0.0001 （HbA1c：ANCOVA 模型包含基準點 HbA1c、治療、腎功能和地區。體重和 FPG：模型與 HbA1c 相同，但分別額外包含基準點體重/基準點 FPG。）

^cFPG (mg/dL)：empagliflozin 10 mg 組， $n=216$ ，empagliflozin 25 mg 組， $n=213$ ，安慰劑組， $n=207$

第 24 週時，empagliflozin 10 mg 組的收縮壓比安慰劑組在統計上顯著低了 -4.1 mmHg（經安慰劑校正， p 值 < 0.0001 ），而 empagliflozin 25 mg 組則顯著低了 -4.8 mmHg（經安慰劑校正， p 值 < 0.0001 ）。

Empagliflozin 與 Metformin 的初始合併療法

總計有 1364 名第二型糖尿病病人參與一項以相對應之個別成分作為比較基準，評估 empagliflozin 併用 metformin 作為初始療法之療效與安全性的雙盲、隨機、活性藥物對照試驗。

未曾接受治療且第二型糖尿病控制狀況不佳的病人先進入開放標示的安慰劑導入期治療 2 週。導入期結束時，血糖控制仍不佳且 HbA1c 介於 7% 和 10.5% 之間的病人會隨機分入 8 個活性治療組的其中一組：empagliflozin 10 mg 或 25 mg；metformin hydrochloride 1000 mg 或 2000 mg；empagliflozin 10 mg 加上 1000 mg 或 2000 mg 的 metformin hydrochloride；或 empagliflozin 25 mg 加上 1000 mg 或 2000 mg 的 metformin。

第 24 週時，與個別成分相較，empagliflozin 併用 metformin 的初始療法可使 HbA1c (p 值 < 0.01) 出現具統計意義顯著性的下降效果（見表 8）。

表 8 作為初始療法，比較 Empagliflozin 和 Metformin 合併療法與個別成分之試驗，24 週時的血糖參數

	Empagliflozin 10 mg + Metformin 1000 mg ^a N=161	Empagliflozin 10 mg + Metformin 2000 mg ^a N=167	Empagliflozin 25 mg + Metformin 1000 mg ^a N=165	Empagliflozin 25 mg + Metformin 2000 mg ^a N=169	Empagliflozin 10 mg N=169	Empagliflozin 25 mg N=163	Metformin 1000 mg ^a N=167	Metformin 2000 mg ^a N=162
HbA1c (%)								
基準點 (平均值)	8.7	8.7	8.8	8.7	8.6	8.9	8.7	8.6
自基準點之變化 (調整後平均值)	-2.0	-2.1	-1.9	-2.1	-1.4	-1.4	-1.2	-1.8
與 empagliflozin 之 差異 (調整後平均 值) (95% CI)	-0.6 ^b (-0.9, -0.4)	-0.7 ^b (-1.0, -0.5)	-0.6 ^c (-0.8, -0.3)	-0.7 ^c (-1.0, -0.5)	--	--	--	--
與 metformin 之差 異 (調整後平均 值) (95% CI)	-0.8 ^b (-1.0, -0.6)	-0.3 ^b (-0.6, -0.1)	-0.8 ^c (-1.0, -0.5)	-0.3 ^c (-0.6, -0.1)	--	--	--	--
達成 HbA1c < 7% 之病人人數 (%)	96 (63%)	112 (70%)	91 (57%)	111 (68%)	69 (43%)	51 (32%)	63 (38%)	92 (58%)

^aMetformin hydrochloride 每日總劑量，以每日給予兩個相等劑量的方式給予。

^bp 值 ≤ 0.0062 (修訂意圖治療族群[觀察案例]；MMRM 模型包含治療、腎功能、地區、回診、回診和治療的交互作用，以及基準點 HbA1c)。

^cp 值 ≤ 0.0056 (修訂意圖治療族群[觀察案例]；MMRM 模型包含治療、腎功能、地區、回診、回診和治療的交互作用，以及基準點 HbA1c)。

以 Empagliflozin 輔助既有 Metformin 和磺醯尿素類藥物的合併療法

總計有 666 名第二型糖尿病病人參與一項評估 empagliflozin 併用 metformin 以及磺醯尿素類藥物時之療效與安全性的雙盲安慰劑對照試驗。

接受每日劑量至少 1500 mg 的 metformin hydrochloride 與磺醯尿素類藥物治療後，仍無法妥善控制病情的第二型糖尿病病人先進入開放標示的安慰劑導入期治療 2 週。導入期結束時，血糖控制仍不佳且 HbA1c 介於 7% 和 10% 之間的病人會隨機分入安慰劑組、empagliflozin 10 mg 組或 empagliflozin 25 mg 組進行治療。

相較於安慰劑，每日 empagliflozin 10 mg 或 25 mg 之治療可使 HbA1c (p<0.0001)、空腹血糖值 (FPG) 與體重產生統計上顯著的下降 (見表 9)。

表 9 Empagliflozin 併用 Metformin 及磺醯尿素類藥物之安慰劑對照試驗於第 24 週時的結果

	Empagliflozin 10 mg + Metformin + SU N=225	Empagliflozin 25 mg + Metformin + SU N=216	安慰劑 + Metformin + SU N=225
HbA1c (%)^a			
基準點 (平均值)	8.1	8.1	8.2
自基準點起之變化 (校正後平均值)	-0.8	-0.8	-0.2
與安慰劑之差異 (校正後平均值) (95% CI)	-0.6 ^b (-0.8, -0.5)	-0.6 ^b (-0.7, -0.4)	--
達成 HbA1c <7% 之病人 (%)	55 (26%)	65 (32%)	20 (9%)
FPG (mg/dL)^c			
基準點 (平均值)	151	156	152
自基準點起之變化 (校正後平均值)	-23	-23	6
與安慰劑之差異 (校正後平均值)	-29	-29	--
體重			
基準點平均值 (kg)	77	78	76
自基準點起之變化百分比 (校正後平均值)	-2.9	-3.2	-0.5
與安慰劑之差異 (校正後平均值) (95% CI)	-2.4 ^b (-3.0, -1.8)	-2.7 ^b (-3.3, -2.1)	--

^a修訂版意圖治療族群。插補第 24 週時缺失的數據時，係採用試驗期間的最後觀察值 (LOCF 法)。第 24 週時，被隨機分配至 empagliflozin 10 mg、empagliflozin 25 mg 和安慰劑組的病人中，分別有 17.8%、16.7% 和 25.3% 的數據是以推估而得。

^b由 ANCOVA 法得到的 p 值 <0.0001 (HbA1c: ANCOVA 模型包含基準點 HbA1c、治療、腎功能和地區。體重和 FPG: 模型與 HbA1c 相同，但分別額外包含基準點體重/基準點 FPG。)

^cFPG (mg/dL): empagliflozin 10 mg 組, n=225, empagliflozin 25 mg 組, n=215, 安慰劑組, n=224

併用 Metformin 並與 Glimepiride 比較的活性藥物對照試驗

總計有 1545 名經 metformin 治療後無法妥善控制病情的第二型糖尿病病人參與一項評估 empagliflozin 療效，以 glimepiride 為活性藥物對照的雙盲對照試驗。

經 2 週導入期後血糖控制仍不佳且 HbA1c 介於 7% 和 10% 之間的病人會隨機分入 glimepiride 組或 empagliflozin 25 mg 組進行治療。

第 52 週時，empagliflozin 25 mg 和 glimepiride 都使 HbA1c 和 FPG 下降 (見表 10、圖 3)。

Empagliflozin 25 mg 和 glimepiride 組在效果大小觀察值上的差異均未涵蓋 0.3% 的預設非劣性臨界值。Glimepiride 的每日平均劑量為 2.7 mg，而在美國的最大核准劑量為 8 mg/日。

表 10 無法以 Metformin 妥善控制病情之病人併用 Empagliflozin 或併用 Glimepiride 作為治療藥物的活性對照試驗於第 52 週時的比較結果

	Empagliflozin 25 mg + Metformin N=765	Glimepiride + Metformin N=780
HbA1c (%)^a		
基準點 (平均值)	7.9	7.9
自基準點起之變化 (校正後平均值)	-0.7	-0.7
與 glimepiride 之差異 (校正後平均值) (97.5% CI)	-0.07 ^b (-0.15, 0.01)	--
FPG (mg/dL)^d		
基準點 (平均值)	150	150
自基準點起之變化 (校正後平均值)	-19	-9
與 glimepiride 之差異 (校正後平均值)	-11	--
體重		
基準點平均值 (kg)	82.5	83
自基準點起之變化百分比 (校正後平均值)	-3.9	2.0
與 glimepiride 之差異 (校正後平均值) (95% CI)	-5.9 ^c (-6.3, -5.5)	--

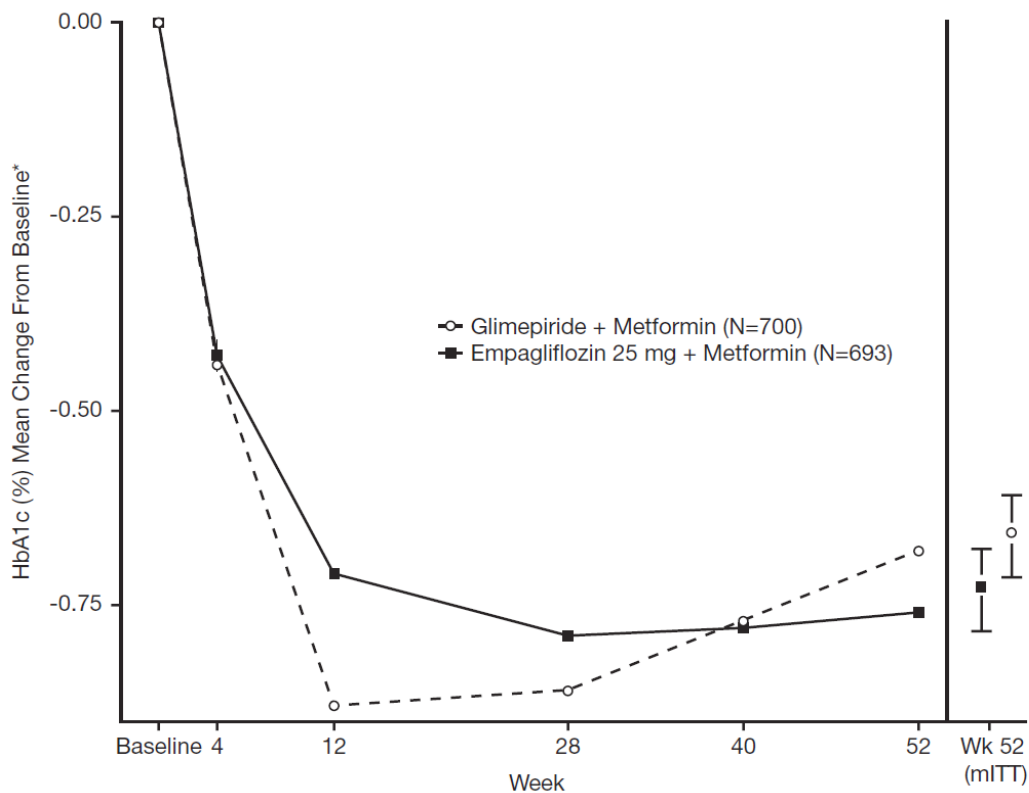
^a修訂版意圖治療族群。插補第 52 週時缺失的數據時，係採用試驗期間的最後觀察值 (LOCF 法)。第 52 週時，被隨機分配至 empagliflozin 25 mg 和 glimepiride 組的病人中，分別有 15.3% 和 21.9% 的數據是以推估而得。

^b不劣性 ANCOVA 模型 p 值 <0.0001 (HbA1c: ANCOVA 模型包含基準點 HbA1c、治療、腎功能和地區)

^cANCOVA p 值 <0.0001 (體重和 FPG: 模型與 HbA1c 相同，但分別額外包含基準點體重/基準點 FPG)

^dFPG (mg/dL): empagliflozin 25 mg, n=764; glimepiride, n=779

圖 3 每個時間點（完成者）及第 52 週時（mITT 族群）的校正後平均 HbA1c 變化 - LOCF 法



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

第 52 週時，收縮壓相較於基準點的校正後平均變化為-3.6 mmHg，而 glimepiride 組則為 2.2 mmHg。兩組的收縮壓變化達到統計顯著差異（p 值<0.0001）。

第 104 週時，HbA1c 相較於基準點的校正後平均變化在 empagliflozin 25 mg 組內為-0.75%，在 glimepiride 組內為-0.66%。校正後平均治療差異是-0.09%，而 97.5%信賴區間為 (-0.32%, 0.15%)（不含預設的不劣性邊界 0.3%）。Glimepiride 的平均每日劑量為 2.7 mg，而在美國的最大核准劑量為每日 8 mg。第 104 週的分析納入了含及不含併用血糖救援藥物的數據，以及非治療期間的數據。在回診中未提供任何資訊的病人，其缺失數據是以所觀察到的非治療期間數據推估而得。在此項多重推估分析中，empagliflozin 25 mg 組有 13.9%的數據是由推估而得，而 glimepiride 組則為 12.9%。

第 104 週時，每天一次 empagliflozin 25 mg 相較於 glimepiride，可在體重相較於基準點的變化呈現統計顯著差異（empagliflozin 25 mg 組為-3.1 kg，glimepiride 組為+1.3 kg；ANCOVA-LOCF，p 值<0.0001）。

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，旨在針對動脈粥樣硬化性心血管疾病的糖尿病病人，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，與其併用時的重大不良心血管事件(MACE)發生風險。在試驗的前 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($HbA1c \geq 7\%$)。基準點時的 $HbA1c$ 平均值為 8.1%，而且 57% 的受試者已罹患糖尿病超過 10 年。分別有大約 31%、22% 與 20% 的受試者向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 m²。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%)和磺醯尿素類藥物(43%)。

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：經證實的冠狀動脈疾病(76%)、中風(23%)或周邊動脈疾病(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。設定風險邊際值為 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)的不劣性，以及若通過不劣性檢定，則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型一錯誤。

Empagliflozin 可顯著減少發生心血管原因死亡、首次非致命性心肌梗塞或首次非致命性中風之主要綜合評估指標的風險(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(請見圖 11 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 11 在主要綜合評估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優越性檢定之 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

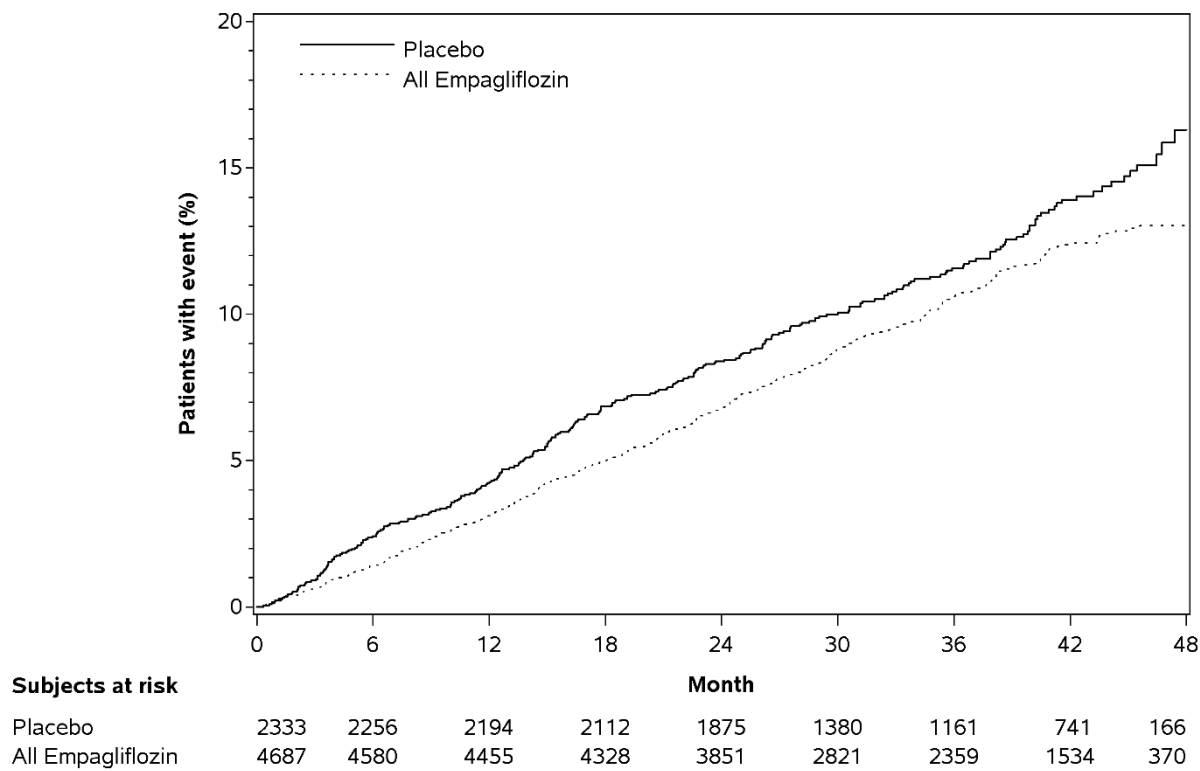
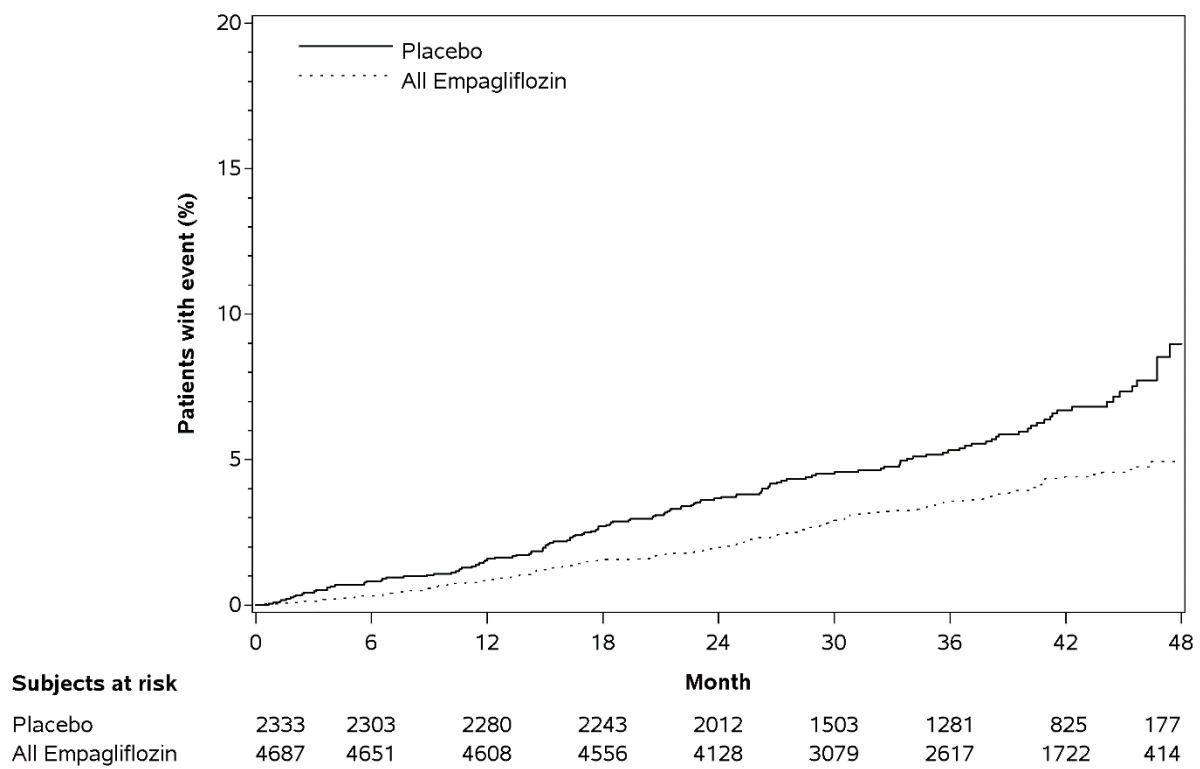


圖 5 心血管原因死亡的累積發生率估計值



就心血管原因死亡而言，empagliflozin 對於主要人口統計與各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 例死亡個例。這些死亡個例大部分被歸於心血管原因死亡，非心血管原因死亡僅佔少部分，且

治療組之間的狀況相近(接受 EMPAGLIFLOZIN 治療者為 2.1%，接受安慰劑治療者為 2.4%)。

16 供應形式／儲存與操作

恩美糖錠劑供應如下：

錠劑藥物含量	膜衣錠顏色／形狀	錠劑標示	包裝規格
5 mg Empagliflozin / 500 mg Metformin	橘黃色、橢圓形、 兩面中央凸起	一面壓印百靈佳殷格翰公司標誌與 「S5」字樣，另一面壓印「500」	4-1000 錠聚氯三氟乙烯 (PCTFE) 泡殼片盒裝。
5 mg Empagliflozin / 850 mg Metformin	米黃色、橢圓形、 兩面中央凸起	一面壓印百靈佳殷格翰公司標誌與 「S5」字樣，另一面壓印「850」	4-1000 錠聚氯三氟乙烯 (PCTFE) 泡殼片盒裝。
5 mg Empagliflozin / 1000 mg Metformin	棕黃色、橢圓形、 兩面中央凸起	一面壓印百靈佳殷格翰公司標誌與 「S5」字樣，另一面壓印「1000」	4-1000 錠聚氯三氟乙烯 (PCTFE) 泡殼片盒裝。
12.5 mg Empagliflozin / 500 mg Metformin	淺棕紫色、橢圓 形、兩面中央凸起	一面壓印百靈佳殷格翰公司標誌與 「S12」字樣，另一面壓印「500」	4-1000 錠聚氯三氟乙烯 (PCTFE) 泡殼片盒裝。
12.5 mg Empagliflozin / 850 mg Metformin	淺粉紅色、橢圓 形、兩面中央凸起	一面壓印百靈佳殷格翰公司標誌與 「S12」字樣，另一面壓印「850」	4-1000 錠聚氯三氟乙烯 (PCTFE) 泡殼片盒裝。
12.5 mg Empagliflozin / 1000 mg Metformin	深棕紫色、橢圓 形、兩面中央凸起	一面壓印百靈佳殷格翰公司標誌與 「S12」字樣，另一面壓印「1000」	4-1000 錠聚氯三氟乙烯 (PCTFE) 泡殼片盒裝。

儲存

請儲存於 30°C 以下。請存放於兒童無法取得的安全處所。

17 病人諮詢資訊

乳酸中毒

告知病人 metformin 成分可能導致之乳酸中毒的危險性、症狀及容易導致該症狀發生的狀況。請病人若發生不明原因的過度換氣、身體不適、肌肉痛、不尋常的嗜睡或其他非特定症狀，應立即停止服用恩美糖，並儘速通知醫師。規勸病人服用恩美糖期間，應避免飲酒過量並告知病人定期檢測腎功能的重要性。請指示病人在接受任何手術或放射程序之前，應告知醫師自己正在服用恩美糖，因為可能需要暫時停用恩美糖，直到確認腎功能正常[請參閱警語及注意事項(5.1)]。

酮酸中毒

請告知病人酮酸中毒為嚴重危及生命的情況，使用 empagliflozin 曾有酮酸中毒的案例通報，有時與疾病或手術相關的其他危險因素有關。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），應停用恩美糖並立即就醫[請參閱警語及注意事項(5.3)]。

體液容量減少

告知病人服用恩美糖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繫[請參閱警語及注意事項(5.3)]。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。

嚴重泌尿道感染

請告知病人可能發生泌尿道感染（可能為嚴重感染）。請向病人提供關於泌尿道感染症狀的資訊。請建議病人於出現泌尿道感染症狀時就醫[請參閱警語及注意事項(5.5)]。

低血糖

請告知病人恩美糖與胰島素分泌促進劑(例如磺醯尿素類藥物)或胰島素併用時，發生低血糖風險會增高，可能需要降低胰島素分泌促進劑或胰島素的劑量，以降低發生低血糖症的風險[請參閱警語及注意事項(5.6)]。

會陰部壞死性筋膜炎(弗尼爾氏壞疽)

請告知病人，曾有使用 empagliflozin(恩美糖的成分)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、發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(5.6)]。

女性的生殖器黴菌感染（如外陰陰道炎）

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。請向病人建議治療選項以及就醫時機[請參閱警語及注意事項(5.7)]。

男性的生殖器黴菌感染（如龜頭炎或龜頭包皮炎）

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。請向病人建議治療選項以及就醫時機[請參閱警語及注意事項(5.7)]。

維生素 B₁₂缺乏

請告知病人服用恩美糖時定期檢測血液學參數的重要性[請參閱警語及注意事項(5.9)]。

過敏反應

請告知病人，曾有使用 empagliflozin(恩美糖的成分)時出現嚴重過敏反應(例如蕁麻疹與血管性水腫)的病例。建議病人，如果出現任何皮膚反應或血管性水腫，應立即通報，並停用藥物，直到諮詢開處方的醫師[請參閱警語及注意事項(5.8)]。

實驗室檢測

請告知病人服用恩美糖時尿液分析中的尿糖升高為正常現象。

懷孕

請告知懷孕病人和具有生育能力的病人，以恩美糖治療可能對胎兒造成風險[請參閱在特定族群的使用(8.1)]。請指示病人，應在懷孕時儘快告知醫師。

授乳

請告知病人，不建議在接受恩美糖治療期間餵哺母乳[請參閱在特定族群的使用(8.2)]。

具有生育能力的病人

請告知病人，metformin 治療可能使得某些無排卵的停經前的病人開始排卵，而導致意外懷孕[請參閱在特定族群的使用(8.3)]。

錯過用藥

請指示病人依照處方服用恩美糖。若錯過一劑藥物，請盡速於記起時服用。請指示病人切勿於下一劑時服用雙倍劑量。

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核准日期: 2021 年 12 月

JARDIANCE DUO® 5/500mg Film-Coated Tablets
JARDIANCE DUO® 5/850mg Film-Coated Tablets
JARDIANCE DUO® 5/1000mg Film-Coated Tablets
JARDIANCE DUO® 12.5/500mg Film-Coated Tablets
JARDIANCE DUO® 12.5/850mg Film-Coated Tablets
JARDIANCE DUO® 12.5/1000mg Film-Coated Tablets

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL [see *Warnings and Precautions* (5.1)].

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.

Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information [see *Dosage and Administration* (2.1), *Contraindications* (4), *Warnings and Precautions* (5.1), *Drug Interactions* (7), and *Use in Specific Populations* (8.6, 8.7)].

If metformin-associated lactic acidosis is suspected, immediately discontinue JARDIANCE DUO and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended [see *Warnings and Precautions* (5.1)].

1 INDICATIONS AND USAGE

JARDIANCE DUO is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who have inadequate glycemic control on metformin or empagliflozin alone, or who are already treated with both empagliflozin and metformin and stabilized

Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease [see *Clinical Studies* (14.2)]. However, the effectiveness of JARDIANCE DUO on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease has not been established.

Limitations of Use

JARDIANCE DUO 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* (5.2)].

2 DOSAGE AND ADMINISTRATION

The product should be used by physician prescription.

2.1 Prior to Initiation of Jardiance Duo

- Assess renal function before initiating Jardiance Duo and as clinically indicated [see *Warnings and Precautions* (5.1, 5.3)].

- In patients with volume depletion, correct this condition before initiating JARDIANCE DUO [see *Warnings and Precautions (5.3) and Use in Specific Populations (8.5, 8.6)*].

2.2 Recommended Dosage and Administration

- Individualize the starting dose of JARDIANCE DUO based on the patient's current regimen:
 - In patients on metformin HCl, switch to JARDIANCE DUO containing empagliflozin 5 mg with a similar total daily dose of metforminHCl;
 - In patients on empagliflozin, switch to JARDIANCE DUO containing metformin HCl 500 mg with a similar total daily dose of empagliflozin;
 - In patients already treated with empagliflozin and metformin HCl, switch to JARDIANCE DUO containing the same total daily doses of each component.
- Monitor effectiveness and tolerability, and adjust dosing as appropriate, not to exceed the maximum recommended daily dose of empagliflozin 25 mg and metformin HCl 2000 mg.
- Take JARDIANCE DUO twice daily with meals; with gradual dose escalation to reduce the gastrointestinal side effects due to metformin.

2.3 Dosage Recommendations in Patients with Renal Impairment

- JARDIANCE DUO is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m². [see *Contraindications (4), Warnings and Precautions (5.1,) and Use in Specific Populations (8.6)*].

3 DOSAGE FORMS AND STRENGTHS

JARDIANCE DUO Film-Coated Tablets:

Empagliflozin Strength	Metformin HCl Strength	Color/Shape	Tablet Markings
5 mg	500 mg	orange yellow, oval, biconvex, film-coated tablet	Boehringer Ingelheim company symbol and "S5" debossed on one side; the other side is debossed with "500"
5mg	850mg	yellowish white, oval, biconvex, film-coated tablets	Boehringer Ingelheim company symbol and "S5" debossed on one side; the other side is debossed with "850"
5 mg	1000 mg	brownish yellow, oval, biconvex, film-coated tablet	Boehringer Ingelheim company symbol and "S5" debossed on one side; the other side is debossed with "1000"
12.5 mg	500 mg	pale brownish purple, oval, biconvex, film-coated tablet	Boehringer Ingelheim company symbol and "S12" debossed on one side; the other side is debossed with "500"
12.5 mg	850mg	pinkish white, oval, biconvex, film-coated tablets	Boehringer Ingelheim company symbol and "S12" debossed on one side; the other side is debossed with "850"
12.5 mg	1000 mg	dark brownish purple, oval, biconvex, film-coated tablet	Boehringer Ingelheim company symbol and "S12" debossed on one side; the other side is debossed with "1000"

4 CONTRAINDICATIONS

JARDIANCE DUO is contraindicated in patients with:

- Severe renal impairment (eGFR less than 30mL/min/1.73 m²), end stage renal disease, or dialysis [*see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)*].
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. [*see Warnings and Precautions (5.1)*]
- Hypersensitivity to empagliflozin, metformin or any of the excipients in JARDIANCE DUO, reactions such as angioedema have occurred [*see Warnings and Precautions (5.8)*].

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

There have been postmarketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension, and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate:pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of JARDIANCE DUO. In JARDIANCE DUO-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with a clearance of up to 170 mL/minute under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue JARDIANCE DUO and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment: The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include [*see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*].

- Before initiating JARDIANCE DUO, obtain an estimated glomerular filtration rate (eGFR).
- JARDIANCE DUO is contraindicated in patients with an eGFR below 30 mL/min/1.73 m² [*see Contraindications (4)*].
- Obtain an eGFR at least annually in all patients taking JARDIANCE DUO. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Drug Interactions: The concomitant use of JARDIANCE DUO with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation [*see Drug Interactions (7.2)*]. Therefore, consider more frequent monitoring of patients.

Age 65 or Greater: The risk of metformin-associated lactic acidosis increases with the patient's age because

elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients [see *Use in Specific Populations (8.5)*].

Radiological Studies with Contrast: Intravascular iodinated contrast has risks to cause acute renal function decrease, therefore metformin should be stopped prior to contrast injection. Re-evaluate eGFR 48 hours after the imaging procedure. Only after confirmation of patients' renal function returns to stable can metformin be resumed. When prescribing metformin-containing medication, patient renal function should be monitored on regular basis.

Surgery and Other Procedures: Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. JARDIANCE DUO should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States: Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue JARDIANCE DUO.

Excessive Alcohol Intake: Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving JARDIANCE DUO.

Hepatic Impairment: Patients with hepatic impairment have developed cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of JARDIANCE DUO in patients with clinical or laboratory evidence of hepatic disease.

5.2 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. JARDIANCE DUO is not indicated for the treatment of patients with type 1 diabetes mellitus [see *Indications and Usage (1)*].

Patients treated with JARDIANCE DUO 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 JARDIANCE DUO may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, JARDIANCE DUO 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 JARDIANCE DUO, 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 JARDIANCE DUO for at least 3 days prior to surgery [see Clinical Pharmacology (12.2, 12.3)].

Consider monitoring for ketoacidosis and temporarily discontinuing JARDIANCE DUO 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 JARDIANCE DUO.

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

5.3 Volume Depletion

Empagliflozin can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine [see Adverse Reactions (6.1)]. 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 JARDIANCE DUO 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 JARDIANCE DUO. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.

5.4 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 (6)].

5.5 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when empagliflozin is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin [see Adverse Reactions (6.1)]. Metformin may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with JARDIANCE DUO.

5.6 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 JARDIANCE DUO 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 JARDIANCE DUO, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

5.7 Genital Mycotic Infections

Empagliflozin increases the risk for genital mycotic infections [*see Adverse Reactions (6.1)*]. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat as appropriate.

5.8 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions, (e.g., angioedema) in patients treated with empagliflozin. If a hypersensitivity reaction occurs, discontinue JARDIANCE DUO; treat promptly per standard of care, and monitor until signs and symptoms resolve. JARDIANCE DUO is contraindicated in patients with hypersensitivity to empagliflozin or any of the excipients in JARDIANCE DUO [*see Contraindications (4)*].

5.9 Vitamin B₁₂ Deficiency

In metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B₁₂ levels, was observed in approximately 7% of metformin-treated patients. Such decrease, possibly due to interference with B₁₂ absorption from the B₁₂-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B₁₂ supplementation. Certain individuals (those with inadequate vitamin B₁₂ or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B₁₂ levels. Measure hematologic parameters on an annual basis and vitamin B₁₂ at 2- to 3-year intervals in patients on Jardiance Duo and manage any abnormalities [*see Adverse Reactions (6.1)*].

6 ADVERSE REACTIONS

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

- Lactic Acidosis [*see Boxed Warning and Warnings and Precautions (5.1)*]
- Ketoacidosis [*see Warnings and Precautions (5.2)*]
- Volume Depletion [*see Warnings and Precautions (5.3)*]
- Urosepsis and Pyelonephritis [*see Warnings and Precautions (5.4)*]
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues [*see Warnings and Precautions (5.5)*]
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) [*see Warnings and Precautions (5.6)*]
- Genital Mycotic Infections [*see Warnings and Precautions (5.7)*]
- Hypersensitivity Reactions [*see Warnings and Precautions (5.8)*]
- Vitamin B₁₂ Deficiency [*see Warnings and Precautions (5.9)*]

6.1 Clinical Trials 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.

The safety of concomitantly administered empagliflozin (daily dose 10 mg and 25 mg) and metformin hydrochloride (mean daily dose of approximately 1800 mg) has been evaluated in 3456 patients with type 2 diabetes mellitus treated for 16 to 24 weeks, of which 926 patients received placebo, 1271 patients received a daily dose of empagliflozin 10 mg, and 1259 patients received a daily dose of empagliflozin 25 mg. Discontinuation of therapy due to adverse events across treatment groups was 3.0%, 2.8%, and 2.9% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Empagliflozin Add-On Combination Therapy with Metformin

In a 24-week placebo-controlled trial of empagliflozin 10 mg and 25 mg administered once daily added to metformin, there were no adverse reactions reported regardless of investigator assessment of causality in $\geq 5\%$ of patients and more commonly than in patients given placebo.

Empagliflozin Add-On Combination Therapy with Metformin and Sulfonylurea

In a 24-week placebo-controlled trial of empagliflozin 10 mg and 25 mg administered once daily added to metformin and sulfonylurea, adverse reactions reported regardless of investigator assessment of causality in $\geq 5\%$ of patients and more commonly than in patients given placebo are presented in Table 1 (see also Table 4).

Table 1 Adverse Reactions Reported in $\geq 5\%$ of Patients Treated with Empagliflozin added on to Metformin plus Sulfonylurea and Greater than with Placebo in a 24-week Placebo Controlled Clinical Study

Adverse Reactions	Placebo (%) n=225	Empagliflozin 10 mg (%) n=224	Empagliflozin 25 mg (%) n=217
Hypoglycemia	9.8	15.6	12.9
Urinary tract infection	6.7	9.4	6.9
Nasopharyngitis	4.9	8.0	6.0

Empagliflozin

The data in Table 2 are derived from a pool of four 24-week placebo-controlled trials and 18-week data from a placebo-controlled trial with basal insulin. Empagliflozin was used as monotherapy in one trial and as add-on therapy in four trials [see *Clinical Studies (14)*].

These data reflect exposure of 1976 patients to empagliflozin with a mean exposure duration of approximately 23 weeks. Patients received placebo (N=995), empagliflozin 10 mg (N=999), or empagliflozin 25 mg (N=977) once daily. The mean age of the population was 56 years and 3% were older than 75 years of age. More than half (55%) of the population was male; 46% were White, 50% were Asian, and 3% were Black or African American. At baseline, 57% of the population had diabetes more than 5 years and had a mean hemoglobin A1c (HbA1c) of 8%. Established microvascular complications of diabetes at baseline included diabetic nephropathy (7%), retinopathy (8%), or neuropathy (16%). Baseline renal function was normal or mildly impaired in 91% of patients and moderately impaired in 9% of patients (mean eGFR 86.8 mL/min/1.73 m²).

Table 2 shows common adverse reactions (excluding hypoglycemia) associated with the use of empagliflozin. The adverse reactions were not present at baseline, occurred more commonly on empagliflozin than on placebo and occurred in greater than or equal to 2% of patients treated with empagliflozin 10 mg or empagliflozin 25 mg.

Table 2 Adverse Reactions Reported in $\geq 2\%$ of Patients Treated with Empagliflozin and Greater than Placebo in Pooled Placebo-Controlled Clinical Studies of Empagliflozin Monotherapy or Combination Therapy

Adverse Reactions	Placebo (%) N=995	Empagliflozin 10 mg (%) N=999	Empagliflozin 25 mg (%) N=977
Urinary tract infection ^a	7.6	9.3	7.6
Female genital mycotic infections ^b	1.5	5.4	6.4
Upper respiratory tract infection	3.8	3.1	4.0
Increased urination ^c	1.0	3.4	3.2
Dyslipidemia	3.4	3.9	2.9
Arthralgia	2.2	2.4	2.3
Male genital mycotic infections ^d	0.4	3.1	1.6
Nausea	1.4	2.3	1.1

^aPredefined adverse event grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis

^bFemale genital mycotic infections include the following adverse reactions: vulvovaginal mycotic infection, vaginal infection, vulvitis, vulvovaginal candidiasis, genital infection, genital candidiasis, genital infection fungal, genitourinary tract infection, vulvovaginitis, cervicitis, urogenital infection fungal, vaginitis bacterial. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=481), empagliflozin 10 mg (N=443), empagliflozin 25 mg (N=420).

^cPredefined adverse event grouping, including, but not limited to, polyuria, pollakiuria, and nocturia

^dMale genital mycotic infections include the following adverse reactions: balanoposthitis, balanitis, genital infections fungal, genitourinary tract infection, balanitis candida, scrotal abscess, penile infection. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=514), empagliflozin 10 mg (N=556), empagliflozin 25 mg (N=557).

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

Volume Depletion

Empagliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. In the pool of five placebo-controlled clinical trials, adverse reactions related to volume depletion (e.g., blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolemia, orthostatic hypotension, and syncope) were reported by 0.3%, 0.5%, and 0.3% of patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Empagliflozin may increase the risk of hypotension in patients at risk for volume contraction [see *Use in Specific Populations* (8.5, 8.6)].

Increased Urination

In the pool of five placebo-controlled clinical trials, adverse reactions of increased urination (e.g., polyuria, pollakiuria, and nocturia) occurred more frequently on empagliflozin than on placebo (see Table 2). Specifically, nocturia was reported by 0.4%, 0.3%, and 0.8% of patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Hypoglycemia

The incidence of hypoglycemia by study is shown in Table 3. The incidence of hypoglycemia increased when empagliflozin was administered with insulin or sulfonylurea.

Table 3 Incidence of Overall^a and Severe^b Hypoglycemic Events in Placebo-Controlled Clinical Studies^c

Monotherapy (24 weeks)	Placebo (n=229)	Empagliflozin 10 mg (n=224)	Empagliflozin 25 mg (n=223)
Overall (%)	0.4	0.4	0.4
Severe (%)	0	0	0
In Combination with Metformin (24 weeks)	Placebo + Metformin (n=206)	Empagliflozin 10 mg + Metformin (n=217)	Empagliflozin 25 mg + Metformin (n=214)
Overall (%)	0.5	1.8	1.4
Severe (%)	0	0	0
In Combination with Metformin + Sulfonylurea (24 weeks)	Placebo (n=225)	Empagliflozin 10 mg + Metformin + Sulfonylurea (n=224)	Empagliflozin 25 mg + Metformin + Sulfonylurea (n=217)
Overall (%)	8.4	16.1	11.5
Severe (%)	0	0	0
In Combination with Pioglitazone +/- Metformin (24 weeks)	Placebo (n=165)	Empagliflozin 10 mg + Pioglitazone +/- Metformin (n=165)	Empagliflozin 25 mg + Pioglitazone +/- Metformin (n=168)
Overall (%)	1.8	1.2	2.4
Severe (%)	0	0	0
In Combination with Basal Insulin +/- Metformin (18 weeks^d)	Placebo (n=170)	Empagliflozin 10 mg (n=169)	Empagliflozin 25 mg (n=155)
Overall (%)	20.6	19.5	28.4
Severe (%)	0	0	1.3
In Combination with MDI Insulin +/- Metformin (18 weeks^d)	Placebo (n=188)	Empagliflozin 10 mg (n=186)	Empagliflozin 25 mg (n=189)
Overall (%)	37.2	39.8	41.3
Severe (%)	0.5	0.5	0.5

^aOverall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL

^bSevere hypoglycemic events: requiring assistance regardless of blood glucose

^cTreated set (patients who had received at least one dose of study drug)

^dInsulin dose could not be adjusted during the initial 18 week treatment period

Genital Mycotic Infections

In the pool of five placebo-controlled clinical trials, the incidence of genital mycotic infections (e.g., vaginal mycotic infection, vaginal infection, genital infection fungal, vulvovaginal candidiasis, and vulvitis) was increased in patients treated with empagliflozin compared to placebo, occurring in 0.9%, 4.1%, and 3.7% of patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with either empagliflozin 10 or 25 mg.

Genital mycotic infections occurred more frequently in female than male patients (see Table 2).

Phimosis occurred more frequently in male patients treated with empagliflozin 10 mg (less than 0.1%) and empagliflozin 25 mg (0.1%) than placebo (0%).

Urinary Tract Infections

In the pool of five placebo-controlled clinical trials, the incidence of urinary tract infections (e.g., urinary tract infection, asymptomatic bacteriuria, and cystitis) was increased in patients treated with empagliflozin compared

to placebo (see Table 2). Patients with a history of chronic or recurrent urinary tract infections were more likely to experience a urinary tract infection. The rate of treatment discontinuation due to urinary tract infections was 0.1%, 0.2%, and 0.1% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Urinary tract infections occurred more frequently in female patients. The incidence of urinary tract infections in female patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg was 16.6%, 18.4%, and 17.0%, respectively. The incidence of urinary tract infections in male patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg was 3.2%, 3.6%, and 4.1%, respectively [*see Use in Specific Populations (8.5)*].

Metformin

The most common (>5%) established adverse reactions due to initiation of metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

Laboratory Tests

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 m², 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. The range of mean baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups.

Increase in Hematocrit: In a pool of four placebo-controlled studies, 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.

Metformin

Decrease in Vitamin B12: In metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of patients.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during postapproval use. 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.

Empagliflozin

- Ketoacidosis
- Urosepsis and Pyelonephritis
- Necrotizing Fasciitis of the Perineum (Fournier's gangrene)
- Angioedema
- Acute Kidney Injury
- Skin Reactions (e.g., rash, urticaria)

Metformin hydrochloride

- Cholestatic, hepatocellular, and mixed hepatocellular liver injury

7 DRUG INTERACTIONS

Table 4 Clinically Relevant Interactions with JARDIANCE DUO

Carbonic Anhydrase Inhibitors	
Clinical Impact	Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis.
Intervention	Concomitant use of these drugs with JARDIANCE DUO may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients.
Drugs that Reduce Metformin Clearance	
Clinical Impact	Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis [see <i>Clinical Pharmacology</i> (12.3)].
Intervention	Consider the benefits and risks of concomitant use.
Alcohol	
Clinical Impact	Alcohol is known to potentiate the effect of metformin on lactate metabolism.
Intervention	Warn patients against excessive alcohol intake while receiving JARDIANCE DUO.
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 JARDIANCE DUO, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating JARDIANCE DUO. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.
Insulin or Insulin Secretagogues	
Clinical Impact	The risk of hypoglycemia is increased when empagliflozin is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin. Metformin may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue.
Intervention	Coadministration of JARDIANCE DUO 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.
Drugs Affecting Glycemic Control	
Clinical Impact	Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid.
Intervention	When such drugs are administered to a patient receiving JARDIANCE DUO, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving JARDIANCE DUO, the patient should be observed closely for 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

The Limited available data with JARDIANCE DUO or empagliflozin in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk (*see Data*). 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 JARDIANCE DUO, 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 metformin was administered to pregnant rats or rabbits (*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

Human Data

Published data from postmarketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data

Empagliflozin: Empagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at 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. These findings were not observed after a 13 week drug-free recovery period. These outcomes occurred with drug 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).

Metformin hydrochloride: Metformin hydrochloride did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits at up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of approximately 2- and 6-times a clinical dose of 2000 mg, based on body surface area (mg/m²) for rats and rabbits, respectively.

Empagliflozin and Metformin hydrochloride: No adverse developmental effects were observed when empagliflozin and metformin hydrochloride were coadministered to pregnant rats during the period of organogenesis at exposures of approximately 35- and 14-times the clinical AUC exposure of empagliflozin associated with the 10 mg and 25 mg doses, respectively, and 4-times the clinical AUC exposure of metformin associated with the 2000 mg dose.

8.2 Lactation

Risk Summary

There is limited information regarding the presence of JARDIANCE DUO or its components (empagliflozin or metformin) in human milk, the effects on the breastfed infant, or the effects on milk production. Limited published studies report that metformin is present in human milk (*see Data*). Empagliflozin is present in the milk of lactating rats (*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 JARDIANCE DUO is not recommended while breastfeeding.

Data

Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

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.

8.3 Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

8.4 Pediatric Use

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

8.5 Geriatric Use

Because renal function abnormalities can occur after initiating empagliflozin, metformin is substantially excreted by the kidney, and aging can be associated with reduced renal function, renal function should be assessed more frequently in elderly patients [see *Dosage and Administration (2.1)* and *Warnings and Precautions (5.1, 5.3)*].

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.

Metformin hydrochloride

clinical studies of metformin did not include sufficient numbers of geriatric patients to determine whether they respond differently from younger patients.

8.6 Renal Impairment

JARDIANCE DUO is contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m²).

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 (5.2)*], volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function.

Metformin hydrochloride

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. [see *Warnings and Precautions (5.1)*].

8.7 Hepatic Impairment

Use of metformin hydrochloride in patients with hepatic impairment has been associated with some cases of lactic acidosis. JARDIANCE DUO is not recommended in patients with hepatic impairment [see *Warnings and Precautions (5.1)*].

10 OVERDOSAGE

In the event of an overdose with JARDIANCE DUO, contact the Poison Control Center.

Overdose of metformin HCl has occurred, including ingestion of amounts greater than 50 grams. Lactic acidosis has been reported in approximately 32% of metformin overdose cases [see *Warnings and Precautions (5.1)*]. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions.

Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdose is suspected.

Removal of empagliflozin by hemodialysis has not been studied.

11 DESCRIPTION

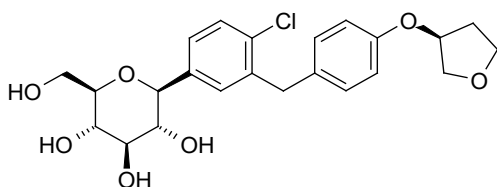
JARDIANCE DUO tablets for oral use contain empagliflozin and metformin hydrochloride.

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).

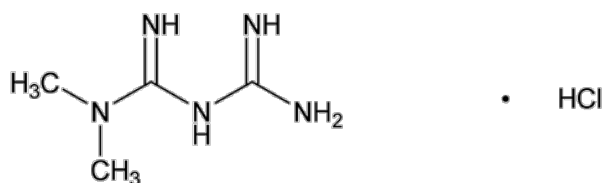
Its molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91. The structural formula is:



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.

Metformin hydrochloride

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is a biguanide. Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is:



JARDIANCE DUO

JARDIANCE DUO tablets for oral administration are available in six dosage strengths containing 5 mg empagliflozin and 500 mg metformin hydrochloride, 5 mg empagliflozin and 850 mg metformin hydrochloride, 5 mg empagliflozin and 1000 mg metformin hydrochloride, 12.5 mg empagliflozin and 500 mg metformin hydrochloride, 12.5 mg empagliflozin and 850 mg metformin hydrochloride, or 12.5 mg empagliflozin and 1000 mg metformin hydrochloride.

Each film-coated tablet of JARDIANCE DUO contains the following inactive ingredients: copovidone, corn starch, colloidal silicon dioxide, magnesium stearate. Film-coating: hypromellose, titanium dioxide, talc, polyethylene glycol 400, and yellow ferric oxide (5 mg/500 mg, 5 mg/850 mg, 5 mg/1000 mg) or red ferric oxide and black ferrosoferric oxide (12.5 mg/500 mg, 12.5 mg/850 mg, 12.5 mg/1000 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

JARDIANCE DUO

JARDIANCE DUO contains: empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and metformin, a biguanide.

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.

Metformin HCl

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. It is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike SUs, metformin does not produce hypoglycemia in either patients with type 2 diabetes mellitus or normal subjects (except in special circumstances) [see *Warnings and Precautions (5.5)*] and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

12.2 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 [see *Clinical Studies (14)*]. 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 dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

12.3 Pharmacokinetics

JARDIANCE DUO

Administration of 12.5 mg empagliflozin/1000 mg metformin hydrochloride under fed conditions resulted in a 9% decrease in AUC and a 28% decrease in $C_{\max}$ for empagliflozin, when compared to fasted conditions. For metformin, AUC decreased by 12% and $C_{\max}$ decreased by 26% compared to fasting conditions. The observed effect of food on empagliflozin and metformin is not considered to be clinically relevant.

Empagliflozin

Absorption

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-calorie 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.

Distribution

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%.

Elimination

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.

Metabolism

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.

Excretion 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.

Metformin

Absorption

The absolute bioavailability of a metformin hydrochloride 500-mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower $C_{\max}$, a 25% lower AUC, and a 35 minute prolongation of time to peak plasma concentration ($T_{\max}$) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin hydrochloride tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time.

Elimination

Metformin has a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Metabolism: Intravenous single-dose studies in normal subjects demonstrate that metformin does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Excretion: Following oral administration, approximately 90% of the absorbed drug is excreted via the renal route within the first 24 hours. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination.

Specific Populations

Renal Impairment

JARDIANCE DUO: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of JARDIANCE DUO in renally impaired patients have not been performed

Empagliflozin: In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m²), moderate (eGFR: 30 to less than 60 mL/min/1.73 m²), and severe (eGFR: less than 30 mL/min/1.73 m²) 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.

Metformin hydrochloride: In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased [*see Contraindications (4) and Warnings and Precautions (5.1)*].

Hepatic Impairment

JARDIANCE DUO: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of JARDIANCE DUO in hepatically impaired patients have not been performed [*see Warnings and Precautions (5.1)*].

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.

Metformin hydrochloride: No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

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 Use in Specific Populations (8.5)*].

Metformin hydrochloride: Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when analyzed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes mellitus, the antihyperglycemic effect of metformin was comparable in males and females.

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin HCl in patients with type 2 diabetes mellitus, the antihyperglycemic effect was comparable in Caucasians (n=249), Blacks (n=51), and Hispanics (n=24).

Geriatric

JARDIANCE DUO: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of JARDIANCE DUO in geriatric patients have not been performed [see *Warnings and Precautions (5.2) and Use in Specific Populations (8.5)*].

Empagliflozin: Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin based on a population pharmacokinetic analysis [see *Use in Specific Populations (8.5)*].

Metformin hydrochloride: Limited data from controlled pharmacokinetic studies of metformin hydrochloride in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared with healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Drug Interactions

Pharmacokinetic drug interaction studies with JARDIANCE DUO have not been performed; however, such studies have been conducted with the individual components empagliflozin and metformin HCl.

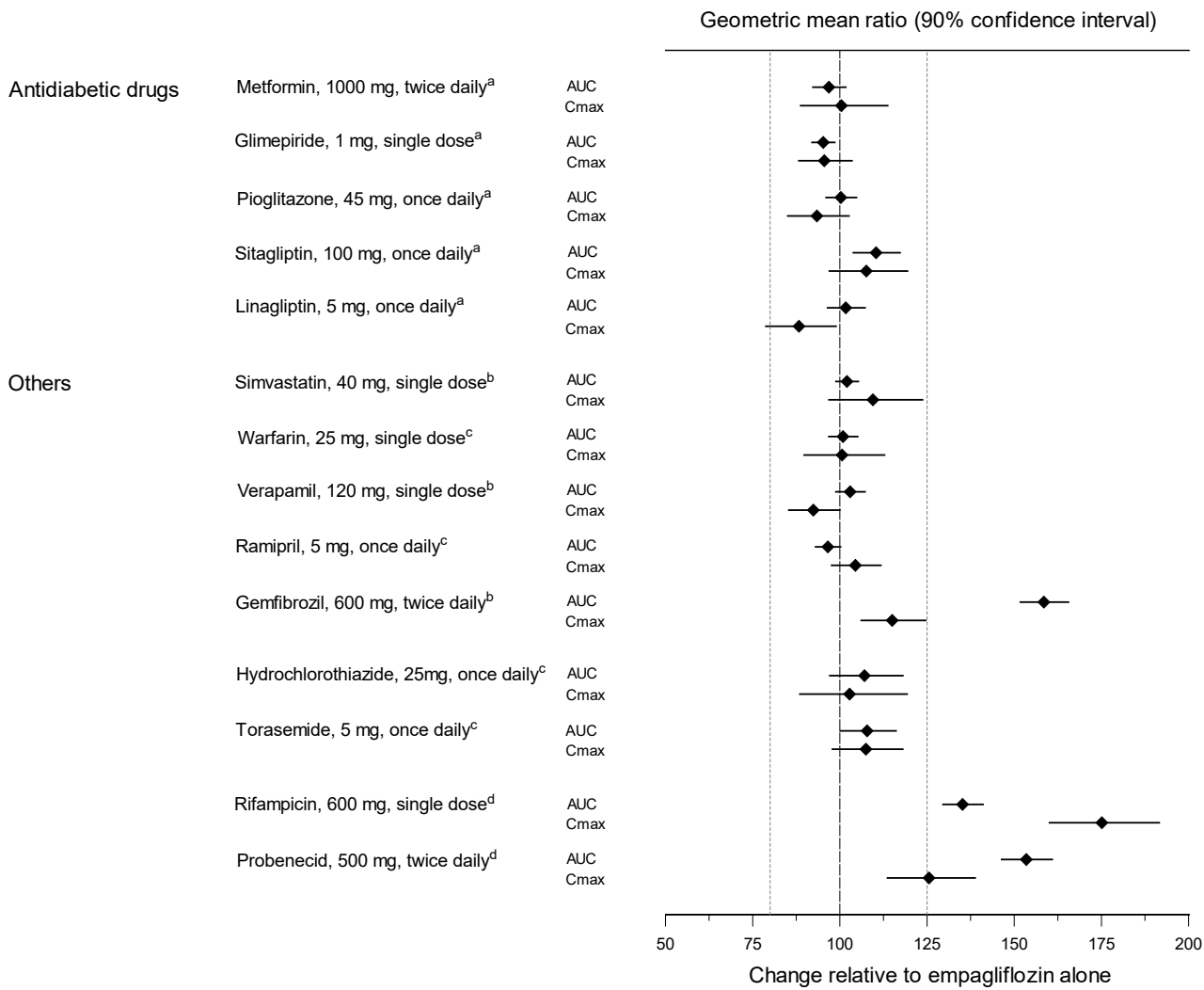
Empagliflozin

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 hydrochloride, 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.

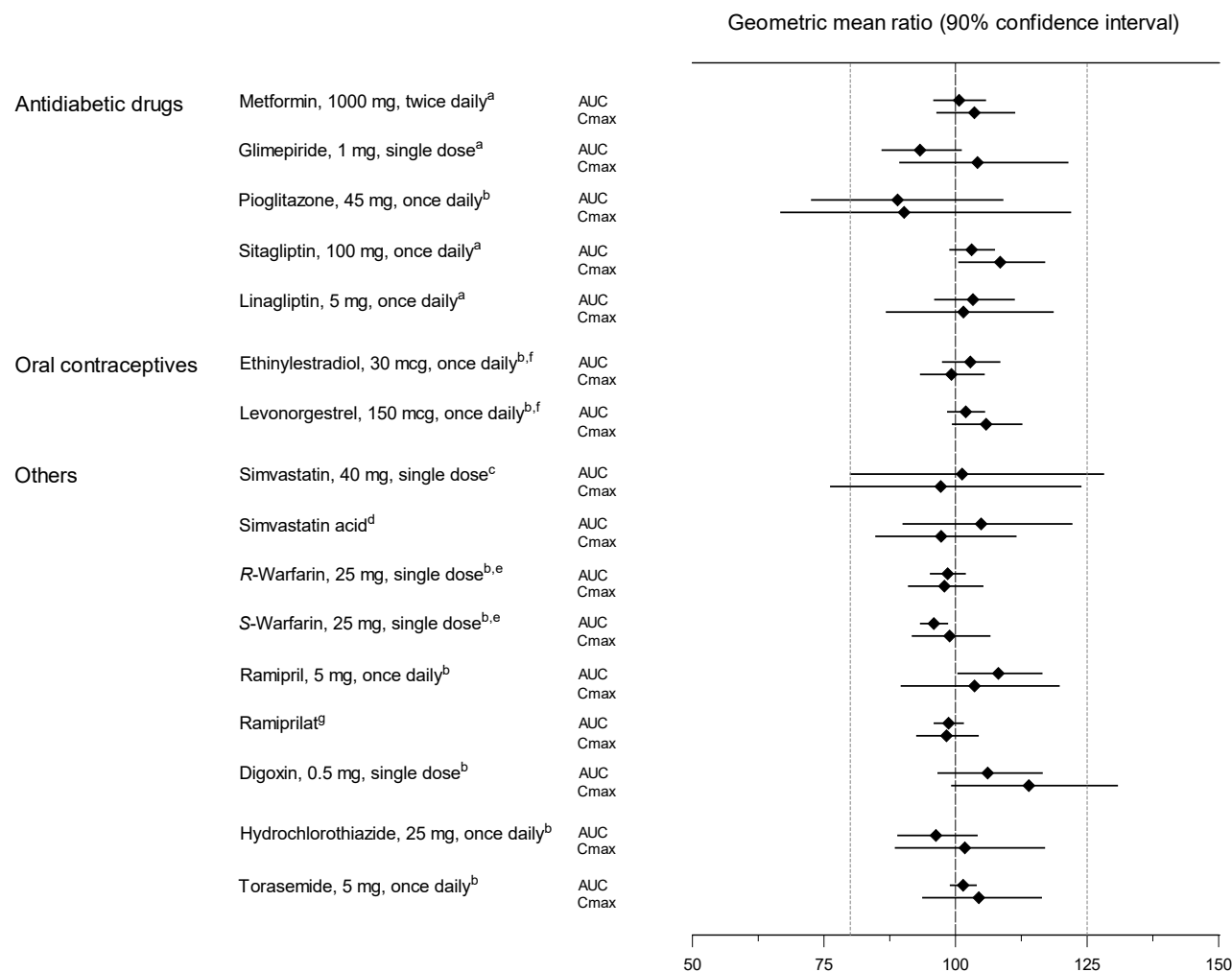
Figure 1 Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



^aempagliflozin, 50 mg, once daily; ^bempagliflozin, 25 mg, single dose; ^cempagliflozin, 25 mg, once daily; ^dempagliflozin, 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 with empagliflozin (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%)]



^aempagliflozin, 50 mg, once daily; ^bempagliflozin, 25 mg, once daily; ^cempagliflozin, 25 mg, single dose; ^dadministered as simvastatin; ^eadministered as warfarin racemic mixture; ^fadministered as Microgynon[®]; ^gadministered as ramipril

Table 5 Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin hydrochloride*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect=1.0		
				AUC [†]	C _{max}
Glyburide	5 mg	850 mg	metformin	0.91 _‡	0.93 _‡
Furosemide	40 mg	850 mg	metformin	1.09 _‡	1.22 _‡
Nifedipine	10 mg	850 mg	metformin	1.16	1.21
Propranolol	40 mg	850 mg	metformin	0.90	0.94
Ibuprofen	400 mg	850 mg	metformin	1.05 _‡	1.07 _‡
Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination [see Drug Interactions (7)].					
Cimetidine	400 mg	850 mg	metformin	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis [see Drug Interactions (7)].					
Topiramate**	100 mg	500 mg	metformin	1.25	1.17

* All metformin and coadministered drugs were given as single doses

[†] AUC = AUC(INF)

_‡ Ratio of arithmetic means

**At steady state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours; AUC = AUC(0-12hours)

Table 6 Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin hydrochloride*	Geometric Mean Ratio (ratio with/without metformin) No effect=1.0		
				AUC [†]	C _{max}
Glyburide	5 mg	500 mg§	glyburide	0.78 _‡	0.63 _‡
Furosemide	40 mg	850 mg	furosemide	0.87 _‡	0.69 _‡
Nifedipine	10 mg	850 mg	nifedipine	1.10§	1.08
Propranolol	40 mg	850 mg	propranolol	1.01§	0.94
Ibuprofen	400 mg	850 mg	ibuprofen	0.97¶	1.01¶
Cimetidine	400 mg	850 mg	cimetidine	0.95§	1.01

* All metformin and coadministered drugs were given as single doses

[†] AUC = AUC(INF) unless otherwise noted

_‡ Ratio of arithmetic means, p-value of difference <0.05

§ AUC(0-24 hours) reported

¶ Ratio of arithmetic means

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

JARDIANCE DUO

No carcinogenicity, mutagenicity, or impairment of fertility studies have been conducted with the combination of empagliflozin and metformin HCl. 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 metformin.

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).

Metformin hydrochloride

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2000 mg/kg/day based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*Salmonella typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 2 times the MRHD based on body surface area comparisons.

14 CLINICAL STUDIES

JARDIANCE DUO Glycemic Control Studies

In patients with type 2 diabetes, treatment with empagliflozin and metformin produced clinically and statistically significant improvements in HbA1c compared to placebo. Reductions in HbA1c were observed across subgroups including age, gender, race, and baseline body mass index (BMI).

Empagliflozin Add-On Combination Therapy with Metformin

A total of 637 patients with type 2 diabetes participated in a double-blind, placebo-controlled study to evaluate the efficacy and safety of empagliflozin in combination with metformin.

Patients with type 2 diabetes inadequately controlled on at least 1500 mg of metformin hydrochloride per day entered an open-label 2-week placebo run-in. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7 and 10% were randomized to placebo, empagliflozin 10 mg, or empagliflozin 25 mg.

At Week 24, treatment with empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (p-value <0.0001), FPG, and body weight compared with placebo (see Table 7).

Table 7 Results at Week 24 From a Placebo-Controlled Study for Empagliflozin used in Combination with Metformin

	Empagliflozin 10 mg + Metformin N=217	Empagliflozin 25 mg + Metformin N=213	Placebo + Metformin N=207
HbA1c (%)^a			
Baseline (mean)	7.9	7.9	7.9
Change from baseline (adjusted mean)	-0.7	-0.8	-0.1
Difference from placebo + metformin (adjusted mean) (95% CI)	-0.6 ^b (-0.7, -0.4)	-0.6 ^b (-0.8, -0.5)	--
Patients [n (%)] achieving HbA1c <7%	75 (38%)	74 (39%)	23 (13%)
FPG (mg/dL)^c			
Baseline (mean)	155	149	156
Change from baseline (adjusted mean)	-20	-22	6
Difference from placebo + metformin (adjusted mean)	-26	-29	--
Body Weight			
Baseline mean in kg	82	82	80
% change from baseline (adjusted mean)	-2.5	-2.9	-0.5
Difference from placebo (adjusted mean) (95% CI)	-2.0 ^b (-2.6, -1.4)	-2.5 ^b (-3.1, -1.9)	--

^aModified intent to treat population. Last observation on study (LOCF) was used to impute missing data at Week 24. At Week 24, 9.7%, 14.1%, and 24.6% was imputed for patients randomized to empagliflozin 10 mg, empagliflozin 25 mg, and placebo, respectively.

^bANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)

^cFPG (mg/dL); for empagliflozin 10 mg, n=216, for empagliflozin 25 mg, n=213, and for placebo, n=207

At Week 24, the systolic blood pressure was statistically significantly reduced compared to placebo by -4.1 mmHg (placebo-corrected, p-value <0.0001) for empagliflozin 10 mg and -4.8 mmHg (placebo-corrected, p-value <0.0001) for empagliflozin 25 mg.

Empagliflozin Initial Combination Therapy with Metformin

A total of 1364 patients with type 2 diabetes participated in a double-blind, randomized, active-controlled study to evaluate the efficacy and safety of empagliflozin in combination with metformin as initial therapy compared to the corresponding individual components.

Treatment-naïve patients with inadequately controlled type 2 diabetes entered an open-label placebo run-in 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 to one of 8 active-treatment arms: empagliflozin 10 mg or 25 mg; metformin hydrochloride 1000 mg, or 2000 mg; empagliflozin 10 mg in combination with 1000 mg or 2000 mg metformin hydrochloride; or empagliflozin 25 mg in combination with 1000 mg or 2000 mg metformin hydrochloride.

At Week 24, initial therapy of empagliflozin in combination with metformin provided statistically significant reductions in HbA1c (p-value <0.01) compared to the individual components (see Table 8).

Table 8 Glycemic Parameters at 24 Weeks in a Study Comparing Empagliflozin and Metformin to the Individual Components as Initial Therapy

	Empagliflozin 10 mg + Metformin 1000 mg ^a N=161	Empagliflozin 10 mg + Metformin 2000 mg ^a N=167	Empagliflozin 25 mg + Metformin 1000 mg ^a N=165	Empagliflozin 25 mg + Metformin 2000 mg ^a N=169	Empagliflozin 10 mg N=169	Empagliflozin 25 mg N=163	Metformin 1000 mg ^a N=167	Metformin 2000 mg ^a N=162
HbA1c (%)								
Baseline (mean)	8.7	8.7	8.8	8.7	8.6	8.9	8.7	8.6
Change from baseline (adjusted mean)	-2.0	-2.1	-1.9	-2.1	-1.4	-1.4	-1.2	-1.8
Comparison vs empagliflozin (adjusted mean) (95% CI)	-0.6 ^b (-0.9, -0.4)	-0.7 ^b (-1.0, -0.5)	-0.6 ^c (-0.8, -0.3)	-0.7 ^c (-1.0, -0.5)	--	--	--	--
Comparison vs metformin (adjusted mean) (95% CI)	-0.8 ^b (-1.0, -0.6)	-0.3 ^b (-0.6, -0.1)	-0.8 ^c (-1.0, -0.5)	-0.3 ^c (-0.6, -0.1)	--	--	--	--
Patients [n (%)] achieving HbA1c <7%	96 (63%)	112 (70%)	91 (57%)	111 (68%)	69 (43%)	51 (32%)	63 (38%)	92 (58%)

^aMetformin hydrochloride total daily dose, administered in two equally divided doses per day.

^bp-value ≤0.0062 (modified intent to treat population [observed case] MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c).

^cp-value ≤0.0056 (modified intent to treat population [observed case] MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c).

Empagliflozin Add-On Combination Therapy with Metformin and Sulfonylurea

A total of 666 patients with type 2 diabetes participated in a double-blind, placebo-controlled study to evaluate the efficacy and safety of empagliflozin in combination with metformin plus a sulfonylurea.

Patients with inadequately controlled type 2 diabetes on at least 1500 mg per day of metformin hydrochloride and on a sulfonylurea, entered a 2-week open-label placebo run-in. At the end of the run-in, patients who remained inadequately controlled and had an HbA1c between 7% and 10% were randomized to placebo, empagliflozin 10 mg, or empagliflozin 25 mg.

Treatment with empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (p-value <0.0001), FPG, and body weight compared with placebo (see Table 9).

Table 9 Results at Week 24 from a Placebo-Controlled Study for Empagliflozin in Combination with Metformin and Sulfonylurea

	Empagliflozin 10 mg + Metformin + SU N=225	Empagliflozin 25 mg + Metformin + SU N=216	Placebo + Metformin + SU N=225
HbA1c (%)^a			
Baseline (mean)	8.1	8.1	8.2
Change from baseline (adjusted mean)	-0.8	-0.8	-0.2
Difference from placebo (adjusted mean) (95% CI)	-0.6 ^b (-0.8, -0.5)	-0.6 ^b (-0.7, -0.4)	--
Patients [n (%)] achieving HbA1c <7%	55 (26%)	65 (32%)	20 (9%)
FPG (mg/dL)^c			
Baseline (mean)	151	156	152
Change from baseline (adjusted mean)	-23	-23	6
Difference from placebo (adjusted mean)	-29	-29	--
Body Weight			
Baseline mean in kg	77	78	76
% change from baseline (adjusted mean)	-2.9	-3.2	-0.5
Difference from placebo (adjusted mean) (95% CI)	-2.4 ^b (-3.0, -1.8)	-2.7 ^b (-3.3, -2.1)	--

^aModified intent to treat population. Last observation on study (LOCF) was used to impute missing data at Week 24. At Week 24, 17.8%, 16.7%, and 25.3% was imputed for patients randomized to empagliflozin 10 mg, empagliflozin 25 mg, and placebo, respectively.

^bANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)

^cFPG (mg/dL); for empagliflozin 10 mg, n=225, for empagliflozin 25 mg, n=215, for placebo, n=224

Active-Controlled Study vs Glimepiride in Combination with Metformin

The efficacy of empagliflozin was evaluated in a double-blind, glimepiride-controlled, study in 1545 patients with type 2 diabetes with insufficient glycemic control despite metformin therapy.

Patients with inadequate glycemic control and an HbA1c between 7% and 10% after a 2-week run-in period were randomized to glimepiride or empagliflozin 25 mg.

At Week 52, empagliflozin 25 mg and glimepiride lowered HbA1c and FPG (see Table 10, Figure 3). The difference in observed effect size between empagliflozin 25 mg and glimepiride excluded the pre-specified non-inferiority margin of 0.3%. The mean daily dose of glimepiride was 2.7 mg and the maximal approved dose in the United States is 8 mg per day.

Table 10 Results at Week 52 from an Active-Controlled Study Comparing Empagliflozin to Glimepiride as Add-On Therapy in Patients Inadequately Controlled on Metformin

	Empagliflozin 25 mg + Metformin N=765	Glimepiride + Metformin N=780
HbA1c (%)^a		
Baseline (mean)	7.9	7.9
Change from baseline (adjusted mean)	-0.7	-0.7
Difference from glimepiride (adjusted mean) (97.5% CI)	-0.07 ^b (-0.15, 0.01)	--
FPG (mg/dL)^d		
Baseline (mean)	150	150
Change from baseline (adjusted mean)	-19	-9
Difference from glimepiride (adjusted mean)	-11	--
Body Weight		
Baseline mean in kg	82.5	83
% change from baseline (adjusted mean)	-3.9	2.0
Difference from glimepiride (adjusted mean) (95% CI)	-5.9 ^c (-6.3, -5.5)	--

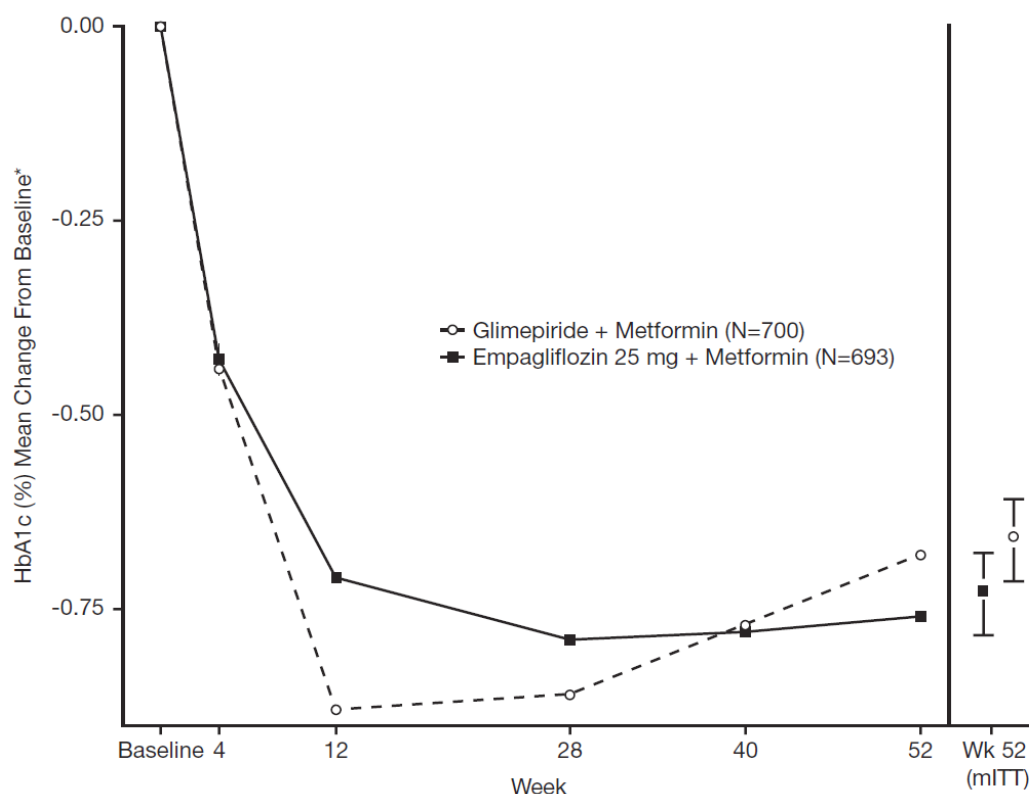
^aModified intent to treat population. Last observation on study (LOCF) was used to impute data missing at Week 52. At Week 52, data was imputed for 15.3% and 21.9% of patients randomized to empagliflozin 25 mg and glimepiride, respectively.

^bNon-inferior, ANCOVA model p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region)

^cANCOVA p-value <0.0001 (Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)

^dFPG (mg/dL); for empagliflozin 25 mg, n=764, for glimepiride, n=779

Figure 3 Adjusted mean HbA1c Change at Each Time Point (Completers) and at Week 52 (mITT Population) - LOCF



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

At Week 52, the adjusted mean change from baseline in systolic blood pressure was -3.6 mmHg, compared to 2.2 mmHg for glimepiride. The differences between treatment groups for systolic blood pressure was statistically significant (p-value <0.0001).

At Week 104, the adjusted mean change from baseline in HbA1c was -0.75% for empagliflozin 25 mg and -0.66% for glimepiride. The adjusted mean treatment difference was -0.09% with a 97.5% confidence interval of (-0.32%, 0.15%), excluding the pre-specified non-inferiority margin of 0.3%. The mean daily dose of glimepiride was 2.7 mg and the maximal approved dose in the United States is 8 mg per day. The Week 104 analysis included data with and without concomitant glycemic rescue medication, as well as off-treatment data. Missing data for patients not providing any information at the visit were imputed based on the observed off-treatment data. In this multiple imputation analysis, 13.9% of the data were imputed for empagliflozin 25 mg and 12.9% for glimepiride.

At Week 104, empagliflozin 25 mg daily resulted in a statistically significant difference in change from baseline for body weight compared to glimepiride (-3.1 kg for empagliflozin 25 mg vs. +1.3 kg for glimepiride; ANCOVA-LOCF, p-value <0.0001).

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 m². At baseline, patients were treated with one (~30%) or more (~70%) antidiabetic medications including metformin (74%), insulin (48%), and sulfonylurea (43%).

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 11 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 11 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)

^aTreated set (patients who had received at least one dose of study drug)

^bp-value for superiority (2-sided) 0.04

^cTotal number of events

Figure 4 Estimated Cumulative Incidence of First MACE

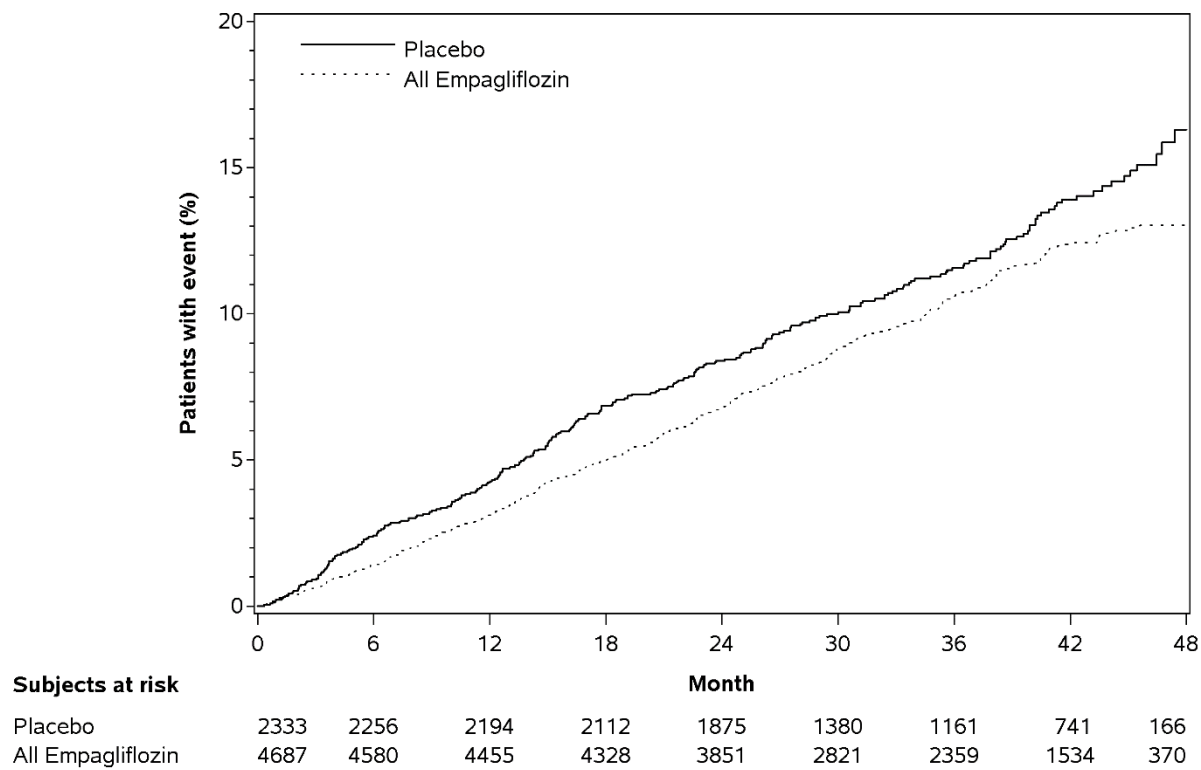
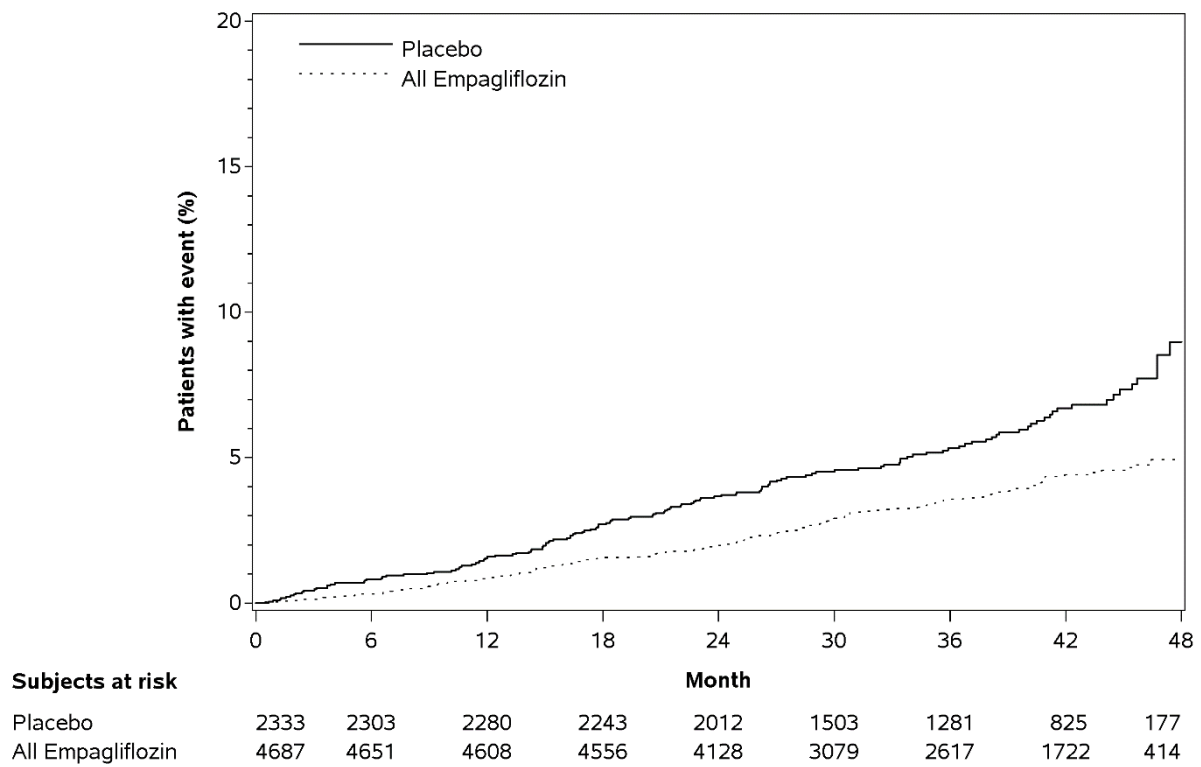


Figure 5 Estimated Cumulative Incidence of Cardiovascular Death



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 m² (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).

16 HOW SUPPLIED/STORAGE AND HANDLING

JARDIANCE DUO tablets are available as follows:

Tablet Strength	Film-Coated Tablet, Color/Shape	Tablet Markings	Package Size
5 mg Empagliflozin 500 mg Metformin HCl	orange yellow, oval, biconvex	Boehringer Ingelheim company symbol and “S5” debossed on one side; the other side is debossed with “500”	4-1000 tablets in PCTFE blister of paper box.
5 mg Empagliflozin 850 mg Metformin HCl	yellowish white, oval, biconvex	Boehringer Ingelheim company symbol and “S5” debossed on one side; the other side is debossed with “850”	4-1000 tablets in PCTFE blister of paper box.
5 mg Empagliflozin 1000 mg Metformin HCl	brownish yellow, oval, biconvex	Boehringer Ingelheim company symbol and “S5” debossed on one side; the other side is debossed with “1000”	4-1000 tablets in PCTFE blister of paper box.
12.5 mg Empagliflozin 500 mg Metformin HCl	pale brownish purple, oval, biconvex	Boehringer Ingelheim company symbol and “S12” debossed on one side; the other side is debossed with “500”	4-1000 tablets in PCTFE blister of paper box.
12.5mg Empagliflozin 850 mg Metformin HCl	pinkish white, oval, biconvex	Boehringer Ingelheim company symbol and “S12” debossed on one side; the other side is debossed with “850”	4-1000 tablets in PCTFE blister of paper box.
12.5 mg Empagliflozin 1000 mg Metformin HCl	dark brownish purple, oval, biconvex	Boehringer Ingelheim company symbol and “S12” debossed on one side; the other side is debossed with “1000”	4-1000 tablets in PCTFE blister of paper box.

Storage

Store below 30°C. Store in a safe place out of reach of children.

17 PATIENT COUNSELING INFORMATION

Lactic Acidosis

Inform patients of the risks of lactic acidosis due to metformin, its symptoms, and conditions that predispose to its development. Advise patients to discontinue JARDIANCE DUO immediately and to notify their doctor promptly if unexplained hyperventilation, malaise, myalgia, unusual somnolence, or other nonspecific symptoms occur. Counsel patients against excessive alcohol intake and inform patients about the importance of regular testing of renal function while receiving JARDIANCE DUO.

Instruct patients to inform their doctor that they are taking JARDIANCE DUO prior to any surgical or radiological procedure, as temporary discontinuation may be required until renal function has been confirmed to be normal [see *Warnings and Precautions (5.1)*].

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 JARDIANCE DUO and seek medical attention immediately [see *Warnings and Precautions (5.2)*].

Volume Depletion

Inform patients that symptomatic hypotension may occur with JARDIANCE DUO and advise them to contact their healthcare provider if they experience such symptoms [see *Warnings and Precautions (5.3)*]. Inform patients that dehydration may increase the risk for hypotension, and to maintain adequate fluid intake.

Serious 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 (5.4)*].

Hypoglycemia

Inform patients that the risk of hypoglycemia is increased when JARDIANCE DUO 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 (5.5)*].

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 JARDIANCE DUO. 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 (5.6)*].

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 (5.7)*].

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 (5.7)*].

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions, such as urticaria and angioedema, have been reported with empagliflozin, a component of JARDIANCE DUO. Advise patients to report immediately any skin

reaction or angioedema, and to discontinue the drug until they have consulted prescribing physician [*see Warnings and Precautions (5.8)*].

Vitamin B₁₂ Deficiency

Inform patients about importance of regular hematological parameters while receiving JARDIANCE DUO [*see Warnings and Precautions (5.9)*].

Laboratory Tests

Inform patients that elevated glucose in urinalysis is expected when taking JARDIANCE DUO.

Pregnancy

Advise pregnant patients, and patients of reproductive potential of the potential risk to a fetus with treatment with JARDIANCE DUO [*see Use in Specific Populations (8.1)*]. Instruct patients to report pregnancies to their physicians as soon as possible.

Lactation

Advise patients that breastfeeding is not recommended during treatment with JARDIANCE DUO [*see Use in Specific Populations (8.2)*].

Patients of Reproductive Potential

Inform patients that treatment with metformin may result in ovulation in some premenopausal anovulatory patients which may lead to unintended pregnancy [*see Use in Specific Populations (8.3)*].

Missed Dose

Instruct patients to take JARDIANCE DUO 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.

MFD. by

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For

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