糖漸平® 膜衣錠 5 毫克
Trajenta® 5mg Film-Coated Tablets

衛署藥輸字第 025537 號

1 適應症

1.1 第二型糖尿病

1.2 使用上的重要限制

TRAJENTA 不可用於第一型糖尿病病人，亦不可用於治療糖尿病酮酸中毒(ketoacidosis)，因為 TRAJENTA 對於此並無效。

由於尚未針對具有胰臟炎病史的病人進行 TRAJENTA 的相關研究，因此目前仍不瞭解具有胰臟炎病史之病人使用 TRAJENTA，是否會增加發生胰臟炎的風險*（請參閱警語及注意事項(5.1)）*。

2 用法用量

本藥須由醫師處方使用。

2.1 建議劑量

TRAJENTA 的建議劑量為 5mg，成人每天一次。

可單獨使用亦可與 metformin、sulfonylurea、insulin、PPARγ 作用劑(如 thiazolidinediones)合併使用，作為飲食控制及運動的輔助療法，以改善血糖的控制*（請參閱臨床試驗(14.1)）*。

TRAJENTA 錠劑可與食物一起服用，亦可空腹服用。

2.2 與磺醯尿素類藥物(Sulfonylurea)或胰島素併用

TRAJENTA 與胰島素促分泌物質(insulin secretagogue)（例如，磺醯尿素類藥物）或胰島素併用時，可能須降低胰島素促分泌物質或胰島素的劑量，以減少低糖血症的風險*（請參閱警語及注意事項(5.2)）*。

3 劑型與藥物含量

TRAJENTA (linagliptin) 5mg 錠劑為淺紅色、圓形、兩面中央凸起、邊緣呈斜面的膜衣錠，兩面分別壓印「D5」字樣及百靈佳殷格翰公司標誌。

4 禁忌症

TRAJENTA 禁用於對 linagliptin 或其賦形劑出現過敏反應的病人（例如：急性過敏、血管性水腫、鱗片狀脫落性皮膚疾病、蕁麻疹或支氣管過敏）*(請參閱警語及注意事項（5.3）、不良反應(6)）*。

5 警語及注意事項

5.1 胰臟炎

於 TRAJENTA 上市後，使用的病人中曾通報發生急性胰臟炎的案例，包括致命的胰臟炎案例。在 CARMELINA 試驗 *(請參閱臨床試驗(14.2))*中，有 9 名（0.3%）接受 TRAJENTA 治療的病人和 5 名（0.1%）接受安慰劑治療的病人發生急性胰臟炎。在 CARMELINA 試驗中有 2 名接受 TRAJENTA 治療發生急性胰臟炎的病人，追蹤報告為死亡。曾有服用 TRAJENTA 的病人發生急性胰臟炎(包括致命案例)的上市後報告。

因此請特別注意是否出現胰臟炎的潛在徵兆與症狀，若懷疑出現胰臟炎，請立即停止使用 TRAJENTA 並開始實施適當的處置。目前仍不瞭解具有胰臟炎病史的病人使用 TRAJENTA，是否會增加發生胰臟

炎的風險。

5.2 與已知會造成低血糖症的藥物併用

已知胰島素促分泌物質或胰島素會造成低血糖症。在臨床試驗中，相較於安慰劑，TRAJENTA 與胰島素促分泌物質（例如，磺醯尿素類藥物）或胰島素併用時的低血糖症發生率較高*（請參閱不良反應(6.1)）*，而嚴重腎功能障礙之受試者併用 TRAJENTA 與胰島素時，低血糖症發生率較高*（請參閱不良反應(6.1)）*；因此，與 TRAJENTA 併用時，可能須降低胰島素促分泌物質或胰島素的劑量，以減少低血糖症的風險。

5.3 過敏反應

TRAJENTA 的上市後報告中曾有嚴重過敏反應的案例，包括急性過敏、血管水腫和鱗片狀脫落性皮膚疾病。這些反應的主要發生時間在 TRAJENTA 治療開始後 3 個月內，有些案例發生在使用第一次劑量之後。如果疑似出現嚴重過敏反應，請停用 TRAJENTA，評估事件的其他可能原因，並改用其他的糖尿病治療。

使用其他雙肽胜肽酶-4 (DPP-4) 抑制劑，也曾有血管水腫的案例。對使用其他 DPP-4 抑制劑曾有血管水腫病史的病人，應特別審慎，這類病人使用 TRAJENTA 是否更容易發生血管水腫，目前尚不清楚。

5.4 嚴重和行動不便之關節疼痛

雙肽胜肽酶-4(DPP-4)抑制劑的上市後報告中曾有嚴重和造成行動不便之關節疼痛案例。這些病人是在開始用藥後第一天或幾年後發生關節痛症狀。病人停藥後則可緩解症狀。部分病人於重新服用相同的藥物或不同的 DPP-4 抑制劑時症狀會復發。在使用 DPP-4 抑制劑的病人，需考慮 DPP-4 抑制劑可能為導致嚴重且持續性關節疼痛的原因並適時停藥。

5.5 大皰性類天皰瘡 (Bullous Pemphigoid)

在CARMELINA試驗(請參閱臨床試驗(14.2))中，有7名（0.2%）接受 TRAJENTA治療的病人發生大皰性類天皰瘡，其中3人（0.1%）需要住院治療；接受安慰劑治療者則無此種病例。DPP-4抑制劑的上市後報告中，曾有需要住院的大皰性類天皰瘡案例。在所報告的病例中，病人通常可在接受局部或全身性免疫抑制治療與停止使用DPP-4抑制劑之後復原。請告知病人，在接受TRAJENTA時出現水泡或糜爛應通報。若懷疑有大皰性類天皰瘡，應停止使用TRAJENTA，並考慮轉診皮膚科醫師接受診斷及適當的治療。

6 不良反應

下列嚴重不良反應將在以下或處方資訊的其他部分描述：

- 胰臟炎 *[請參閱警語及注意事項 (5.1)]*
- 與已知會造成低血糖症的藥物併用 [*請參閱警語及注意事項(5.2)]*
- 過敏反應 [*請參閱警語及注意事項 (5.3)*]
- 嚴重和行動不便之關節疼痛 *[請參閱警語及注意事項 (5.4)]*
- 大皰性類天皰瘡 *[請參閱警語及注意事項 (5.5)]*

6.1 臨床試驗經驗

由於臨床試驗係於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，無法與另一種藥物的臨床試驗中所觀察到者直接進行比較，亦無法反映實際臨床狀況中的發生率。

TRAJENTA 5 mg（一天一次）的安全性評估已於臨床試驗中針對第二型糖尿病病人進行評估，包括 14

項以安慰劑對照、1 項以有效藥物做對照，以及 1 項以嚴重腎功能障礙者為對象的試驗。在 14 項安慰劑對照試驗中，經隨機分配使用 TRAJENTA 5 mg（一天一次）者共 3625 人、而使用安慰劑者共 2176 人。病人於試驗中接受 TRAJENTA 治療的平均時間為 29.6 週，追蹤工作最長持續 78 週。

TRAJENTA 5 mg（一天一次）單獨療法已在 3 項分別為期 18 週與 24 週、以安慰劑對照的試驗，以及另外 5 項為期短於 18 週、以安慰劑對照的試驗，並於 6 項以安慰劑對照的試驗中，針對 TRAJENTA 與其他降高血糖藥物併用進行研究：其中 2 項與 metformin 併用（治療時間分別為 12 週與 24 週）；1 項與磺醯尿素類藥物併用（治療時間 18 週）；1 項與 metformin 及磺醯尿素類藥物併用（治療時間 24 週）；1 項與 pioglitazone 併用（治療時間 24 週）；以及 1 項與胰島素併用（主要試驗終點於第 24 週）。

針對 14 項以安慰劑對照的試驗進行整合分析後，接受 TRAJENTA (n = 3625)者的發生率≥2%，且高於安慰劑組(n = 2176)的不良反應如表 1 所示。整體不良反應於 Trajenta 治療組與安慰劑組發生率相當。

表 1：在以安慰劑對照的 TRAJENTA 單獨療法或合併療法臨床試驗中，在 TRAJENTA 組發生率≥2%，且高於安慰劑組的不良反應

	病人數(%)	
	TRAJENTA 5 mg **n = 3625**	安慰劑 **n = 2176**
鼻咽炎	254 (7.0)	132 (6.1)
腹瀉	119 (3.3)	65 (3.0)
咳嗽	76 (2.1)	30 (1.4)

TRAJENTA 搭配特定糖尿病藥物使用時，TRAJENTA 5 mg 與安慰劑的不良反應比例如下：泌尿道感染(3.1%/0%) 與高三酸甘油酯症(2.4%/0%)（添加於磺醯尿素類藥物時）；高脂血症(2.7%/0.8%)與體重增加(2.3%/0.8%)（添加於 pioglitazone 時）；以及便秘(2.1%/1%)（添加於基礎胰島素治療時）。
在 TRAJENTA 臨床試驗中所提出的其他不良反應包括過敏（例如：蕁麻疹、血管性水腫、局部脫皮或支氣管過敏）與肌肉痛。
在一項比較 TRAJENTA 與 glimepiride 的對照試驗中，所有的受試者亦同時接受 metformin 治療，在為期 104 週的治療之後，TRAJENTA 組(n = 776)發生率≥5%且高於磺醯尿素類藥物組(n = 775)的不良反應為背痛（分別為 9.1%與 8.4%）、關節痛（8.1%與 6.1%）、上呼吸道感染（8.0%與 7.6%）、頭痛（6.4%與 5.2%）、咳嗽（6.1%與 4.9%）以及肢體疼痛（5.3%比上 3.9%）。

在臨床試驗中，接受 TRAJENTA 治療者於每一萬病人年中出現 15.2 例胰臟炎，接受對照藥物(安慰劑與活性對照藥物磺醯尿素)者，則於每一萬病人年中出現 3.7 例。在使用最後一劑 linagliptin 之後，又出現另外 3 個胰臟炎病例。

低血糖症

表 2 總結 TRAJENTA 與安慰劑組對照研究中的低血糖發生率。當 TRAJENTA 與磺醯尿素類藥物(Sulfonylurea)或胰島素一起給藥時，低血糖的發生率增加。

表 2: 第二型糖尿病病人於 TRAJENTA 與安慰劑組對照研究中的低血糖發生率(%)

合併磺醯尿素類藥物(18 週)	**安慰劑(N=84)**	**TRAJENTA (N=161)**
低血糖(血糖 <54 mg/dL)	1.2%	1.9%
嚴重* 低血糖(%)	0%	0%
合併 Metformin 和磺醯尿素類藥物 (24 週)	**安慰劑(N=263)**	**TRAJENTA (N=792)**
低血糖(血糖 <54 mg/dL)	5.3%	8.1%
嚴重* 低血糖(%)	0.8%	0.6%
合併基礎胰島素(52 週)	**安慰劑(N=630)**	**TRAJENTA (N=631)**
低血糖(血糖 <54 mg/dL)	21.6%	19.8%
嚴重* 低血糖(%)	1.1%	1.7%

*因低血糖需要他人協助施予碳水化合物、升糖素，或採取急救行動。

在 TRAJENTA 對照活性藥物 (glimepiride)的心血管安全性臨床試驗(CAROLINA)，其治療時間中位數為 5.9 年，TRAJENTA 組(N=3014)和 glimepiride 組(N=3000)嚴重低血糖的發生率分別為 0.3%和 2.2%。

腎功能

以 133 位嚴重腎功能不全（腎絲球過濾估計值低於 30 mL／分）病人為對象，於既有糖尿病療法加入 TRAJENTA 進行為期 52 週的治療，並與安慰劑比較的試驗中，最初 12 週內背景糖尿病療法均維持穩定，包括胰島素、磺醯尿素類藥物、glinides 及 pioglitazone。試驗剩餘期間內則可對背景糖尿病療法進行劑量調整。

一般而言，嚴重低血糖症等不良事件的發生率與其他 TRAJENTA 試驗的通報狀況相近，然觀察所得的低血糖發生率較高（TRAJENTA 為 63%，而安慰劑為 49%），其原因為前 12 週維持穩定背景降醣治療期間無症狀低血糖事件較多。接受 TRAJENTA 與安慰劑治療的病人分別有 10 位(15%)及 11 位(17%)曾通報至少一起經確認之症狀性低血糖（且血糖儀數值低於 54mg/dL）。在同一時段中，接受 TRAJENTA 與安慰劑治療的病人均有 3 位（TRAJENTA 為 4.4%，安慰劑為 4.6%）發生嚴重低血糖事件（定義為需要他人主動協助施予碳水化合物、升糖素，或採取急救行動）的案例，而接受 TRAJENTA 與安慰劑治療的病人中，發生危及生命或需要住院的事件者分別為 2 位(2.9%)與 1 位(1.5%)病人。

經 52 週治療後，經平均腎絲球過濾率估算值及肌酸酐清除率測定腎功能，與安慰劑相比未發生變化。

實驗室檢測

接受 TRAJENTA 5mg 與接受安慰劑治療者的實驗室檢測結果相近。

尿酸增加： TRAJENTA 組發生率較安慰劑組高至少 1%的實驗室檢測值變化為尿酸增加（安慰劑組為 1.3%，TRAJENTA 組為 2.7 %）。

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

*澱粉酶增加：*在第二型糖尿病病人比較TRAJENTA治療組和glimpiride治療組之心血管安全性臨床試驗，TRAJENTA治療組與glimpiride治療組觀察到澱粉酶濃度高於正常值上限3倍的病人分別有1%與0.5%

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因並無胰臟炎徵兆和症狀發生，使用TRAJENTA發生脂酶和澱粉酶濃度升高的臨床意義尚不清楚 *(詳見警語及注意事項 (5.1))*。

生命徵象
接受 TRAJENTA 治療者的生命徵象並未出現具臨床意義的變化。

6.2 上市後使用經驗
在 TRAJENTA 上市後期間所新增的不良反應。由於這些反應是由不確定人數之族群自願通報，因此無法正確預測其發生率，也無法確立與藥物暴露之間的因果關係。

- 急性胰臟炎，包含致命的胰臟炎 *（請參閱適應症(1.2)）*
- *過敏性反應，包括急性過敏、血管水腫和鱗片狀脫落性皮膚疾病*
- 嚴重和行動不便之關節疼痛
- 大皰性類天皰瘡
- 皮疹
- 口腔潰瘍、口腔炎
- 橫紋肌溶解症

7 藥物交互作用
7.1 P-gp 或 CYP3A4 酵素之誘發劑
Rifampin 可降低 linagliptin 的暴露量，顯示 TRAJENTA 與強效 P-gp 或 CYP 3A4 誘發劑併用時，其功效可能降低。因此，當 linagliptin 須與強效 P-gp 或 CYP 3A4 誘發劑併用時，強烈建議應改用其他替代療法 *（請參閱臨床藥理學(12.3)）*。

7.2 **胰島素促泌劑或胰島素**
TRAJENTA 與胰島素促泌劑(例如磺醯尿素類藥物)或胰島素併用時，可能須降低胰島素促泌劑或胰島素的劑量，以減少低血糖症的風險 *[請參閱警語及注意事項 (5.2)]*。

8 在特定族群的使用
8.1 懷孕

風險摘要
在懷孕婦女使用 TRAJENTA 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。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)。

在動物生殖研究中，根據暴露量計算，在懷孕的大鼠之器官形成期間使用接近臨床最高建議劑量的 linagliptin 劑量時，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 6-10%，在 HbA1c >10 的女性則高達 20-25%，但不知道此族群的流產背景風險估計值。在美國一般族群之經臨床確認的懷孕中，重大先天缺陷與流產的背景風險估計值分別為 2-4%與 15-20%。

臨床考量

疾病相關的母體和/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、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

動物實驗數據

於懷孕 Wistar Han 大鼠與喜馬拉雅兔的器官形成期間使用 linagliptin (劑量分別最高達一天 240 mg/kg 與 150 mg/kg)時，皆未觀察到不良的發育結果。根據暴露量計算，在大鼠與兔子使用的這些劑量約分別為臨床劑量 5 mg 的 943 與 1943 倍。在 Wistar Han 大鼠懷孕第 6 天到泌乳第 21 天期間，使用臨床劑量 5 mg 之 49 倍的 linagliptin 劑量時 (根據暴露量計算)，並未在幼鼠觀察到不良的功能、行為或生殖結果。

8.2 授乳

風險摘要

關於 linagliptin 是否會進入人類的乳汁以及其對哺乳嬰兒或乳汁生成有何影響，目前尚無相關資料。然而，linagliptin 會分泌到授乳中大鼠的乳汁內。因此應考量餵哺母乳對嬰兒發育與健康的益處，以及母親對 TRAJENTA 的臨床需求，以及 TRAJENTA 或潛在母體狀況可能對哺乳嬰兒造成的任何不利影響。

8.4 兒童使用

TRAJENTA 用於未滿 18 歲兒童病人時的安全性與有效性，尚未獲得確立。

8.5 老年人使用

15 項使用 linagliptin 進行第二型糖尿病臨床試驗中，linagliptin 治療組年滿 65 歲以上有 1085 人(其中包含年滿 75 歲以上 131 人)。 15 項試驗中有 12 項為雙盲安慰劑對照試驗，在這 12 項試驗中，linagliptin 治療組年滿 65 歲以上有 591 人 (其中包含年滿 75 歲以上 82 人)。在這些 linagliptin 臨床試驗中，整體而言在安全性或有效性上，老年人與較年輕的受試者並無差異。

8.6 腎功能不全

對於腎功能不全病人並無劑量調整建議*（請參閱臨床藥理學(12.3)）*。

於 CARMELINA 試驗（ (請參閱臨床試驗(14.2))之 TRAJENTA 治療組，有 2200 名（63%）腎功能不全病人(eGFR<60 mL／min／1.73 m^2)，其中約 20%受試者其 eGFR ≥45 但<60 mL／min／1.73 m^2，28%受試者其 eGFR ≥30 但<45 mL／min／1.73 m^2，15%受試者其 eGFR <30 mL／min／1.73 m^2。在不良反應的整體發生率上，TRAJENTA 與安慰劑兩治療組之間大致相近。

8.7 肝功能不全

對於肝功能不全病人並無劑量調整建議*（請參閱臨床藥理學(12.3)）*。

10 用藥過量

若發生 TRAJENTA 用藥過量的情形，請立即就診。此時亦可依據病人的臨床狀況施予慣常使用的支持性措施，例如：從腸胃道移除尚未吸收的物質、進行臨床監測，以及給予該機構之支持性治療。
Linagliptin 無法透過血液透析或腹膜透析方式清除。

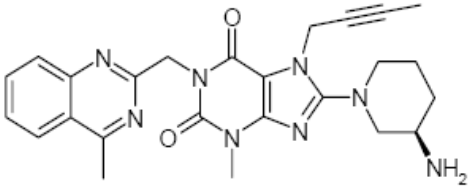
在針對健康受試者所進行的有對照組之臨床試驗期間，使用單一劑量最高 600 mg 的 TRAJENTA（相當於每日建議劑量的 120 倍）時，並未發生具劑量相關性的臨床不良藥物反應。然而，尚無在人體使用高於 600 mg 劑量的經驗。

11 性質說明

TRAJENTA (linagliptin)錠劑的活性成分為具口服活性的二肽基肽酶-4（dipeptidyl peptidase-4，簡稱「DPP-4」）酵素抑制劑。

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

化學最簡式為 $C_{25}H_{28}N_8O_2$，分子量為 472.54 g/mol。結構式為：



Linagliptin 為白色至淡黃色、不具或稍具吸濕性的固體物質，水溶性極低(0.9 mg/mL)。Linagliptin 可溶於甲醇（約 60 mg/mL）、略溶於乙醇（約 10 mg/mL）、幾乎不溶於異丙醇(isopropanol) (<1 mg/mL)與丙酮（約 1 mg/mL）。

每顆 TRAJENTA 膜衣錠均含有 5 mg linagliptin 及下列賦形劑：甘露醇(mannitol)、預糊化澱粉、玉米澱粉、copovidone、硬脂酸鎂(magnesium stearate)、羥丙甲纖維素(hypromellose)、二氧化鈦、滑石粉、polyethylene glycol 與紅氧化鐵(red ferric oxide)。

12 臨床藥理學

12.1 作用機轉

Linagliptin 為 DPP-4 抑制劑，而 DPP-4 為分解腸泌素(incretin)荷爾蒙升糖素樣胜肽-1（glucagon-like peptide-1，簡稱「GLP-1」）與葡萄糖依賴性促胰島素多胜肽（glucose-dependent insulinotropic polypeptide，簡稱「GIP」）的酵素；因此，linagliptin 可使活性腸泌素荷爾蒙的濃度增高，在葡萄糖依賴性的狀態刺激胰島素的釋出，並降低循環中的升糖素濃度。這兩種腸泌素荷爾蒙均參與了葡萄糖體內平衡的生理調節作用。平時即有基本濃度的低量腸泌素荷爾蒙分泌，但其濃度可於用餐後立即上升。在血糖濃度正常與升高時，GLP-1 與 GIP 皆可增加胰島素的生合成以及從胰臟 β 細胞的分泌。此外，GLP-1 亦可降低胰臟 α 細胞的升糖素分泌，而導致肝臟的葡萄糖輸出量降低。

12.2 藥效學

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

心臟電生理學

在一項隨機分組、有安慰劑及活性比較劑的四向交叉(4-way crossover)研究中，共有 36 名健康受試者接受單一劑口服 linagliptin 5 mg、linagliptin 100 mg（建議劑量的 20 倍）、moxifloxacin 與安慰劑。無論使用建議劑量(5 mg)或 100 mg 劑量，QTc 皆未延長。與使用 5 mg 劑量後的血漿中最高 linagliptin 濃度

相較，使用 100 mg 劑量後的最高濃度大約高 38 倍。

12.3 藥物動力學

已針對健康受試者與第二型糖尿病病人進行 linagliptin 的藥物動力學研究。健康受試者口服單劑 5 mg linagliptin 之後約 1.5 小時(T_{max})達到最高血漿中濃度；血漿中的曲線下面積(AUC)平均為 139 nmol*h/L，最高濃度(C_{max})為 8.9 nmol/L。

血漿中的 linagliptin 濃度以至少兩階段的方式下降，終端排除半衰期(terminal half-life)極長（>100 小時），此與 linagliptin 和 DPP-4 呈飽和性結合有關。清除期長與藥物蓄積無關。Linagliptin 蓄積的有效半衰期（口服多劑 linagliptin 5 mg）約為 12 小時。Linagliptin 5 mg 一天一次用藥之後，血中濃度可於第三劑達到穩定狀態，與第一劑相較，穩定狀態時的 C_{max} 與 AUC 增加 1.3 倍。受試者內與受試者間的 linagliptin AUC 變異係數皆不大（分別為 12.6%與 28.5%）。在 1 至 10 mg 劑量範圍內，血漿中 linagliptin AUC 並未隨劑量等比例增加。健康受試者與第二型糖尿病病人具有相近的藥物動力學性質。

吸收

Linagliptin 的絕對生體可用率約為 30%。高脂膳食可使 C_{max} 降低 15%，AUC 增加 4%；此影響不具臨床重要性。TRAJENTA 可與食物一起服用，亦可空腹服用。

分佈

健康受試者接受靜脈注射單劑 linagliptin 5 mg 之後，穩定狀態的虛擬分佈體積(apparent volume of distribution)平均約為 1110 L，顯示 linagliptin 廣泛分佈於各組織。Linagliptin 與血漿中蛋白質的結合具濃度相關性，血中濃度 1 nmol/L 下的蛋白質結合率約 99%，≥30 nmol/L 則下降至 75~89%；此現象顯示，當 linagliptin 濃度增加時，其與 DPP-4 的結合可達到飽和。在高濃度下，DPP-4 會完全飽和，因此有 70%至 80%的 linagliptin 為結合狀態，有 20%至 30%則在血漿中呈未結合狀態。在腎功能或肝功能受損的病人，此藥物在血漿中的結合狀況並未改變。

排除

穩定狀態時 lingliptin 終端排除半衰期約為 200 小時，而蓄積半衰期約為 11 小時。穩定狀態時的腎臟清除率約為 70 mL/min。

代謝

口服之後，大部分（約 90%）的 linagliptin 皆以原形式排出，顯示經代謝清除的路徑僅佔小部分。僅極小部分的 linagliptin 會被代謝為不具藥理活性的代謝物，穩定狀態時其暴露量約為 linagliptin 的 13.3%。

排泄

健康受試者口服一劑[^{14}C]-linagliptin 之後，所服用的放射活性約有 85%於 4 天內經由腸肝系統(80%)或尿液(5%)清除。

特定族群

<u>腎功能不全</u>

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

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

在穩定狀態下，中度腎功能不全病人的 linagliptin 平均暴露量較健康受試者高（$AUC_{\tau,ss}$ 增加 71%，C_{max} 增加 46%）。此暴露量增加與蓄積半衰期延長、終端排除半衰期或蓄積係數增加皆無關聯性。由腎臟排除的藥物量低於 5%，且不受腎功能降低影響。

相較於腎功能正常的第二型糖尿病病人，重度腎功能不全之第二型糖尿病病人的穩定狀態暴露量約增加 40%（$AUC_{\tau,ss}$ 增加 42%，C_{max} 增加 35%）。這兩組第二型糖尿病病人的腎臟清除量皆低於所用劑量的 7%。

族群藥物動力學分析支持上述結果。

<u>肝功能不全</u>
相較於健康受試者，輕度肝功能不全（Child-Pugh 第 A 級）病人的穩定狀態 linagliptin 暴露量($AUC_{\tau,ss}$)大約低 25%，$C_{max,ss}$ 則約低 36%；而中度肝功能不全（Child-Pugh 第 B 級）病人的 linagliptin AUC_{ss} 大約低 14%，$C_{max,ss}$ 則約低 8%。就 linagliptin 暴露量 AUC_{0-24} 而言，重度肝功能不全（Child-Pugh 第 C 級）病人與健康受試者相近，C_{max} 則較健康受試者約低 23%。在肝功能不全者所觀察到的藥物動力學參數下降情形，並未降低其對於 DPP-4 的抑制作用。

<u>身體質量指數(BMI)／體重</u>
無須依據 BMI／體重調整劑量。族群藥物動力學分析結果顯示，BMI／體重對於 linagliptin 的藥物動力學性質不存在具臨床意義的影響。

<u>性別</u>
無須依據性別調整劑量。族群藥物動力學分析結果顯示，性別對於 linagliptin 的藥物動力學性質不存在具臨床意義的影響。

<u>老年人</u>
族群藥物動力學分析結果顯示，年齡對於 linagliptin 的藥物動力學性質不存在具臨床意義的影響。

<u>兒童</u>
尚未針對兒童病人進行 linagliptin 之藥物動力學研究。

<u>人種</u>
無須依據人種調整劑量。依據現有的藥物動力學資料（包含：白人、西班牙裔、黑人與亞洲人種）顯示，人種對於 linagliptin 的藥物動力學性質不存在具臨床意義的影響。

藥物交互作用
<u>體外藥物交互作用評估</u>
Linagliptin 為 CYP3A4 的弱至中度抑制劑，但對其他 CYP 同功酶則無抑制作用，亦非 CYP 同功酶的誘發劑，包括：CYP1A2、2A6、2B6、2C8、2C9、2C19、2D6、2E1 與 4A11。

Linagliptin 為 P-glycoprotein(P-gp)受質，在高濃度下可抑制 P-gp 所媒介的 digoxin 運送。這些結果以及體內藥物交互研究皆顯示，治療濃度下的 linagliptin 不太可能與其他 P-gp 受質產生交互作用。

體內藥物交互作用評估

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

表 3：併用藥物對 Linagliptin 之全身暴露量的影響

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

*多劑量（穩定狀態），除非另有註明

**相關資訊請參考臨床建議[詳見藥物交互作用(7.1)]

單劑量

†單劑量治療：AUC = AUC（0 至 24 小時）；多劑量治療：AUC = AUC (TAU)

QD = 一天一次

BID = 一天兩次

TID = 一天三次

表 4：Linagliptin 對併用藥物之全身暴露量的影響

併用藥物	**併用藥物的用法用量***	**Linagliptin 的用法用量***	**幾何平均比值（有／無併用藥物的比值）無影響= 1.0**		
				AUC†	C_{max}
Metformin	850 mg TID	10 mg QD	metformin	1.01	0.89
Glyburide	1.75 mg#	5 mg QD	glyburide	0.86	0.86
Pioglitazone	45 mg QD	10 mg QD	pioglitazone 代謝物 M-III 代謝物 M-IV	0.94 0.98 1.04	0.86 0.96 1.05
Digoxin	0.25 mg QD	5 mg QD	digoxin	1.02	0.94
Simvastatin	40 mg QD	10 mg QD	simvastatin simvastatin acid	1.34 1.33	1.10 1.21
Warfarin	10 mg#	5 mg QD	R-warfarin S-warfarin INR PT	0.99 1.03 0.93** 1.03**	1.00 1.01 1.04** 1.15**
Ethinylestradiol 與 levonorgestrel	ethinylestradiol 0.03 mg 與 levonorgestrel 0.150 mg QD	5 mg QD	ethinylestradiol levonorgestrel	1.01 1.09	1.08 1.13

*多劑量（穩定狀態），除非另有註明

單劑量
†單劑量治療：AUC = AUC（INF）；多劑量治療：AUC = AUC (TAU)
**藥效學評估指標：AUC=AUC (0-168)，C_{max}=E_{max}
INR =國際標準凝血時間比(International Normalized Ratio)
PT = 凝血酶原時間(Prothrombin Time)
QD = 一天一次
TID = 一天三次

13 非臨床毒物學
13.1 致癌性、致突變性、生育力受損
在一項為期兩年的研究中，6、18 與 60 mg/kg 劑量的 linagliptin 並未增加雄性與雌性大鼠的腫瘤發生率。根據 AUC 暴露量，此最高劑量(60 mg/kg)約為臨床劑量（5 mg/天）的 418 倍。在一項為期兩年的研究中，最高 80 mg/kg（雄性）與 25 mg/kg（雌性）劑量的 linagliptin 並未增加小鼠的腫瘤發生率，根據 AUC 暴露量，此劑量約為臨床劑量的 35 與 270 倍。根據 AUC 暴露量，更高劑量的 linagliptin (80 mg/kg)（根據 AUC 暴露量，約為臨床劑量的 215 倍）可導致雌性小鼠的淋巴瘤發生率增加。

在 Ames 細菌致突變性檢測、染色體畸變檢測與體內微核檢測(micronucleus assay)中，linagliptin 皆不具有致突變性或誘變性(clastogenic)（不論有或無代謝活化作用）。

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

14 臨床試驗
14.1 血糖控制試驗
已在臨床試驗中對 TRAJENTA 單獨療法以及與 metformin、磺醯尿素類藥物、pioglitazone 及胰島素(insulin)的合併療法進行研究，亦曾針對嚴重慢性腎功能不全的第二型糖尿病病人進行 TRAJENTA 研究。

相較於安慰劑，接受 TRAJENTA 治療的第二型糖尿病病人在 HbA1c (A1C)、空腹血糖(FPG)與飯後 2 小時血糖(PPG)方面，皆出現具臨床意義的顯著改善。

單方治療
共有 730 名第二型糖尿病病人參與兩項雙盲、以安慰劑對照的試驗（分別為期 18 與 24 週），以評估 TRAJENTA 的療效與安全性。在這兩項單獨療法試驗中，正在接受抗高血糖藥物治療的病人停用藥物，接受飲食控制、運動以及約 6 週的藥物洗除期（包括最後兩週的開放標示安慰劑導入期）。洗除期之後血糖控制不良（A1C 為 7%至 10%）的病人即可接受隨機分組；當時並未接受抗高血糖藥物治療且血糖控制不良（A1C 為 7%至 10%）的病人（停止治療至少 8 週），則於完成為期兩週的開放標示安慰劑導入期之後接受隨機分組。為期 18 週的研究僅收錄不適合以 metformin 治療的病人，有 76 名受試者經隨機分派至安慰劑組，有 151 人分派至 TRAJENTA 5 mg 組。在為期 24 週的試驗中，有 167 名受試者經隨機分派至安慰劑組，有 336 人分派至 TRAJENTA 5 mg 組。在為期 18 週的試驗期間無法達到特定血糖目標的受試者，可接受 pioglitazone 及／或胰島素救援治療；在為期 24 週的試驗中則以 metformin 作為救援療法。

相較於安慰劑，一天 5 mg 的 TRAJENTA 可使 A1C、FPG 與 2 小時 PPG 獲得具統計顯著性的改善（表 5）。在為期 18 週的試驗中，TRAJENTA 5 mg 組與安慰劑組分別有 12%與 18%的受試者需要救援治療。在為期 24 週的試驗中，TRAJENTA 5 mg 組與安慰劑組分別有 10.2%與 20.9%的受試者需要救援治

療。相較於安慰劑組的 A1C 改善狀況不受性別、年齡、人種、先前之抗高血糖治療、基準點 BMI 或胰島素阻抗性標準指數(HOMA-IR)的影響。如同第二型糖尿病藥物試驗的典型狀況，使用 TRAJENTA 時的 A1C 平均降幅與基準點時 A1C 升高的程度有關。在這兩個為期 18 與 24 週的試驗中，TRAJENTA 組的 A1C 與基準值的差異分別為-0.4%與-0.4%，安慰劑組則分別為 0.1%與 0.3%。在體重與基準值的變化上，兩治療組間並無顯著差異。

表 5：以安慰劑對照之 TRAJENTA 單獨療法試驗中的血糖參數*

	18 週試驗		**24 週試驗**	
	TRAJENTA 5 mg	**安慰劑**	**TRAJENTA 5 mg**	**安慰劑**
A1C (%)				
受試者人數	n = 147	n = 73	n = 333	n = 163
基準值（平均）	8.1	8.1	8.0	8.0
與基準值的變化（校正後的平均值***）	-0.4	0.1	-0.4	0.3
與安慰劑組的差異（校正後的平均值）(95% CI)	-0.6 (-0.9, -0.3)		-0.7 (-0.9, -0.5)	
達 A1C <7%**目標的受試者(%)	32 (23.5%)	8 (11.8%)	77 (25%)	17 (12%)
FPG (mg/dL)				
受試者人數	n = 138	n = 66	n = 318	n = 149
基準值（平均）	178	176	164	166
與基準值的變化（校正後的平均值***）	-13	7	-9	15
與安慰劑組的差異（校正後的平均值）(95% CI)	-21 (-31, -10)		-23 (-30, -16)	
2 小時 PPG (mg/dL)				
受試者人數	無此數據	無此數據	n = 67	n = 24
基準值（平均）			258	244
與基準值的變化（校正後的平均值***）			-34	25
與安慰劑組的差異（校正後的平均值）(95% CI)			-58.4 (-82.3, -34.4)	

*使用參與試驗時最後一次觀察值的全分析族群

**18 週試驗：安慰劑組 n=68；TRAJENTA 組 n=136

24 週試驗：安慰劑組 n=147；TRAJENTA 組 n=306

***18 週試驗。HbA1c：共變數分析（ANCOVA）模型是以療法、無法耐受 metformin 之原因、與先前使用的口服降血糖藥（OAD）數目作為類別效應共變項，並以 HbA1c 基準值作為連續共變項。FPG：ANCOVA 模型是以療法、無法耐受 metformin 之原因、與先前使用的 OAD 數目作為類別效應，並以 HbA1c 基準值和 FPG 基準值作為連續共變項。

24 週試驗：HbA1c：ANCOVA 模型是以療法及先前使用的 OAD 數目作為類別效應，並以 HbA1c 基準值作為連續共變項。FPG：ANCOVA 模型是以療法及先前使用的 OAD 數目作為類別效應共變項，並以 HbA1c 基準值和 FPG 基準值作為連續共變項。PPG：ANCOVA 模型是以療法及先前使用的 OAD 數目作為類別效應，並以 HbA1c 基準值和飯後 2 小時血糖基準值作為共變項。

添加 Metformin 的合併療法

在一項評估 TRAJENTA 與 metformin 合併療法之療效的 24 週、隨機分組、雙盲、以安慰劑對照的試驗中，總共收錄 701 名第二型糖尿病病人。已在使用每天至少 1500 mg 劑量 metformin 的病人(n = 491)，於完成 2 週的開放標示安慰劑導入期之後接受隨機分組；已在使用 metformin 與另一種抗高血糖藥物的病人(n = 207)，則於約 6 週的 metformin 單獨療法（至少一天 1500 mg）導入期之後接受隨機分組。將受試者隨機分派至添加 TRAJENTA 5 mg 或安慰劑一天一次的治療組。試驗期間無法達到特定血糖控制目標的受試者可接受 glimepiride 救援治療。

與 metformin 併用時，相較於安慰劑，TRAJENTA 可使 A1C、FPG 與 2 小時 PPG 出現具統計顯著性的改善（表 6）。TRAJENTA 5 mg 組與安慰劑組分別有 7.8%與 18.9%的受試者接受救援治療。在為期 24 週的治療期間，TRAJENTA／metformin 組與安慰劑／metformin 組的 A1C 與基準點之平均變化如圖 2 所示。兩治療組的體重下降幅度相近。

表 6：以安慰劑對照之 TRAJENTA 與 Metformin 合併療法試驗中的血糖參數*

	TRAJENTA 5 mg + Metformin	**安慰劑+ Metformin**
A1C (%)		
受試者人數	n = 513	n = 175
基準值（平均）	8.1	8.0
與基準值的變化（校正後的平均值***）	-0.5	0.15
與安慰劑+ metformin 組的差異（校正後的平均值）(95% CI)	-0.6 (-0.8, -0.5)	--
達 A1C <7%**目標的受試者(%)	127 (26.2)	15 (9.2)
FPG (mg/dL)		
受試者人數	n = 495	n = 159
基準值（平均）	169	164
與基準值的變化（校正後的平均值***）	-11	11
與安慰劑+ metformin 組的差異（校正後的平均值）(95% CI)	-21 (-27, -15)	--
2 小時 P**PG (mg/dL)**		
受試者人數	n = 78	n = 21
基準值（平均）	270	274
與基準值的變化（校正後的平均值***）	-49	18
與安慰劑+ metformin 組的差異（校正後的平均值）(95% CI)	-67 (-95, -40)	--

*使用參與試驗時最後一次觀察值的全分析族群

**TRAJENTA 5mg + Metformin n=485；安慰劑 + Metformin n=163

***HbA1c：ANCOVA 模型是以療法及先前使用的 OAD 數目作為類別效應共變項，並以 HbA1c 基準值作為連續共變項。FPG：ANCOVA 模型是以療法及先前使用的 OAD 數目作為類別效應，並以 HbA1c 基準值和 FPG 基準值作為連續共變項。PPG：ANCOVA 模型是以療法及先前使用的 OAD 數目作為類別效應共變項，並以 HbA1c 基準值和飯後 2 小時血糖基準值作為共變項。

與 Metformin 之初始併用

在一項以安慰劑對照，針對 TRAJENTA 與 metformin 初始併用療法評估療效的因子試驗中(factorial

study)，共 791 位經飲食調整與運動後，仍無法有效控制血糖的第二型糖尿病病人參與為期 24 週、隨機、雙盲的試驗部分。使用降血糖藥物的病人(52%)均接受為期 4 週的藥品洗除期，並進行為期 2 週的單盲安慰劑導入期。之後對血糖控制不良（A1C ≥7.0%，但≤10.5%的病人）進行隨機分配。進入試驗時未使用降血糖藥物，且血糖控制不良（A1C ≥7.5%，但＜11.0%）的病人(48%)則直接進入為期 2 週的單盲安慰劑導入期，並接受隨機分配。隨機分配分層條件為 A1C 基準值（A1C <8.5%或≥8.5%）與先前是否曾經使用口服糖尿病藥物(無或單一療法）。病人依 1:2:2:2:2:2 的比例分配至安慰劑組，或五個治療組其中之一。以 5mg TRAJENTA（每天一次）、500 或 1000mg metformin（每天兩次），或 2.5 mg linagliptin（每天兩次）搭配 500 或 1000mg metformin（每天兩次）做為初始療法。若病人於試驗期間無法達到特定血糖目標值，則以磺醯尿素類藥物、thiazolidinedione 或胰島素做為救援療法。

以 linagliptin 搭配 metformin 做為初始療法時，A1C、空腹血糖(FPG)的改善量顯著高於安慰劑、單獨使用 metformin 及單獨使用 linagliptin（請參閱表 7）。

第 24 週（最後觀察值推估[LOCF]）時，linagliptin 2.5 mg/metformin 1000mg（每天兩次）相較於 metformin 1000mg（每天兩次）的 A1C 校正後治療差異平均值為-0.5%（95%信賴區間：-0.7，-0.3，p<0.0001），而 linagliptin 2.5 mg/metformin 1000mg（每天兩次）相較於 TRAJENTA 5mg（每天一次）則為-1.1%（95%信賴區間：-1.4，-0.9，p<0.0001），linagliptin 2.5 mg/metformin 500mg（每天兩次）相較於 metformin 500mg（每天兩次）為-0.6%（95%信賴區間：-0.8，-0.4，p<0.0001），linagliptin 2.5 mg/metformin 500mg（每天兩次）相較於 TRAJENTA 5mg（每天一次）為-0.8%（95%信賴區間：-1.0，-0.6，p<0.0001）。

治療的血脂反應大致緩和，六個治療組的體重並無具意義之變化。

表7　透過飲食與運動無法有效控制血糖的第二型糖尿病病人為對象，所進行的24週隨機試驗中，將Linagliptin及Metformin做為單獨或合併療法時，於最後一次回診所得之血糖參數**

	安慰劑	**TRAJENTA 5 mg(每天一次)**	**Metformin 500 mg(每天兩次)**	**Linagliptin 2.5 mg(每天兩次)* + Metformin 500 mg(每天兩次)**	**Metformin 1000 mg (每天兩次)**	**Linagliptin 2.5 mg(每天兩次)* + Metformin 1000 mg (每天兩次)**
A1C (%)						
受試者人數	n = 65	n = 135	n = 141	n = 137	n = 138	n = 140
基準值（平均）	8.7	8.7	8.7	8.7	8.5	8.7
與基準值的變化（校正後的平均值***）	0.1	-0.5	-0.6	-1.2	-1.1	-1.6
與安慰劑組的差異（校正後的平均值）(95% CI)	--	-0.6 (-0.9, -0.3)	-0.8 (-1.0, -0.5)	-1.3 (-1.6, -1.1)	-1.2 (-1.5, -0.9)	-1.7 (-2.0, -1.4)
達成 A1C <7%***之病人數(%)	7 (10.8)	14 (10.4)	26 (18.6)	41 (30.1)	42 (30.7)	74 (53.6)
接受救援藥物的病人數	29.2	11.1	13.5	7.3	8.0	4.3

(%)						
空腹血糖(mg/dL)						
受試者人數	n = 61	n = 134	n = 136	n = 135	n = 132	n = 136
基準值（平均）	203	195	191	199	191	196
與基準值的變化（校正後的平均值****）	10	-9	-16	-33	-32	-49
與安慰劑組的差異（校正後的平均值）(95% CI)	--	-19 (-31, -6)	-26 (-38, -14)	-43 (-56, -31)	-42 (-55, -30)	-60 (-72, -47)

*TRAJENTA每日總劑量相當於5 mg

**使用參與試驗時最後一次觀察值的全分析族群

***Metformin 500 mg（每天兩次）n=140；Linagliptin 2.5 mg（每天兩次）+ Metformin 500mg（每天兩次）n=136；Metformin 1000 mg（每天兩次）n=137；Linagliptin 2.5 mg（每天兩次）及Metformin 1000 mg（每天兩次）n=138.

****HbA1c：ANCOVA 模型是以治療及先前使用的 OAD 數目為類別效應共變項，並以 HbA1c 基準值為連續共變項。FPG：ANCOVA 模型是以治療及先前使用的 OAD 數目為類別效應共變項，並以 HbA1c 基準值和 FPG 基準值為連續共變項。

以 Glimepiride 作為活性對照劑的 Metformin 併用試驗

在一項為期 104 週、雙盲、以 glimepiride 對照的不劣性試驗中，針對無法以 metformin 有效控制血糖的第二型糖尿病病人評估添加 TRAJENTA 的療效。正在接受 metformin 單獨療法的受試者須進入為期 2 週的導入期，而正在接受 metformin 加另一種抗高血糖藥物治療的受試者則須進入為期 6 週的 metformin 單獨療法（劑量 ≥1500 mg/天）導入期及洗除另一種藥物，再接受 2 週的安慰劑導入期，隨後將血糖控制不佳（A1C 6.5%至 10%）的受試者隨機分派(1:1)至添加 TRAJENTA 5 mg 一天一次或 glimepiride 的治療組。隨機分組時，根據 HbA1c 基準值(分為<8.5%和≥8.5%），以及先前使用降血糖藥物（分為單獨使用 metformin 和 metformin 合併一種其他的口服降血糖藥）進行分組。Glimepiride 組受試者的 glimepiride 初始劑量為 1 mg/天，然後視需要於隨後 12 週期間調整劑量（最高 4 mg/天），以達到最理想的血糖控制。之後，glimepiride 的劑量即維持固定，除非是為了預防低血糖症而調降劑量。

治療 52 週和 104 週之後，TRAJENTA 與 glimepiride 皆可使 A1C 較基準點(平均值 7.7%)降低（52 週：TRAJENTA 組降低 0.4%，glimepiride 組降低 0.6%；104 週：TRAJENTA 組降低 0.2%，glimepiride 組降低 0.4%）（表 8）。針對意圖治療族群，採用最後觀察值前推方法時，兩治療組間在 HbA1c 相較於基準值之變化上的差異為 0.2% （雙側 97.5%信賴區間：0.1%至 0.3%）。這些結果與完成試驗者分析(completers analysis)的結果一致。

表 8：針對無法以 Metformin 有效控制血糖者比較添加 TRAJENTA 與 Glimepiride 的試驗中第 52 週和第 104 週時的血糖參數**

	第 52 週	**第 104 週**		
	TRAJENTA 5 mg + Metformin	**Glimepiride + Metformin（Glimepiride 平均劑量 3 mg）**	**TRAJENTA 5 mg + Metformin**	**Glimepiride + Metformin（Glimepiride 平均劑量 3 mg）**
A1C (%)				
受試者人數	n = 764	n = 755	n = 764	n = 755

基準值（平均）	7.7	7.7	7.7	7.7
與基準值的變化（校正後的平均值****）	-0.4	-0.6	-0.2	-0.4
與 glimepiride 組的差異（校正後的平均值）(97.5%CI)	0.2 (0.1, 0.3)	--	0.2 (0.1, 0.3)	--
FPG (mg/dL)				
受試者人數	n = 733	n = 725	n = 733	n = 725
基準值（平均）	164	166	164	166
與基準值的變化（校正後的平均值****）	-8*	-15	-2†	-9
低血糖症發生率(%)* **				
受試者人數	n = 776	N = 775	n = 776	n = 775
發生率****	5.3*	31.1	7.5*	36.1

*p<0.0001（相較於 glimepiride）；†p=0.0012（相較於 glimepiride）
**使用參與試驗時最後一次觀察值的全分析族群
***低血糖症發生率，包括無症狀事件（未發生典型症狀，且血漿葡萄糖濃度 ≤70 mg/dL）和有症狀事件（有發生低血糖症的典型症狀，且血漿葡萄糖濃度≤70 mg/dL）。
****HbA1c：ANCOVA 模型是以療法及先前使用的 OAD 數目作為類別效應共變項，並以 HbA1c 基準值作為連續共變項。FPG：ANCOVA 模型是以療法及先前使用的 OAD 數目作為類別效應共變項，並以 HbA1c 基準值和 FPG 基準值作為連續共變項。低血糖症發生率(%)：針對接受治療分派的受試者族群進行 Cochran-Mantel-Haenszel 檢定，藉此比較接受 linagliptin 治療者和接受 glimepiride 治療者發生低血糖症事件的受試者比例。

接受 linagliptin 治療之受試者的平均體重基準值為 86 kg，以及在 52 週和 104 週觀察到的校正後平均體重下降量，分別為 1.1 kg 和 1.4 kg。接受 glimepiride 治療之受試者的平均體重基準值為 87 kg，以及在 52 週和 104 週觀察到的體重，相較於基準值的校正後平均上升量，分別為 1.4 kg 和 1.3 kg（兩時間點之治療差異，p 值均<0.0001）。

添加至 Pioglitazone 的合併療法
在一項評估 TRAJENTA 與 pioglitazone 合併療法之療效的 24 週、隨機分組、雙盲、以安慰劑對照的試驗中，總共收錄 389 名第二型糖尿病病人。正在接受口服抗高血糖治療的受試者須停止治療 6 週（4 週加 2 週開放標示安慰劑導入期）。未曾接受治療的受試者，可直接進入 2 週的安慰劑導入期。於導入期之後，將受試者隨機分派接受 TRAJENTA 5 mg 或安慰劑，兩者皆分別併用一天 30 mg 的 TRAJENTA。試驗期間無法達到特定血糖控制目標的受試者，可接受 metformin 救援治療。血糖評估指標量值為 A1C 與 FPG。

相較於安慰劑與 pioglitazone 合併療法，TRAJENTA 5 mg 與 pioglitazone 30 mg 起始併用時，可使 A1C 與 FPG 出現具統計顯著性的改善（表 9）。TRAJENTA 5 mg／pioglitazone 30 mg 組與安慰劑／pioglitazone 組分別有 7.9%與 14.1%的受試者接受救援治療。試驗期間，兩組受試者的體重皆有所增加，TRAJENTA 5 mg／pioglitazone 30 mg 組與安慰劑／pioglitazone 組校正後的平均體重分別較基準點增加 2.3 與 1.2 公斤(p = 0.0141)。

表 9：以安慰劑對照之 TRAJENTA 與 Pioglitazone 合併療法試驗中的血糖參數*

	TRAJENTA 5 mg + Pioglitazone	**安慰劑 + Pioglitazone**
A1C (%)		
受試者人數	n = 252	n =128
基準值（平均）	8.6	8.6
與基準值的變化（校正後的平均值**）	-1.1	-0.6
與安慰劑+ pioglitazone 組的差異（校正後的平均值）(95% CI)	-0.5 (-0.7, -0.3)	--
達 A1C <7%目標的受試者，n (%)	108 (42.9)	39 (30.5)
FPG (mg/dL)		
受試者人數	n = 243	n = 122
基準值（平均）	188	186
與基準值的變化（校正後的平均值**）	-33	-18
與安慰劑+ pioglitazone 組的差異（校正後的平均值）(95% CI)	-14 (-21, -7)	--

*使用參與試驗時最後一次觀察值的全分析族群

**HbA1c：ANCOVA 模型是以療法及先前使用的 OAD 數目作為類別效應共變項，並以 HbA1c 基準值作為連續共變項。FPG：ANCOVA 模型是以療法及先前使用的 OAD 數目作為類別效應，並以 HbA1c 基準值和 FPG 基準值作為連續共變項。

添加磺醯尿素類藥物的合併療法

在一項評估 TRAJENTA 與磺醯尿素類藥物(SU)合併療法之療效的 18 週、隨機分組、雙盲、以安慰劑對照的試驗中，共收錄 245 名第二型糖尿病病人。正在接受磺醯尿素類藥物單獨療法的受試者(n = 142)於完成 2 週的單盲安慰劑導入期之後接受隨機分組。正在接受磺醯尿素類藥物加另一種口服抗高血糖藥物治療的受試者(n = 103)，則於 4 週的洗除期與 2 週的單盲安慰劑導入期之後接受隨機分組。將受試者隨機分派至添加 TRAJENTA 5 mg 或安慰劑，皆為一天一次的治療組。試驗期間無法達到特定血糖控制目標的受試者，可接受 metformin 救援治療。血糖評估指標量值包括 A1C 與 FPG。

與磺醯尿素類藥物併用時，相較於安慰劑，以 TRAJENTA 治療 18 週後，可使 A1C 出現具統計顯著性的改善；使用 TRAJENTA 時所觀察到的 FPG 改善幅度相較於安慰劑則不具統計顯著性（表 10）。TRAJENTA 5 mg 組與安慰劑組分別有 7.6%與 15.9%的受試者接受救援治療。TRAJENTA 組與安慰劑組的體重變化並無顯著差異。

表 10：以安慰劑對照之 TRAJENTA 與磺醯尿素類藥物合併療法試驗中的血糖參數*

	TRAJENTA 5 mg + SU	**安慰劑 + SU**
A1C (%)		
受試者人數	n = 158	n = 82
基準值（平均）	8.6	8.6
與基準值的變化（校正後的平均值***）	-0.5	-0.1
與安慰劑+ SU 組的差異（校正後的平均值）(95% CI)	-0.5 (-0.7, -0.2)	--
達 A1C <7%**目標的受試者(%)	23 (14.7)	3 (3.7)
FPG (mg/dL)		
受試者人數	n = 155	n = 78

基準值（平均）	180	171
與基準值的變化（校正後的平均值***）	-8	-2
與安慰劑+ SU 組的差異（校正後的平均值）(95% CI)	-6 (-17, 4)	--

SU = 磺醯尿素類藥物(sulfonylurea)
*使用參與試驗時最後一次觀察值的全分析族群
**TRAJENTA 5 mg+SU，n=156；安慰劑+ SU，n=82
***HbA1c：ANCOVA 模型是以療法及先前使用的 OAD 數目作為類別效應共變項，並以 HbA1c 基準值作為連續共變項。FPG：ANCOVA 模型是以療法及先前使用的 OAD 數目作為類別效應共變項，並以 HbA1c 基準值和 FPG 基準值作為連續共變項。

添加至 Metformin 及一種磺醯尿素類藥物的合併療法
在一項評估 TRAJENTA 與一種磺醯尿素類藥物及 metformin 合併療法之療效的 24 週、隨機分組、雙盲、以安慰劑對照的試驗中，共收錄 1058 名第二型糖尿病病人。此項試驗中最常使用的磺醯尿素類藥物為：glimepiride (31%)、glibenclamide (26%)與 gliclazide（26%，尚未在美國上市）。正在接受一種磺醯尿素類藥物及 metformin 治療的受試者，經隨機分派接受 TRAJENTA 5 mg 或安慰劑皆為一天一次的治療。試驗期間無法達到特定血糖控制目標的受試者，可接受 pioglitazone 救援治療。血糖評估指標量值包括 A1C 與 FPG。

與磺醯尿素類藥物及 metformin 併用時，相較於安慰劑，TRAJENTA 可使 A1C 與 FPG 出現具統計顯著性的改善（表 11）。相較於安慰劑，整個試驗族群（接受 TRAJENTA 與磺醯尿素類藥物及 metformin 合併療法者）的 A1C 平均降低 0.6%，FPG 亦降低 13 mg/dL。TRAJENTA 5 mg 組與安慰劑組分別有 5.4%與 13%的受試者接受救援治療。在體重與基準點的變化上，兩組間並無顯著差異。

表 11：以安慰劑對照之 TRAJENTA 與 Metformin 及磺醯尿素類藥物合併療法試驗中的血糖參數*

	TRAJENTA 5 mg + Metformin +SU	**安慰劑+ Metformin + SU**
A1C (%)		
受試者人數	n = 778	n = 262
基準值（平均）	8.2	8.1
與基準值的變化（校正後的平均值***）	-0.7	-0.1
與安慰劑組的差異（校正後的平均值）(95% CI)	-0.6 (-0.7, -0.5)	--
達 A1C <7%**目標的受試者，n (%)	217 (29.2)	20 (8.1)
FPG (mg/dL)		
受試者人數	n = 739	n = 248
基準值（平均）	159.	163
與基準值的變化（校正後的平均值***）	-5	8
與安慰劑組的差異（校正後的平均值）(95% CI)	-13 (-18, -7)	--

SU = 磺醯尿素類藥物(sulfonylurea)
*使用參與試驗時最後一次觀察值的全分析族群
**TRAJENTA 5 mg+Metformin，n=742；安慰劑+ Metformin，n=247
***HbA1c：ANCOVA 模型是以療法作為類別效應共變項，並以 HbA1c 基準值作為連續共變項。

FPG：ANCOVA 模型是以療法作為類別效應共變項，並以 HbA1c 基準值和 FPG 基準值作為連續共變項。

添加胰島素之併用療法

在一項為期 24 週、評估 TRAJENTA 添加至基礎胰島素療法所得療效之隨機、雙盲、安慰劑對照試驗中，受試者包括 1261 位無法單獨以基礎胰島素，或以基礎胰島素搭配口服藥物有效控制血糖的第二型糖尿病病人。隨機分層條件為 HbA1C 基準值（<8.5%或≥8.5%）、腎功能不全狀態（根據腎絲球過濾率估算值之基準值），以及同時使用的口服糖尿病藥物（無、只有 metformin、只有 pioglitazone，或 metformin+pioglitazone）。該試驗納入 A1C 基準值≥7%且≤10%的病人，其中包括 709 位具有腎功能不全者（腎絲球過濾率估算值低於每分鐘 90mL），且大部分(n = 575)經分類為輕度腎功能不全者（腎絲球過濾率估算值每分鐘 60mL 以上，但未滿 90mL）。病人進行為期 2 週的安慰劑導入期，均接受基礎胰島素（例如：insulin glargine、insulin detemir 或 NPH insulin），其中有或無 metformin 及／或 pioglitazone 背景療法。導入期結束後，血糖控制不良的病人接受隨機分配，加入每天一次的 5 mg TRAJENTA 或安慰劑。在收案前、導入期及最初 24 週治療期中，病人均維持穩定劑量的胰島素。在雙盲治療期未達到特定血糖目標值的病人均透過提高背景胰島素劑量，做為救援療法。

經 24 週的 TRAJENTA 與胰島素併用（有或無 metformin 及／或 pioglitazone）療法後，A1C 和 FPG 的改善程度顯著高於安慰劑（表 12）。TRAJENTA 組與安慰劑組中，胰島素每日總劑量平均基準值分別為 42 與 40 單位。基準點背景糖尿病療法包括：只使用胰島素(16.1%)、胰島素僅搭配 metformin (75.5%)、胰島素搭配 metformin 和 pioglitazone(7.4%)，以及胰島素僅搭配 pioglitazone (1%)。TRAJENTA 組與安慰劑組的胰島素劑量從基準點至第 24 週的變化量分別為+0.6 IU 及+1.3 IU。兩組的體重從基準點至第 24 週的變化量大致相近。

表12　　安慰劑對照試驗中， TRAJENTA搭配胰島素治療後之血糖參數*

	TRAJENTA 5 mg + 胰島素	**安慰劑 + 胰島素**
A1C (%)		
受試者人數	n = 618	n = 617
基準值（平均）	8.3	8.3
與基準值的變化（校正後的平均值***）	-0.6	0.1
與安慰劑組的差異（校正後的平均值***）(95% CI)	-0.7 (-0.7, -0.6)	--
達A1C <7%**目標的受試者，n (%)	116 (19.5)	48 (8.1)
FPG (mg/dL)		
受試者人數	n = 613	n = 608
基準值（平均）	147	151
與基準值的變化（校正後的平均值***）	-8	3
與安慰劑組的差異（校正後的平均值***）(95% CI)	-11 (-16, -6)	--

*使用參與試驗時最後一次觀察值的全分析族群

**TRAJENTA+胰島素，N=595；安慰劑+胰島素，N=593

***HbA1c：ANCOVA模型是以療法、腎功能不全狀態分類及併用之OAD作為類別效應共變項，並以HbA1c基準值為連續共變項。FPG：ANCOVA模型是以療法、腎功能不全狀態分類及併用之OAD作為類別效應共變項，並以HbA1c基準值和FPG基準值作為連續共變項。

經Linagliptin與安慰劑治療24週後，無腎功能不全（腎絲球過濾率達每分鐘90mL以上，n = 539）、輕度腎功能不全（腎絲球過濾率每分鐘60mL以上但未滿90mL，n = 565）及中度腎功能不全（腎絲球過濾率達每分鐘30mL以上但未滿60mL，n = 124）之HbA1c基準值之校正後平均值變化量相當。

腎功能不全

在一項為期52週、以患有第二型糖尿病且伴隨嚴重慢性腎功能不全病人為對象，評估TRAJENTA療效與安全性的雙盲、隨機、安慰劑對照試驗中，共133位第二型糖尿病病人參加試驗。該試驗收案條件為腎絲球過濾率〔根據四變數腎臟疾病飲食調整(MDRD)公式〕估算值(eGFR)低於每分鐘30mL。隨機分配分層條件為HbA1c基準值（≤8%或>8%）、背景糖尿病療法（胰島素或任何胰島素併用療法、SU或glinides單藥療法，以及pioglitazone或除DPP-4抑制劑以外的任何其他糖尿病藥物）。最初12週試驗中，背景糖尿病療法均維持穩定，包括胰島素、磺醯尿素類藥物、glinides與pioglitazone。在剩餘試驗中，可調整背景糖尿病療法劑量。該試驗中，62.5%病人於基準點僅以胰島素，以及12.5%僅以磺醯尿素類藥物做為背景糖尿病療法。

經12週治療後，TRAJENTA 5 mg 對於A1C的改善顯著優於安慰劑，經最後觀察值推估分析所得校正後平均值變化量與安慰劑之差異為-0.6%（95%信賴區間：-0.9，-0.3）。最初12週之後可調整的背景糖尿病療法，療效可持續至52週，經最後觀察值推估 (last observation carried forward) 分析所得A1C與基準值的平均值變化經校正後，與安慰劑之差異為-0.7%（95%信賴區間：-1.0，-0.4）。

14.2 心血管安全性試驗

CARMELINA

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

基期時，平均受試者年齡為 66 歲，受試者族群 63%為男性，80%為白種人，9%為亞洲人，6%為黑人。HbA1c 平均值為 8.0%，罹患第二型糖尿病的平均期間約為 15 年。試驗族群包括≥75 歲的病人，占 17%，腎功能不全病人 eGFR <60 mL／min／1.73 m^2，占 62%。平均 eGFR 為 55 mL／min／1.73 m^2，27%受試者為輕度腎功能不全(eGFR 60-90 mL／min／1.73 m^2)，47%受試者為中度腎功能不全(eGFR 30-<60 mL／min／1.73 m^2)及 15%為重度腎功能不全(eGFR <30 mL／min／1.73 m^2)。 97%的受試者服用至少一種抗糖尿病藥物。分別為胰島素及其類似物占 57%，metformin 占 54%，磺醯尿素類占 32%。96%的受試者服用抗血壓藥物，76%受試者服用降血脂藥物(其中 72%為司他汀類藥物)及阿斯匹靈 62%。CARMELINA 試驗的主要評估指標為：首次出現重大心臟血管綜合不良事件（MACE）三者之任一項的時間。重大心臟血管不良事件的定義為心血管原因死亡或非致命性心肌梗塞（MI）或非致命性中風。此為不劣性試驗設計，預先設定風險比值之臨界點為 1.3。

CARMELINA 試驗的主要評估指標結果如表 13 所示。TRAJENTA 相較於安慰劑的 MACE 風險比值為 1.02（95%信賴區間：0.89, 1.17）。此信賴區間的上限值為 1.17，低於預先界定的風險比值 1.3。第一次發生重大心血管不良事件（MACE），Kaplan-Meier 存活分析描述於圖 1。

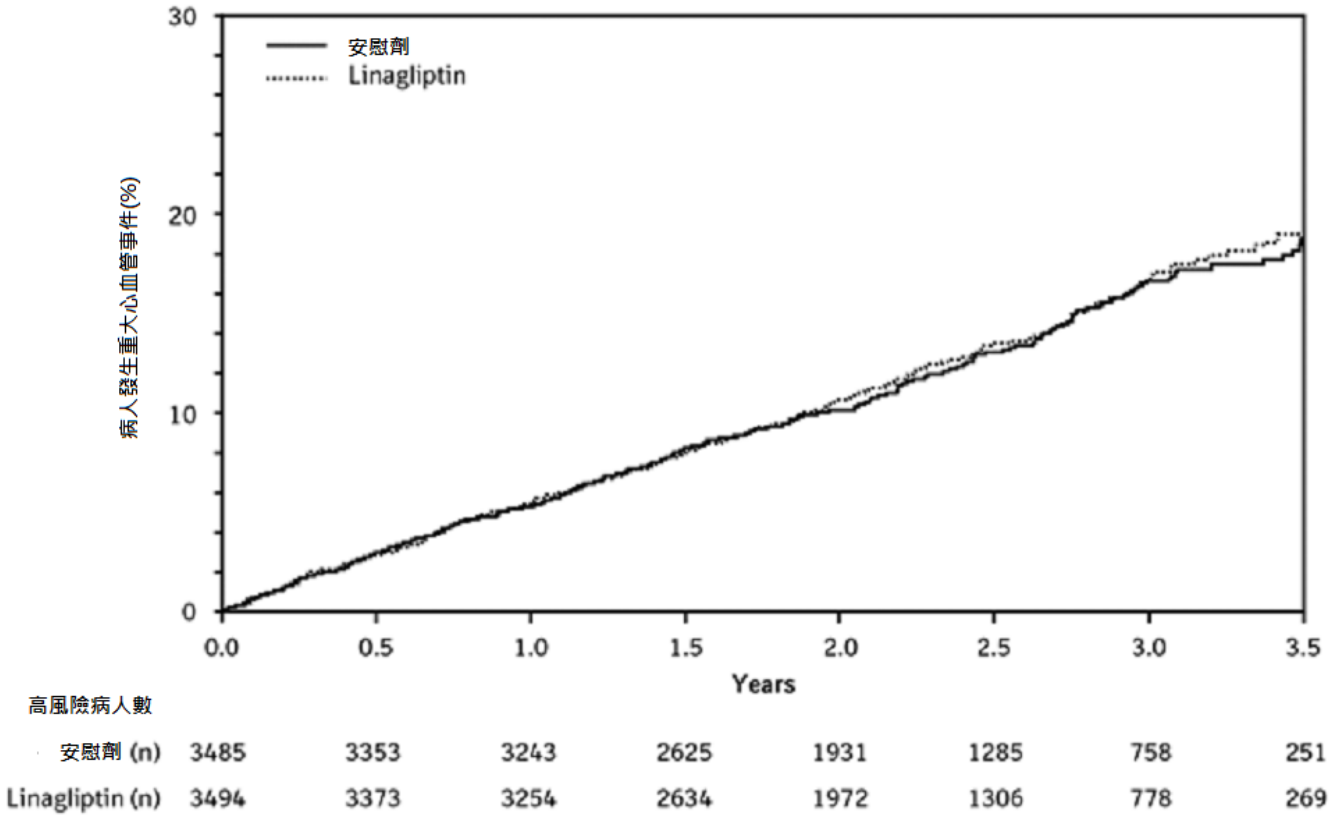
表 13　CARMELINA 試驗中個別治療組的重大不良心血管事件（MACE）

	TRAJENTA 5 mg n = 3494		安慰劑 n = 3485		風險比
	受試者人數(%)	發生率／1000 PY*	受試者人數(%)	發生率／1000 PY*	(95% CI)
首例心血管原因死亡、非致命性心肌梗塞或非致命性中風的綜合指標(MACE)	434 (12.4)	57.7	420 (12.1)	56.3	1.02 (0.89, 1.17)
心血管原因死亡**	255 (7.3)	32.6	264 (7.6)	34.0	0.96 (0.81, 1.14)
非致命性心肌梗塞**	156 (4.5)	20.6	135 (3.9)	18.0	1.15 (0.91, 1.45)
非致命性中風**	65 (1.9)	8.5	73 (2.1)	9.6	0.88 (0.63, 1.23)

*PY=病人年

**一個病人可能會經歷多於一次的不良心血管事件，故事件加總數目會大於病人數

圖 1　Kaplan-Meier: CARMELINA 試驗中首次發生 MACE 的時間



CAROLINA

CAROLINA 試驗，針對第二型糖尿病之成人且過去有心血管病史和/或多種心血管風險因素，評估 TRAJENTA 對心血管風險的影響；此試驗為多中心、多國、隨機分組、雙盲、以 TRAJENTA (N=3023) 和 glimepiride (N=3010)作為平行組別的臨床試驗。此項試驗將 TRAJENTA 與 glimepiride 合併糖尿病及其他心血管危險因子的標準療法，比較兩組出現之重大不良心血管事件(MACE)的風險。此試驗為事件

驅動設計，追蹤時間中位數為 6.23 年，取得 99.3%受試者的存活狀態資料。
納入此臨床試驗之標準為:患有第二型糖尿病且血糖控制不佳(定義為糖化血色素為 6.5%~8.5%或 6.5%~7.5%，取決於是否未曾治療、單方治療或合併治療)，且高心血管風險如先前有心血管疾病、有末端器官損傷實證、年齡≥70 歲和/或 2 個心血管風險因素(糖尿病史≥10 年、收縮壓> 140mmHg、正在抽菸者、低密度膽固醇≥135 mg/dL)。
基期時，平均受試者年齡為 64 歲，受試者族群 60%為男性，73%為白種人，18%為亞洲人，5%為黑人。HbA1c 平均值為 7.15%，罹患第二型糖尿病的持續時間平均約為 7.6 年。試驗族群包括≥70 歲的病人占 34%， 定義為 eGFR <60 mL/min/1.73 m^2 的腎功能不全病人占 19%，平均 eGFR 為 77 mL/min/1.73 m^2， 91%的受試者服用至少一種抗糖尿病藥物。最常見為 metformin 占 83%，磺醯尿素類占 28%。89%的受試者服用抗血壓藥物，70%受試者服用降血脂藥物，65%受試者服用司他汀類藥物及 47%受試者服用阿斯匹靈。
試驗的主要評估指標為：首次出現重大心臟血管綜合不良事件（MACE）三者之任一項的時間。重大心臟血管不良事件的定義為心血管原因死亡或非致命性心肌梗塞（MI）或非致命性中風。此為不劣性試驗設計，預先設定 95%信賴區間上限值不高於風險比值之臨界點為 1.3。

CAROLINA 試驗的主要評估指標結果如表 14 所示。第一次發生重大不良心血管事件(MACE)，Kaplan-Meier 存活分析描述於圖 2。

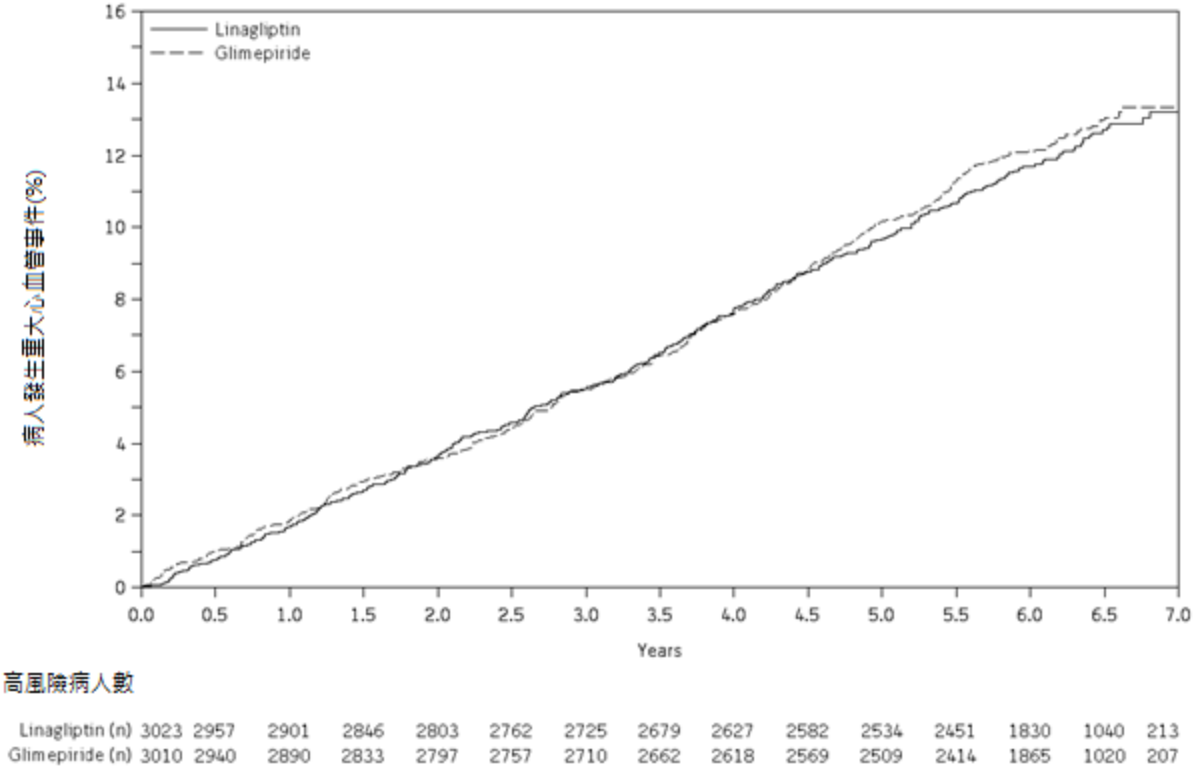
表14 CAROLINA試驗中個別治療組的重大不良心血管事件（MACE）

	TRAJENTA 5 mg n=3023		**Glimepiride (1 mg to 4 mg) n=3010**		**風險比**
	受試者人數(%)	**發生率／1000 PY***	**受試者人數(%)**	**發生率／1000 PY***	**(95% CI)**
首例心血管原因死亡、非致命性心肌梗塞或非致命性中風的綜合指標(MACE)	356 (11.8)	20.7	362 (12.0)	21.2	0.98 (0.84, 1.14)
心血管原因死亡**	169 (5.6)	9.2	168 (5.6)	9.2	1.00 (0.81, 1.24)
非致命性心肌梗塞**	145 (4.8)	8.3	142 (4.7)	8.2	1.01 (0.80, 1.28)
非致命性中風**	91 (3.0)	5.2	104 (3.5)	6.0	0.87 (0.66, 1.15)

*PY=病人年

**一個病人可能會經歷多於一次的不良心血管事件，故事件加總數目會大於病人數

圖2 CAROLINA試驗中首次發生3P-MACE的時間



16 供應形式／儲存與操作

TRAJENTA 錠劑為含有 5 mg linagliptin 的淺紅色、圓形、兩面中央凸起、邊緣呈斜面的膜衣錠，兩面分別壓印「D5」字樣與百靈佳殷格翰公司標誌。

以下列包裝供應：
2- 1000 錠鋁箔盒裝。

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。
保存期限請見外盒。

17 病人諮詢資訊

用藥指南
請病人於開始接受 TRAJENTA 治療之前先詳閱用藥指南，並於每次處方更新時重新閱讀。請病人於出現任何不尋常的症狀，或任何已知的症狀持續存在或惡化時，通知醫師或藥師。

請告知病人 TRAJENTA 可能具有的風險與益處，以及替代療法。亦請告知病人配合飲食方針、規律運動、定期血糖監測與 A1C 檢測、低血糖症與高血糖症之辨識與控制以及糖尿病併發症之評估的重要性。請病人於出現發燒、外傷、感染或手術等壓力時立即就醫，因為病人需要的藥物可能有所改變。

<u>胰臟炎</u>
請告知病人，曾在 TRAJENTA 使用期間通報發生急性胰臟炎的案例，並告知病人持續性嚴重腹痛（有時會牽引至背部，且可能會發生嘔吐，也可能不會發生嘔吐）為急性胰臟炎的典型症狀。請指示病人，應在發生持續性嚴重腹痛時，立即停止使用 TRAJENTA 並與醫師聯繫*（請參閱警語及注意事項*

(5.1)）。

低血糖

請告知病人：若在磺醯尿素或胰島素療法中添加 TRAJENTA，將會增加低血糖症的發生率，因此可能需要調降磺醯尿素或胰島素的劑量，以降低發生低血糖症的風險*（請參閱警語及注意事項(5.2)）*。

過敏反應

請告知病人 TRAJENTA 上市後使用期間，曾發生嚴重過敏反應，例如急性過敏、血管水腫和鱗片狀脫落性皮膚疾病。如果發生過敏反應症狀 (例如皮疹、皮膚剝落或脫皮、蕁麻疹、皮膚腫脹；或臉部、嘴唇、舌頭和喉嚨腫脹，可能造成呼吸或吞嚥困難)，必須停用 TRAJENTA 並立即就醫*（請參閱警語及注意事項(5.3)）*。

嚴重和行動不便之關節疼痛

請告知病人使用 DPP4 抑制劑這類藥可能發生嚴重和行動不便之關節疼痛，有可能在用藥後第 1 天或幾年後發生。請告知病人如果發生嚴重關節疼痛症狀，必須立即就醫*（請參閱警語及注意事項(5.4)）*。

大皰性類天皰瘡

請告知病人，使用此類藥物時可能發生大皰性類天皰瘡。請告知病人，出現水泡或糜爛時應就醫。*（請參閱警語及注意事項(5.5)）*

錯過服藥

請病人務必依照處方服用 TRAJENTA。若錯過一劑藥物，請勿於下一劑時服用雙倍劑量。

血糖與 A1C 監測

請告知病人，對於所有糖尿病療法的反應，均必須藉由定期測量血糖與 A1C 濃度進行監測，目標是將此等濃度降至正常範圍。A1C 監測對於長期血糖控制狀況的評估尤其有用。

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Dragenopharm Apotheker Püschl GmbH
Göllstraβe 1, 84529 Tittmoning, Germany
國外許可證持有者
Boehringer Ingelheim International GmbH
Binger Strasse 173, 55216 Ingelheim am Rhein, Germany

藥商/地址
台灣百靈佳殷格翰股份有限公司
台北市民生東路三段 2 號 12 樓
修正日期 2022 年 3 月
核准日期 2022 年 9 月

1 INDICATIONS

1.1 Type 2 diabetes mellitus.

1.2 Important

Limitations of Use

TRAJENTA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

TRAJENTA has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using TRAJENTA *[see Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

The product should be used by physician prescription.

2.1 Recommended Dosing

The recommended dose of TRAJENTA is 5 mg once daily in an adult.

TRAJENTA can be used as monotherapy or as combination therapy with metformin, a sulfonylurea, an insulin, a PPARγ agonist (e.g., thiazolidinedione) as an adjunct to diet and exercise to improve glycemic control [see Clinical Studies (14.1)]

TRAJENTA tablets can be taken with or without food.

2.2 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

When TRAJENTA is used in combination with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.2)]*.

3 DOSAGE FORMS AND STRENGTHS

TRAJENTA (linagliptin) 5 mg tablets are light red, round, biconvex, bevel-edged, film-coated tablets with "D5" debossed on one side and the Boehringer Ingelheim logo debossed on the other side.

4 CONTRAINDICATIONS

TRAJENTA is contraindicated in patients with hypersensitivity to linagliptin or any of the excipients in TRAJENTA, reactions such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity have occurred *[see Warnings and Precautions (5.3) and Adverse Reactions (6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Pancreatitis

Acute pancreatitis, including fatal pancreatitis, has been reported in patients treated with TRAJENTA. In the CARMELINA trial *[see Clinical Studies (14.2)]*, acute pancreatitis was reported in 9 (0.3%) patients treated with TRAJENTA and in 5 (0.1%) patients treated with placebo. Two patients treated with TRAJENTA in the CARMELINA trial had acute pancreatitis with a fatal outcome. There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients treated with TRAJENTA.

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

5.2 Use with Medications Known to Cause Hypoglycemia

Insulin secretagogues and insulin are known to cause hypoglycemia. The use of TRAJENTA in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin was associated with a higher rate of hypoglycemia compared with placebo in clinical trials *[see Adverse Reactions (6.1)]*. The use of TRAJENTA in combination with insulin in subjects with severe renal impairment was associated with a higher rate of hypoglycemia *[see Adverse Reactions (6.1)]*. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with TRAJENTA.

5.3 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with TRAJENTA. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred predominantly within the first 3 months after initiation of treatment with TRAJENTA, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue TRAJENTA, assess for other potential causes for the event, and institute alternative treatment for diabetes.

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

5.4 Severe and Disabling Arthralgia

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

5.5 Bullous Pemphigoid

Bullous pemphigoid was reported in 7 (0.2%) patients treated with TRAJENTA compared to none in patients treated with placebo in the CARMELINA trial *[see Clinical Studies (14.2)]*, and 3 of these patients were hospitalized due to bullous pemphigoid. Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving TRAJENTA. If bullous pemphigoid is suspected, TRAJENTA should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Pancreatitis *[see Warnings and Precautions (5.1)]*
- Use with Medications Known to Cause Hypoglycemia *[see Warnings and Precautions (5.2)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.3)]*
- Severe and Disabling Arthralgia *[see Warnings and Precautions (5.4)]*
- Bullous Pemphigoid *[see Warnings and Precautions (5.5)]*

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 evaluation of TRAJENTA 5 mg once daily in patients with type 2 diabetes is based on 14 placebo-controlled trials, 1 active-controlled study, and one study in patients with severe renal impairment. In the 14 placebo-controlled studies, a total of 3625 patients were randomized and treated with TRAJENTA 5 mg daily and 2176 with placebo. The mean exposure in patients treated with TRAJENTA across studies was 29.6 weeks. The maximum follow-up was 78 weeks.

TRAJENTA 5 mg once daily was studied as monotherapy in three placebo-controlled trials of 18 and 24 weeks' duration and in five additional placebo-controlled studies lasting ≤18 weeks. The use of TRAJENTA in combination with other antihyperglycemic agents was studied in six placebo-controlled trials: two with metformin (12 and 24 weeks' treatment duration); one with a sulfonylurea (18 weeks' treatment duration); one with metformin and sulfonylurea (24 weeks' treatment duration); one with pioglitazone (24 weeks' treatment duration); and one with insulin (primary endpoint at 24 weeks).

In a pooled dataset of 14 placebo-controlled clinical trials, adverse reactions that occurred in ≥2% of patients receiving TRAJENTA (n = 3625) and more commonly than in patients given placebo (n = 2176), are shown in Table 1. The overall incidence of adverse events with TRAJENTA were similar to placebo.

Table 1 Adverse Reactions Reported in ≥2% of Patients Treated with TRAJENTA and Greater than Placebo in Placebo-Controlled Clinical Studies of TRAJENTA Monotherapy or Combination Therapy

	Number (%) of Patients	
	TRAJENTA 5 mg n = 3625	**Placebo n = 2176**
Nasopharyngitis	254 (7.0)	132 (6.1)
Diarrhea	119 (3.3)	65 (3.0)
Cough	76 (2.1)	30 (1.4)

Rates for other adverse reactions for TRAJENTA 5 mg vs placebo when TRAJENTA was used in combination with specific anti-diabetic agents were: urinary tract infection (3.1% vs 0%) and hypertriglyceridemia (2.4% vs 0%) when TRAJENTA was used as add-on to sulfonylurea; hyperlipidemia (2.7% vs 0.8%) and weight increased (2.3% vs 0.8%) when TRAJENTA was used as add-on to pioglitazone; and constipation (2.1% vs 1%) when TRAJENTA was used as add-on to basal insulin therapy. Other adverse reactions reported in clinical studies with treatment of TRAJENTA were hypersensitivity (e.g., urticaria, angioedema, localized skin exfoliation, or bronchial hyperreactivity) and myalgia.

Following 104 weeks' treatment in a controlled study comparing TRAJENTA with glimepiride in which all patients were also receiving metformin, adverse reactions reported in ≥5% of patients treated with TRAJENTA (n = 776) and more frequently than in patients treated with a sulfonylurea (n = 775) were back pain (9.1% vs 8.4%), arthralgia (8.1% vs 6.1%), upper respiratory tract infection (8.0% vs 7.6%), headache (6.4% vs 5.2%), cough (6.1% vs 4.9%), and pain in extremity (5.3% vs 3.9%).

In the clinical trial program, pancreatitis was reported in 15.2 cases per 10,000 patient year exposure while being treated with TRAJENTA compared with 3.7 cases per 10,000 patient year exposure while being treated with comparator (placebo and active comparator, sulfonylurea). Three additional cases of pancreatitis were reported following the last administered dose of linagliptin.

Hypoglycemia

Table 2 summarizes the incidence of hypoglycemia in placebo-controlled studies of TRAJENTA. The incidence of hypoglycemia increased when TRAJENTA was administered with sulfonylurea or insulin.

Table 2: Incidence (%) of Hypoglycemia in Placebo-Controlled Clinical Studies of TRAJENTA in Patients with Type 2 Diabetes Mellitus

Add-on to Sulfonylurea (18 Weeks)	**Placebo (N=84)**	**TRAJENTA (N=161)**
Hypoglycemia with plasma glucose <54 mg/dL	1.2%	1.9%
Severe* hypoglycemia (%)	0%	0%
Add-on to Metformin and Sulfonylurea (24 Weeks)	**Placebo (N=263)**	**TRAJENTA (N=792)**
Hypoglycemia with plasma glucose <54 mg/dL	5.3%	8.1%
Severe* hypoglycemia (%)	0.8%	0.6%
Add-on to Basal Insulin (52 Weeks)	**Placebo (N=630)**	**TRAJENTA (N=631)**
Hypoglycemia with plasma glucose <54 mg/dL	21.6%	19.8%
Severe* hypoglycemia (%)	1.1%	1.7%

*Hypoglycemia requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

In an active-controlled (glimepiride) cardiovascular safety study with TRAJENTA (CAROLINA) with median time on treatment of 5.9 years, the incidence of severe hypoglycemia was 0.3% in the TRAJENTA group (N=3014) and 2.2% in glimepiride group (N=3000).

Use in Renal Impairment

TRAJENTA was compared to placebo as add-on to pre-existing antidiabetic therapy over 52 weeks in 133 patients with severe renal impairment (estimated GFR <30 mL/min). For the initial 12 weeks of the study, background antidiabetic therapy was kept stable and included insulin, sulfonylurea, glinides, and pioglitazone. For the remainder of the trial, dose adjustments in antidiabetic background therapy were allowed.

In general, the incidence of adverse events including severe hypoglycemia was similar to those reported in other TRAJENTA trials. The observed incidence of hypoglycemia was higher (TRAJENTA, 63% compared to placebo, 49%) due to an increase in asymptomatic hypoglycemic events especially during the first 12 weeks when background glycemic therapies were kept stable. Ten TRAJENTA-treated patients (15%) and 11 placebo-treated patients (17%) reported at least one episode of confirmed symptomatic hypoglycemia (accompanying finger stick glucose ≤54 mg/dL). During the same time period, severe hypoglycemic events, defined as an event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions, were reported in 3 (4.4%) TRAJENTA-treated patients and 3 (4.6%) placebo-treated patients. Events that were considered life-threatening or required hospitalization were reported in 2 (2.9%) patients on TRAJENTA and 1 (1.5%) patient on placebo.

Renal function as measured by mean eGFR and creatinine clearance did not change over 52 weeks' treatment compared to placebo.

Laboratory Tests
Changes in laboratory findings were similar in patients treated with TRAJENTA 5 mg compared to patients treated with placebo.

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

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

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

The clinical significance of elevations in lipase and amylase with TRAJENTA is unknown in the absence of potential signs and symptoms of pancreatitis *[see Warnings and Precautions (5.1)].*

Vital Signs
No clinically meaningful changes in vital signs were observed in patients treated with TRAJENTA.

6.2 Postmarketing Experience
Additional adverse reactions have been identified during postapproval use of TRAJENTA. 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.

- Acute pancreatitis, including fatal pancreatitis *[see Indications and Usage (1.2))]*
- Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions
- Severe and disabling arthralgia
- Bullous pemphigoid
- Rash
- Mouth ulceration, stomatitis
- Rhabdomyolysis

7 DRUG INTERACTIONS
7.1 Inducers of P-glycoprotein or CYP3A4 Enzymes
Rifampin decreased linagliptin exposure, suggesting that the efficacy of TRAJENTA may be reduced when administered in combination with a strong P-gp or CYP3A4 inducer. Therefore, use of alternative treatments is strongly recommended when linagliptin is to be administered with a strong P-gp or CYP3A4 inducer *[see Clinical Pharmacology (12.3)]*.

7.2 Insulin Secretagogues or Insulin
Coadministration of TRAJENTA 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 *[see Warnings and Precautions*

(5.2)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited data with TRAJENTA use in pregnant women are not sufficient to inform of drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*.

In animal reproduction studies, no adverse developmental effects were observed when linagliptin was administered to pregnant rats during the period of organogenesis at doses similar to the maximum recommended clinical dose, based on exposure *[see Data]*.

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

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

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

8.2 Lactation

Risk Summary

There is no information regarding the presence of linagliptin in human milk, the effects on the breastfed infant, or the effects on milk production. However, linagliptin is present in rat milk. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRAJENTA and any potential adverse effects on the breastfed child from TRAJENTA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of TRAJENTA in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

In the 15 type 2 diabetes studies with linagliptin, 1085 linagliptin-treated patients were 65 years of age and older (including 131 linagliptin-treated patients 75 years of age and older). Of these 15 studies, 12 were double-blind placebo-controlled. In these 12 studies, 591 linagliptin-treated patients were 65 years of age and

older (including 82 linagliptin-treated patients 75 years of age and older). In these linagliptin studies, no overall differences in safety or effectiveness of linagliptin were observed between geriatric patients and younger adult patients.

8.6 Renal Impairment

No dose adjustment is recommended for patients with renal impairment *[see Clinical Pharmacology (12.3)].*

In the TRAJENTA treatment arm of the CARMELINA trial *[see Clinical Studies (14.2)]*, 2200 (63%) patients had renal impairment (eGFR <60 mL/min/1.73 m^2). Approximately 20% of the population had eGFR ≥45 to <60 mL/min/1.73 m^2, 28% of the population had eGFR ≥30 to <45 mL/min/1.73 m^2 and 15% had eGFR <30 mL/min/1.73 m^2. The overall incidence of adverse reactions were generally similar between the TRAJENTA and placebo treatment arms.

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

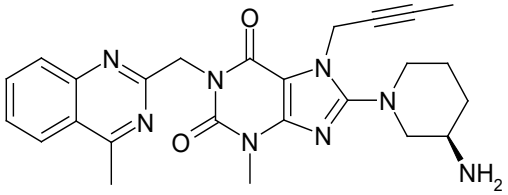
In the event of an overdose with TRAJENTA, please consult a doctor immediately. Employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of linagliptin by hemodialysis or peritoneal dialysis is unlikely.

DURING CONTROLLED CLINICAL TRIALS IN HEALTHY SUBJECTS, WITH SINGLE DOSES OF UP TO 600 MG OF TRAJENTA (EQUIVALENT TO 120 TIMES THE RECOMMENDED DAILY DOSE) THERE WERE NO DOSE-RELATED CLINICAL ADVERSE DRUG REACTIONS. THERE IS NO EXPERIENCE WITH DOSES ABOVE 600 MG IN HUMANS.11 DESCRIPTION

TRAJENTA (linagliptin) tablets contain, as the active ingredient, an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme.

Linagliptin is described chemically as 1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]-

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



Linagliptin is a white to yellowish, not or only slightly hygroscopic solid substance. It is very slightly soluble in water (0.9 mg/mL). Linagliptin is soluble in methanol (ca. 60 mg/mL), sparingly soluble in ethanol (ca. 10 mg/mL), very slightly soluble in isopropanol (<1 mg/mL), and very slightly soluble in acetone (ca. 1 mg/mL).

Each film-coated tablet of TRAJENTA contains 5 mg of linagliptin free base and the following inactive ingredients: mannitol, pregelatinized starch, corn starch, copovidone, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: hypromellose, titanium dioxide, talc, polyethylene glycol, and red ferric oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

The pharmacokinetics of linagliptin has been characterized in healthy subjects and patients with type 2 diabetes. After oral administration of a single 5-mg dose to healthy subjects, peak plasma concentrations of linagliptin occurred at approximately 1.5 hours post dose (T_{max}); the mean plasma area under the curve (AUC) was 139 nmol*h/L and maximum concentration (C_{max}) was 8.9 nmol/L.

Plasma concentrations of linagliptin decline in at least a biphasic manner with a long terminal half-life (>100 hours), related to the saturable binding of linagliptin to DPP-4. The prolonged elimination phase does not contribute to the accumulation of the drug. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of linagliptin 5 mg, is approximately 12 hours. After once-daily dosing, steady-state plasma concentrations of linagliptin 5 mg are reached by the third dose, and C_{max} and AUC increased by a factor of 1.3 at steady-state compared with the first dose. The intra-subject and inter-subject coefficients of variation for linagliptin AUC were small (12.6% and 28.5%, respectively). Plasma AUC of linagliptin increased in a less than dose-proportional manner in the dose range of 1 to 10 mg. The pharmacokinetics of linagliptin is similar in healthy subjects and in patients with type 2 diabetes.

Absorption

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

Distribution

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

Elimination

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

Metabolism

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

Excretion

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

Specific Populations

Renal Impairment

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

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

In patients with moderate renal impairment under steady-state conditions, mean exposure of linagliptin increased ($AUC_{\tau,ss}$ by 71% and C_{max} by 46%) compared with healthy subjects. This increase was not associated with a prolonged accumulation half-life, terminal half-life, or an increased accumulation factor. Renal excretion of linagliptin was below 5% of the administered dose and was not affected by decreased renal function.

Patients with type 2 diabetes mellitus and severe renal impairment showed steady-state exposure approximately 40% higher than that of patients with type 2 diabetes mellitus and normal renal function (increase in $AUC_{\tau,ss}$ by 42% and C_{max} by 35%). For both type 2 diabetes mellitus groups, renal excretion was below 7% of the administered dose.

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

Hepatic Impairment

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

Body Mass Index (BMI)/Weight
No dose adjustment is necessary based on BMI/weight. BMI/weight had no clinically meaningful effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis.

Gender
No dose adjustment is necessary based on gender. Gender had no clinically meaningful effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis.

Geriatric
Age did not have a clinically meaningful impact on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis.

Pediatric
Studies characterizing the pharmacokinetics of linagliptin in pediatric patients have not yet been performed.

Race
No dose adjustment is necessary based on race. Race had no clinically meaningful effect on the pharmacokinetics of linagliptin based on available pharmacokinetic data, including subjects of White, Hispanic, Black, and Asian racial groups.

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

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

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

Table 3 Effect of Coadministered Drugs on Systemic Exposure of Linagliptin

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

*Multiple dose (steady-state) unless otherwise noted
**For information regarding clinical recommendations *[see Drug Interactions (7.1)].*

#Single dose
†AUC = AUC(0 to 24 hours) for single-dose treatments and AUC = AUC(TAU) for multiple-dose treatments
QD = once daily
BID = twice daily
TID = three times daily

Table 4 Effect of Linagliptin on Systemic Exposure of Coadministered Drugs

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

approximately 215 times the clinical dose based on AUC exposure.

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

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

14 CLINICAL STUDIES

14.1 Glycemic Control Trials

TRAJENTA has been studied as monotherapy and in combination with metformin, sulfonylurea, pioglitazone, and insulin. TRAJENTA has also been studied in patients with type 2 diabetes and severe chronic renal impairment.

In patients with type 2 diabetes, treatment with TRAJENTA produced clinically significant improvements in hemoglobin A1c (A1C), fasting plasma glucose (FPG), and 2-hour post-prandial glucose (PPG) compared with placebo.

Monotherapy

A total of 730 patients with type 2 diabetes participated in 2 double-blind, placebo-controlled studies, one of 18 weeks' and another of 24 weeks' duration, to evaluate the efficacy and safety of TRAJENTA monotherapy. In both monotherapy studies, patients currently on an antihyperglycemic agent discontinued the agent and underwent a diet, exercise, and drug washout period of about 6 weeks that included an open-label placebo run-in during the last 2 weeks. Patients with inadequate glycemic control (A1C 7% to 10%) after the washout period were randomized; patients not currently on antihyperglycemic agents (off therapy for at least 8 weeks) with inadequate glycemic control (A1C 7% to 10%) were randomized after completing the 2-week, open-label, placebo run-in period. In the 18-week study, only patients ineligible for metformin were recruited. In the 18-week study, 76 patients were randomized to placebo and 151 to TRAJENTA 5 mg; in the 24-week study, 167 patients were randomized to placebo and 336 to TRAJENTA 5 mg. Patients who failed to meet specific glycemic goals during the 18-week study received rescue therapy with pioglitazone and/or insulin; metformin rescue therapy was used in the 24-week trial.

Treatment with TRAJENTA 5 mg daily provided statistically significant improvements in A1C, FPG, and 2-hour PPG compared with placebo (Table 5). In the 18-week study, 12% of patients receiving TRAJENTA 5 mg and 18% who received placebo required rescue therapy. In the 24-week study, 10.2% of patients receiving TRAJENTA 5 mg and 20.9% of patients receiving placebo required rescue therapy. The improvement in A1C compared with placebo was not affected by gender, age, race, prior antihyperglycemic therapy, baseline BMI, or a standard index of insulin resistance (HOMA-IR). As is typical for trials of agents to treat type 2 diabetes, the mean reduction in A1C with TRAJENTA appears to be related to the degree of A1C elevation at baseline. In these 18- and 24-week studies, the changes from baseline in A1C were -0.4% and -0.4%, respectively, for those given TRAJENTA, and 0.1% and 0.3%, respectively, for those given placebo. Change from baseline in body weight did not differ significantly between the groups.

Table 5 Glycemic Parameters in Placebo-Controlled Monotherapy Studies of TRAJENTA*

	18-Week Study		24-Week Study	
	TRAJENTA 5 mg	**Placebo**	**TRAJENTA 5 mg**	**Placebo**
A1C (%)				
Number of patients	n = 147	n = 73	n = 333	n = 163
Baseline (mean)	8.1	8.1	8.0	8.0
Change from baseline (adjusted mean***)	-0.4	0.1	-0.4	0.3
Difference from placebo (adjusted mean) (95% CI)	-0.6 (-0.9, -0.3)	--	-0.7 (-0.9, -0.5)	--
Patients [n (%)] achieving A1C <7%**	32 (23.5)	8 (11.8)	77 (25)	17 (12)
FPG (mg/dL)				
Number of patients	n = 138	n = 66	n = 318	n = 149
Baseline (mean)	178	176	164	166
Change from baseline (adjusted mean***)	-13	7	-9	15
Difference from placebo (adjusted mean) (95% CI)	-21 (-31, -10)	--	-23 (-30, -16)	--
2-hour PPG (mg/dL)				
Number of patients	Data not available	Data not available	n = 67	n = 24
Baseline (mean)	--	--	258	244
Change from baseline (adjusted mean***)	--	--	-34	25
Difference from placebo (adjusted mean) (95% CI)	--	--	-58 (-82, -34)	--

*Full analysis population using last observation on study
**18-week study: Placebo, n=68; TRAJENTA, n=136
24-week study: Placebo, n=147; TRAJENTA, n=306
***18-week study. HbA1c: ANCOVA model included treatment, reason for metformin intolerance and number of prior oral anti-diabetic medicine(s) (OADs) as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment, reason for metformin intolerance and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.
24-week study. HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates. PPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline postprandial glucose after two hours as covariate.

Add-on Combination Therapy with Metformin
A total of 701 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of TRAJENTA in combination with metformin. Patients already on metformin (n = 491) at a dose of at least 1500 mg per day were randomized after completing a 2-week, open-label, placebo run-in period. Patients on metformin and another antihyperglycemic agent (n = 207) were randomized after a run-in period of approximately 6 weeks on metformin (at a dose of at least 1500 mg per day) in monotherapy. Patients were randomized to the addition of either TRAJENTA 5 mg or placebo,

administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with glimepiride rescue.

In combination with metformin, TRAJENTA provided statistically significant improvements in A1C, FPG, and 2-hour PPG compared with placebo (Table 6). Rescue glycemic therapy was used in 7.8% of patients treated with TRAJENTA 5 mg and in 18.9% of patients treated with placebo. A similar decrease in body weight was observed for both treatment groups.

Table 6 Glycemic Parameters in Placebo-Controlled Study for TRAJENTA in Combination with Metformin*

	TRAJENTA 5 mg + Metformin	**Placebo + Metformin**
A1C (%)		
Number of patients	n = 513	n = 175
Baseline (mean)	8.1	8.0
Change from baseline (adjusted mean***)	-0.5	0.15
Difference from placebo + metformin (adjusted mean) (95% CI)	-0.6 (-0.8, -0.5)	--
Patients [n (%)] achieving A1C <7%**	127 (26.2)	15 (9.2)
FPG (mg/dL)		
Number of patients	n = 495	n = 159
Baseline (mean)	169	164
Change from baseline (adjusted mean***)	-11	11
Difference from placebo + metformin (adjusted mean) (95% CI)	-21 (-27, -15)	--
2-hour PPG (mg/dL)		
Number of patients	n = 78	n = 21
Baseline (mean)	270	274
Change from baseline (adjusted mean***)	-49	18
Difference from placebo + metformin (adjusted mean) (95% CI)	-67 (-95, -40)	--

*Full analysis population using last observation on study
**TRAJENTA 5 mg + Metformin, n=485; Placebo + Metformin, n=163
***HbA1c: ANCOVA model included treatment and number of prior oral OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates. PPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline postprandial glucose after two hours as covariate.

Initial Combination Therapy with Metformin
A total of 791 patients with type 2 diabetes mellitus and inadequate glycemic control on diet and exercise participated in the 24-week, randomized, double-blind, portion of this placebo-controlled factorial study designed to assess the efficacy of TRAJENTA as initial therapy with metformin. Patients on an antihyperglycemic agent (52%) underwent a drug washout period of 4 weeks' duration. After the washout period and after completing a 2-week single-blind placebo run-in period, patients with inadequate glycemic control (A1C ≥7.0% to ≤10.5%) were randomized. Patients with inadequate glycemic control (A1C ≥7.5% to <11.0%) not on antihyperglycemic agents at study entry (48%) immediately entered the 2-week, single-blind, placebo run-in period and then were randomized. Randomization was stratified by baseline A1C (<8.5% vs ≥8.5%) and use of a prior oral antidiabetic drug (none vs monotherapy). Patients were randomized in a

1:2:2:2:2:2 ratio to either placebo or one of 5 active-treatment arms. Approximately equal numbers of patients were randomized to receive initial therapy with 5 mg of TRAJENTA once daily, 500 mg or 1000 mg of metformin twice daily, or 2.5 mg of linagliptin twice daily in combination with 500 mg or 1000 mg of metformin twice daily. Patients who failed to meet specific glycemic goals during the study were treated with sulfonylurea, thiazolidinedione, or insulin rescue therapy.

Initial therapy with the combination of linagliptin and metformin provided significant improvements in A1C and fasting plasma glucose (FPG) compared to placebo, to metformin alone, and to linagliptin alone (Table 7).

The adjusted mean treatment difference in A1C from baseline to week 24 (LOCF) was -0.5% (95% CI -0.7, -0.3; p<0.0001) for linagliptin 2.5 mg/metformin 1000 mg twice daily compared to metformin 1000 twice daily; -1.1% (95% CI -1.4, -0.9; p<0.0001) for linagliptin 2.5 mg/metformin 1000 mg twice daily compared to TRAJENTA 5 mg once daily; -0.6% (95% CI -0.8, -0.4; p<0.0001) for linagliptin 2.5 mg/metformin 500 mg twice daily compared to metformin 500 mg twice daily; and -0.8% (95% CI -1.0, -0.6; p<0.0001) for linagliptin 2.5 mg/metformin 500 mg twice daily compared to TRAJENTA 5 mg once daily.

Lipid effects were generally neutral. No meaningful change in body weight was noted in any of the 6 treatment groups.

Table 7 Glycemic Parameters at Final Visit (24-Week Study) for Linagliptin and Metformin, Alone and in Combination in Randomized Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Diet and Exercise**

	Placebo	**TRAJENTA 5 mg Once Daily***	**Metformin 500 mg Twice Daily**	**Linagliptin 2.5 mg Twice Daily* + Metformin 500 mg Twice Daily**	**Metformin 1000 mg Twice Daily**	**Linagliptin 2.5 mg Twice Daily* + Metformin 1000 mg Twice Daily**
A1C (%)						
Number of patients	n = 65	n = 135	n = 141	n = 137	n = 138	n = 140
Baseline (mean)	8.7	8.7	8.7	8.7	8.5	8.7
Change from baseline (adjusted mean****)	0.1	-0.5	-0.6	-1.2	-1.1	-1.6
Difference from placebo (adjusted mean) (95% CI)	--	-0.6 (-0.9, -0.3)	-0.8 (-1.0, -0.5)	-1.3 (-1.6, -1.1)	-1.2 (-1.5, -0.9)	-1.7 (-2.0, -1.4)
Patients [n (%)] achieving A1C <7%***	7 (10.8)	14 (10.4)	26 (18.6)	41 (30.1)	42 (30.7)	74 (53.6)
Patients (%) receiving rescue medication	29.2	11.1	13.5	7.3	8.0	4.3
FPG (mg/dL)						
Number of patients	n = 61	n = 134	n = 136	n = 135	n = 132	n = 136
Baseline (mean)	203	195	191	199	191	196
Change from baseline (adjusted mean****)	10	-9	-16	-33	-32	-49

Difference from placebo (adjusted mean) (95% CI)	--	-19 (-31, -6)	-26 (-38, -14)	-43 (-56, -31)	-42 (-55, -30)	-60 (-72, -47)

*Total daily dose of TRAJENTA is equal to 5 mg
**Full analysis population using last observation on study
***Metformin 500 mg twice daily, n=140; Linagliptin 2.5 mg twice daily + Metformin 500 twice daily, n=136; Metformin 1000 mg twice daily, n=137; Linagliptin 2.5 mg twice daily + Metformin 1000 mg twice daily, n=138
****HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.

Active-Controlled Study vs Glimepiride in Combination with Metformin
The efficacy of TRAJENTA was evaluated in a 104-week, double-blind, glimepiride-controlled, non-inferiority study in patients with type 2 diabetes with insufficient glycemic control despite metformin therapy. Patients being treated with metformin only entered a run-in period of 2 weeks' duration, whereas patients pretreated with metformin and one additional antihyperglycemic agent entered a run-in treatment period of 6 weeks' duration with metformin monotherapy (dose of ≥1500 mg/day) and washout of the other agent. After an additional 2-week placebo run-in period, those with inadequate glycemic control (A1C 6.5% to 10%) were randomized 1:1 to the addition of TRAJENTA 5 mg once daily or glimepiride. Randomization was stratified by baseline HbA1c (<8.5% vs ≥8.5%), and the previous use of antidiabetic drugs (metformin alone vs metformin plus one other OAD). Patients receiving glimepiride were given an initial dose of 1 mg/day and then electively titrated over the next 12 weeks to a maximum dose of 4 mg/day as needed to optimize glycemic control. Thereafter, the glimepiride dose was to be kept constant, except for down-titration to prevent hypoglycemia.

After 52 and 104 weeks, TRAJENTA and glimepiride both had reductions from baseline in A1C (52 weeks: -0.4% for TRAJENTA, -0.6% for glimepiride; 104 weeks: -0.2% for TRAJENTA, -0.4% for glimepiride) from a baseline mean of 7.7% (Table 8). The mean difference between groups in A1C change from baseline was 0.2% with 2-sided 97.5% confidence interval (0.1%, 0.3%) for the intent-to-treat population using last observation carried forward. These results were consistent with the completers analysis.

Table 8 Glycemic Parameters at 52 and 104 Weeks in Study Comparing TRAJENTA to Glimepiride as

Add-On Therapy in Patients Inadequately Controlled on Metformin**

	Week 52		Week 104	
	TRAJENTA 5 mg + Metformin	**Glimepiride + Metformin (mean Glimepiride dose 3 mg)**	**TRAJENTA 5 mg + Metformin**	**Glimepiride + Metformin (mean Glimepiride dose 3 mg)**
A1C (%)				
Number of patients	n = 764	n = 755	n = 764	n = 755
Baseline (mean)	7.7	7.7	7.7	7.7
Change from baseline (adjusted mean****)	-0.4	-0.6	-0.2	-0.4
Difference from glimepiride (adjusted mean) (97.5% CI)	0.2 (0.1, 0.3)	--	0.2 (0.1, 0.3)	--
FPG (mg/dL)				
Number of patients	n = 733	n = 725	n = 733	n = 725
Baseline (mean)	164	166	164	166
Change from baseline (adjusted mean****)	-8*	-15	-2†	-9
Hypoglycemia incidence (%)* **				
Number of patients	n = 776	n = 775	n = 776	n = 775
Incidence****	5.3 *	31.1	7.5 *	36.1

*p<0.0001 vs glimepiride; †p=0.0012 vs glimepiride
**Full analysis population using last observation on study
***Hypoglycemic incidence included both asymptomatic events (not accompanied by typical symptoms and plasma glucose concentration of ≤70 mg/dL) and symptomatic events with typical symptoms of hypoglycemia and plasma glucose concentration of ≤70 mg/dL.
****HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates. Hypoglycemia incidence (%): Cochran-Mantel-Haenszel test was performed on the patient population contained in the treated set, to compare the proportion of patients with hypoglycemic events between patients treated with linagliptin and patients treated with glimepiride.

Patients treated with linagliptin had a mean baseline body weight of 86 kg and were observed to have an adjusted mean decrease in body weight of 1.1 kg at 52 weeks and 1.4 kg at 104 weeks. Patients on glimepiride had a mean baseline body weight of 87 kg and were observed to have an adjusted mean increase from baseline in body weight of 1.4 kg at 52 weeks and 1.3 kg at 104 weeks (treatment difference p<0.0001 for both timepoints).

Add-On Combination Therapy with Pioglitazone
A total of 389 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of TRAJENTA in combination with pioglitazone. Therapy was stopped in patients on oral antihyperglycemic therapy for a period of 6 weeks (4 weeks followed by a 2-week, open-label, placebo run-in period). Drug-naïve patients entered directly into the 2-week placebo run-in period. After the run-in period, patients were randomized to receive either TRAJENTA 5 mg or placebo, both in addition to pioglitazone 30 mg daily. Patients who failed to meet specific glycemic goals during the studies

were treated with metformin rescue. Glycemic endpoints measured were A1C and FPG.

In initial combination with pioglitazone 30 mg, TRAJENTA 5 mg provided statistically significant improvements in A1C and FPG compared to placebo with pioglitazone (Table 9). Rescue therapy was used in 7.9% of patients treated with TRAJENTA 5 mg/pioglitazone 30 mg and 14.1% of patients treated with placebo/pioglitazone 30 mg. Patient weight increased in both groups during the study with an adjusted mean change from baseline of 2.3 kg and 1.2 kg in the TRAJENTA 5 mg/pioglitazone 30 mg and placebo/pioglitazone 30 mg groups, respectively (p = 0.0141).

Table 9 Glycemic Parameters in Placebo-Controlled Study for TRAJENTA in Combination Therapy with Pioglitazone*

	TRAJENTA 5 mg + Pioglitazone	**Placebo + Pioglitazone**
A1C (%)		
Number of patients	n = 252	n = 128
Baseline (mean)	8.6	8.6
Change from baseline (adjusted mean**)	-1.1	-0.6
Difference from placebo + pioglitazone (adjusted mean) (95% CI)	-0.5 (-0.7, -0.3)	--
Patients [n (%)] achieving A1C <7%	108 (42.9)	39 (30.5)
FPG (mg/dL)		
Number of patients	n = 243	n = 122
Baseline (mean)	188	186
Change from baseline (adjusted mean**)	-33	-18
Difference from placebo + pioglitazone (adjusted mean) (95% CI)	-14 (-21, -7)	--

*Full analysis population using last observation on study
**HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.

Add-On Combination with Sulfonylureas

A total of 245 patients with type 2 diabetes participated in an 18-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of TRAJENTA in combination with sulfonylurea (SU). Patients on sulfonylurea monotherapy (n = 142) were randomized after completing a 2-week, single-blind, placebo run-in period. Patients on a sulfonylurea plus one additional oral antihyperglycemic agent (n = 103) were randomized after a wash-out period of 4 weeks and a 2-week, single-blind, placebo run-in period. Patients were randomized to the addition of TRAJENTA 5 mg or to placebo, each administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with metformin rescue. Glycemic endpoints measured included A1C and FPG.

In combination with a sulfonylurea, TRAJENTA provided statistically significant improvements in A1C compared with placebo following 18 weeks' treatment; the improvements in FPG observed with TRAJENTA were not statistically significant compared with placebo (Table 10). Rescue therapy was used in 7.6% of patients treated with TRAJENTA 5 mg and 15.9% of patients treated with placebo. There was no significant difference between TRAJENTA and placebo in body weight.

Table 10 Glycemic Parameters in Placebo-Controlled Study for TRAJENTA in Combination with

Sulfonylurea*

	TRAJENTA 5 mg + SU	Placebo + SU
A1C (%)		
Number of patients	n = 158	n = 82
Baseline (mean)	8.6	8.6
Change from baseline (adjusted mean***)	-0.5	-0.1
Difference from placebo + SU (adjusted mean) (95% CI)	-0.5 (-0.7, -0.2)	--
Patients [n (%)] achieving A1C <7%**	23 (14.7)	3 (3.7)
FPG (mg/dL)		
Number of patients	n = 155	n = 78
Baseline (mean)	180	171
Change from baseline (adjusted mean***)	-8	-2
Difference from placebo + SU (adjusted mean) (95% CI)	-6 (-17, 4)	--

SU = sulfonylurea
*Full analysis population using last observation on study
**TRAJENTA 5 mg + SU, n=156; Placebo + SU, n=82
***HbA1c: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment and number of prior OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates

Add-On Combination Therapy with Metformin and a Sulfonylurea
A total of 1058 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of TRAJENTA in combination with a sulfonylurea and metformin. The most common sulfonylureas used by patients in the study were: glimepiride (31%), glibenclamide (26%), and gliclazide (26%, not available in the United States). Patients on a sulfonylurea and metformin were randomized to receive TRAJENTA 5 mg or placebo, each administered once daily. Patients who failed to meet specific glycemic goals during the study were treated with pioglitazone rescue. Glycemic endpoints measured included A1C and FPG.

In combination with a sulfonylurea and metformin, TRAJENTA provided statistically significant improvements in A1C and FPG compared with placebo (Table 11). In the entire study population (patients on TRAJENTA in combination with sulfonylurea and metformin), a mean reduction from baseline relative to placebo in A1C of -0.6% and in FPG of -13 mg/dL was seen. Rescue therapy was used in 5.4% of patients treated with TRAJENTA 5 mg and in 13% of patients treated with placebo. Change from baseline in body weight did not differ significantly between the groups.

Table 11 Glycemic Parameters in Placebo-Controlled Study for TRAJENTA in Combination with Metformin and Sulfonylurea*

	TRAJENTA 5 mg + Metformin + SU	Placebo + Metformin + SU
A1C (%)		
Number of patients	n = 778	n = 262
Baseline (mean)	8.2	8.1
Change from baseline (adjusted mean***)	-0.7	-0.1
Difference from placebo (adjusted mean) (95% CI)	-0.6 (-0.7, -0.5)	--

Patients [n (%)] achieving A1C <7%**	217 (29.2)	20 (8.1)
FPG (mg/dL)		
Number of patients	n = 739	n = 248
Baseline (mean)	159	163
Change from baseline (adjusted mean***)	-5	8
Difference from placebo (adjusted mean) (95% CI)	-13 (-18, -7)	--

SU = sulfonylurea
*Full analysis population using last observation on study
**TRAJENTA 5 mg + Metformin + SU, n=742; Placebo + Metformin + SU, n=247
***HbA1c: ANCOVA model included treatment as class-effects and baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.

Add-On Combination Therapy with Insulin

A total of 1261 patients with type 2 diabetes inadequately controlled on basal insulin alone or basal insulin in combination with oral drugs participated in a randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy of TRAJENTA as add-on therapy to basal insulin over 24 weeks. Randomization was stratified by baseline HbA1c (<8.5% vs ≥8.5%), renal function impairment status (based on baseline eGFR), and concomitant use of oral antidiabetic drugs (none, metformin only, pioglitazone only, metformin + pioglitazone). Patients with a baseline A1C of ≥7% and ≤10% were included in the study including 709 patients with renal impairment (eGFR <90 mL/min), most of whom (n=575) were categorized as mild renal impairment (eGFR 60 to <90 mL/min). Patients entered a 2 week placebo run-in period on basal insulin (e.g., insulin glargine, insulin detemir, or NPH insulin) with or without metformin and/or pioglitazone background therapy. Following the run-in period, patients with inadequate glycemic control were randomized to the addition of either 5 mg of TRAJENTA or placebo, administered once daily. Patients were maintained on a stable dose of insulin prior to enrollment, during the run-in period, and during the first 24 weeks of treatment. Patients who failed to meet specific glycemic goals during the double-blind treatment period were rescued by increasing background insulin dose.

TRAJENTA used in combination with insulin (with or without metformin and/or pioglitazone), provided statistically significant improvements in A1C and FPG compared to placebo (Table 12) after 24 weeks of treatment. The mean total daily insulin dose at baseline was 42 units for patients treated with TRAJENTA and 40 units for patients treated with placebo. Background baseline diabetes therapy included use of: insulin alone (16.1%), insulin combined with metformin only (75.5%), insulin combined with metformin and pioglitazone (7.4%), and insulin combined with pioglitazone only (1%). The mean change from baseline to Week 24 in the daily dose of insulin was +1.3 IU in the placebo group and +0.6 IU in the TRAJENTA group. The mean change in body weight from baseline to Week 24 was similar in the two treatment groups.

Table 12 Glycemic Parameters in Placebo-Controlled Study for TRAJENTA in Combination with Insulin*

	TRAJENTA 5 mg + Insulin	**Placebo + Insulin**
A1C (%)		
Number of patients	n = 618	n = 617
Baseline (mean)	8.3	8.3
Change from baseline (adjusted mean***)	-0.6	0.1
Difference from placebo (adjusted mean) (95% CI)	-0.7 (-0.7, -0.6)	--

Patients [n (%)] achieving A1C <7%**	116 (19.5)	48 (8.1)
FPG (mg/dL)		
Number of patients	n = 613	n = 608
Baseline (mean)	147	151
Change from baseline (adjusted mean***)	-8	3
Difference from placebo (adjusted mean) (95% CI)	-11 (-16, -6)	--

*Full analysis population using last observation carried forward (LOCF) method on study
**TRAJENTA + Insulin, n=595; Placebo + Insulin, n=593
***HbA1c: ANCOVA model included treatment, categorical renal function impairment status and concomitant OADs as class-effects, as well as baseline HbA1c as continuous covariates. FPG: ANCOVA model included treatment, categorical renal function impairment status and concomitant OADs as class-effects, as well as baseline HbA1c and baseline FPG as continuous covariates.

The difference between treatment with linagliptin and placebo in terms of adjusted mean change from baseline in HbA1c after 24 weeks was comparable for patients with no renal impairment (eGFR ≥90 mL/min, n=539), with mild renal impairment (eGFR 60 to <90 mL/min, n= 565), or with moderate renal impairment (eGFR 30 to <60 mL/min, n=124).

Renal Impairment
A total of 133 patients with type 2 diabetes participated in a 52 week, double-blind, randomized, placebo-controlled trial designed to evaluate the efficacy and safety of TRAJENTA in patients with both type 2 diabetes and severe chronic renal impairment. Participants with an estimated (based on the four variables modified diet in renal disease [MDRD] equation) GFR value of <30 mL/min were eligible to participate in the study. Randomization was stratified by baseline HbA1c (≤8% and >8%) and background antidiabetic therapy (insulin or any combination with insulin, SU or glinides as monotherapy and pioglitazone or any other antidiabetics excluding any other DPP-4 inhibitors). For the initial 12 weeks of the study, background antidiabetic therapy was kept stable and included insulin, sulfonylurea, glinides, and pioglitazone. For the remainder of the trial, dose adjustments in antidiabetic background therapy were allowed. At baseline in this trial, 62.5% of patients were receiving insulin alone as background diabetes therapy, and 12.5% were receiving sulfonylurea alone.

After 12 weeks of treatment, TRAJENTA 5 mg provided statistically significant improvement in A1C compared to placebo, with an adjusted mean change of -0.6% compared to placebo (95% confidence interval -0.9, -0.3) based on the analysis using last observation carried forward (LOCF). With adjustments in antidiabetic background therapy after the initial 12 weeks, efficacy was maintained for 52 weeks, with an adjusted mean change from baseline in A1C of -0.7% compared to placebo (95% confidence interval -1.0, -0.4) based on analysis using LOCF.

14.2 Cardiovascular Safety Trials

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

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

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

The primary endpoint, MACE, was the time to first occurrence of one of three composite outcomes which included cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The study was designed as a non-inferiority trial with a pre-specified risk margin of 1.3 for the hazard ratio of MACE.

The results of CARMELINA, including the contribution of each component to the primary composite endpoint, are shown in Table 13. The estimated hazard ratio for MACE associated with TRAJENTA relative to placebo was 1.02 with a 95% confidence interval of (0.89, 1.17). The upper bound of this confidence interval, 1.17, excluded the risk margin of 1.3. The Kaplan-Meier curve depicting time to first occurrence of MACE is shown in Figure 1.

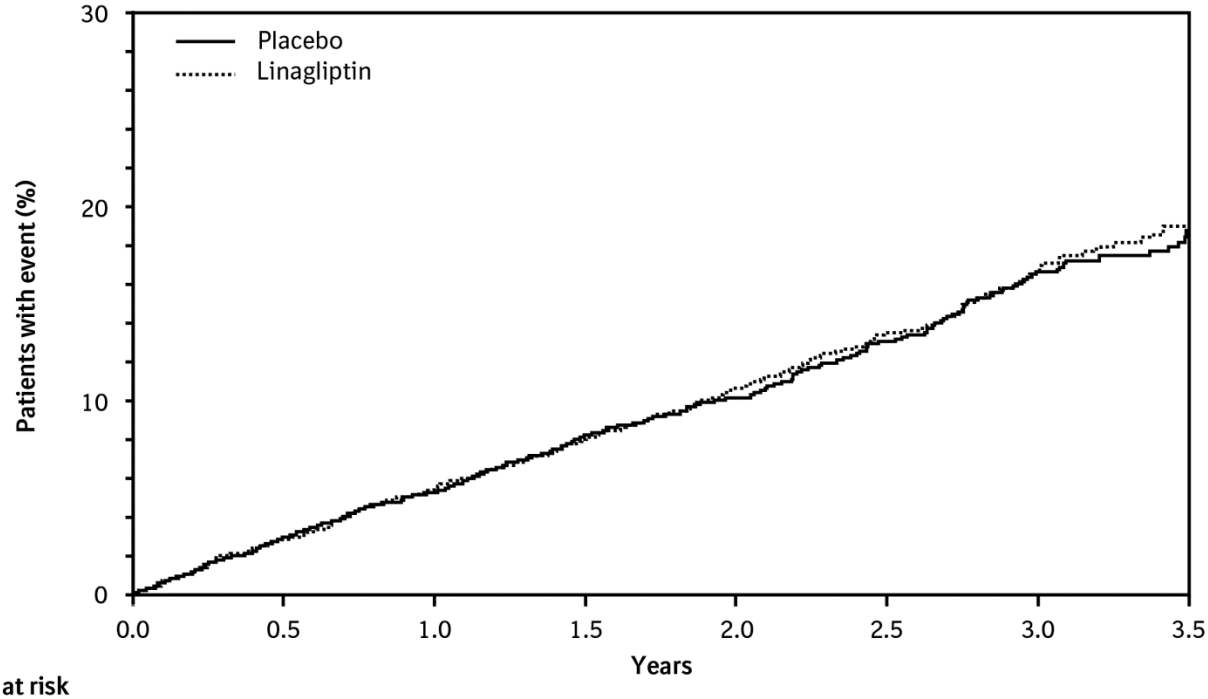
Table 13 Major Adverse Cardiovascular Events (MACE) by Treatment Group in the CARMELINA Trial

	TRAJENTA 5 mg n = 3494		**Placebo n = 3485**		**Hazard Ratio**
	Number of Subjects (%)	**Incidence Rate per 1000 PY***	**Number of Subjects (%)**	**Incidence Rate per 1000 PY***	**(95% CI)**
Composite of first event of CV death, non-fatal myocardial infarction (MI), or non-fatal stroke (MACE)	434 (12.4)	57.7	420 (12.1)	56.3	1.02 (0.89, 1.17)
CV death**	255 (7.3)	32.6	264 (7.6)	34.0	0.96 (0.81, 1.14)
Non-fatal MI**	156 (4.5)	20.6	135 (3.9)	18.0	1.15 (0.91, 1.45)
Non-fatal stroke**	65 (1.9)	8.5	73 (2.1)	9.6	0.88 (0.63, 1.23)

*PY=patient years

**A patient may have experienced more than one component; therefore, the sum of the components is larger than the number of patients who experienced the composite outcome.

Figure 1 Kaplan-Meier: Time to First Occurrence of MACE in the CARMELINA Trial



Patients at risk								
Placebo (n)	3485	3353	3243	2625	1931	1285	758	251
Linagliptin (n)	3494	3373	3254	2634	1972	1306	778	269

CAROLINA

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

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

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

The primary endpoint, MACE, was the time to first occurrence of one of three composite outcomes which included cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The study was designed as a non-inferiority trial with a pre-specified risk margin of 1.3 for the upper bound of the 95% CI for the hazard

ratio of MACE.

The results of CAROLINA, including the contribution of each component to the primary composite endpoint, are shown in Table 14. The Kaplan-Meier curve depicting time to first occurrence of MACE is shown in Figure 2.

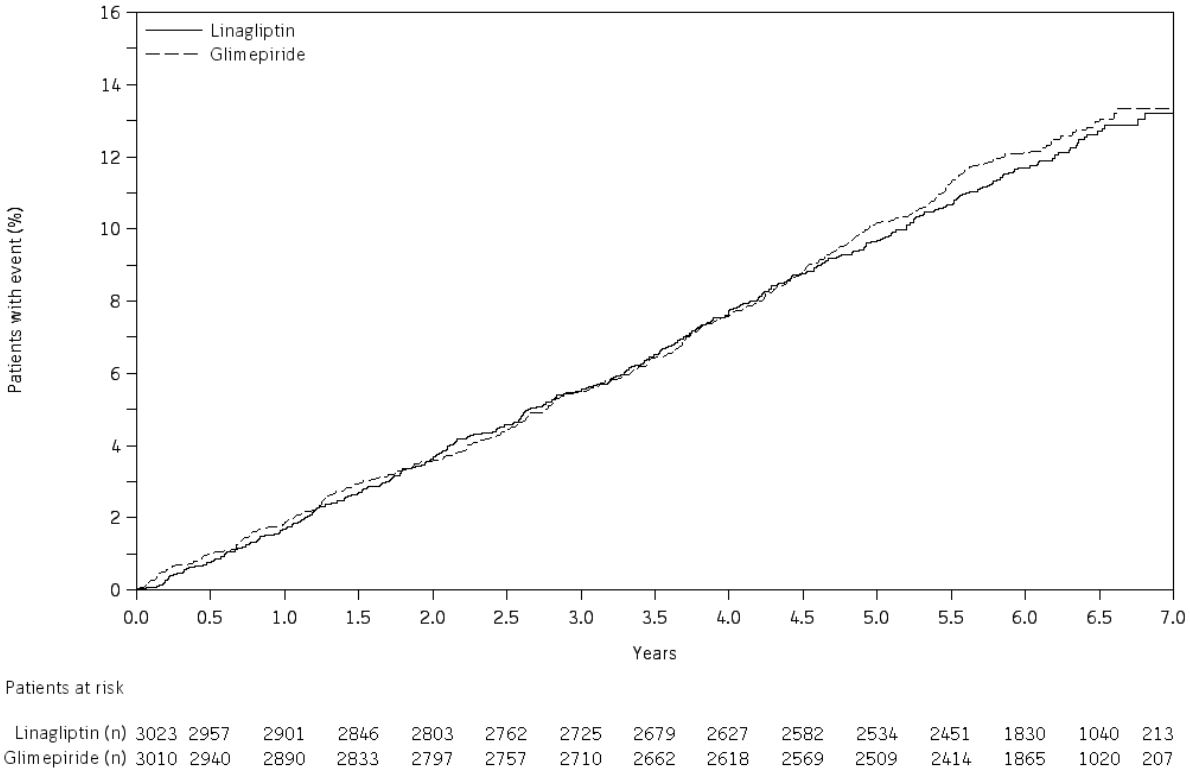
Table 14 Major Adverse Cardiovascular Events (MACE) by Treatment Group in the CAROLINA Study

	TRAJENTA 5 mg n=3023		**Glimepiride (1 mg to 4 mg) n=3010**		**Hazard Ratio**
	Number of Subjects (%)	**Incidence Rate per 1000 PY***	**Number of Subjects (%)**	**Incidence Rate per 1000 PY***	**(95% CI)**
Composite of first event of CV death, non-fatal myocardial infarction (MI), or non-fatal stroke (MACE)	356 (11.8)	20.7	362 (12.0)	21.2	0.98 (0.84, 1.14)
CV death**	169 (5.6)	9.2	168 (5.6)	9.2	1.00 (0.81, 1.24)
Non-fatal MI**	145 (4.8)	8.3	142 (4.7)	8.2	1.01 (0.80, 1.28)
Non-fatal stroke**	91 (3.0)	5.2	104 (3.5)	6.0	0.87 (0.66, 1.15)

*PY=patient years

**A patient may have experienced more than one component; therefore, the sum of the components is larger than the number of patients who experienced the composite outcome

Figure 2 Time to First Occurrence of 3P-MACE in CAROLINA



16 HOW SUPPLIED/STORAGE AND HANDLING

TRAJENTA tablets are available as light red, round, biconvex, bevel-edged, film-coated tablets containing 5 mg of linagliptin. TRAJENTA tablets are debossed with “D5” on one side and the Boehringer Ingelheim logo on the other side.

They are supplied as follows:
2-1000 tablets in aluminium blister of paper box.

Storage
Store below 30°C. Store in a safe place and keep out of the reach of children.
Expiry date please see folding box.

17 PATIENT COUNSELING INFORMATION

Medication Guide

Inform patients of the potential risks and benefits of TRAJENTA and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Pancreatitis

Inform patients that acute pancreatitis has been reported during use of TRAJENTA. Inform patients that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue TRAJENTA promptly and contact their physician if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.1)]*.

Hypoglycemia

Inform patients that the incidence of hypoglycemia is increased when TRAJENTA is added to a sulfonylurea or insulin and that a lower dose of the sulfonylurea or insulin may be required to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.2)]*.

Hypersensitivity Reactions

Inform patients that serious allergic reactions, such as anaphylaxis, angioedema, and exfoliative skin conditions, have been reported during postmarketing use of TRAJENTA. If symptoms of allergic reactions (such as rash, skin flaking or peeling, urticaria, swelling of the skin, or swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking TRAJENTA and seek medical advice promptly *[see Warnings and Precautions (5.3)]*.

Severe and Disabling Arthralgia

Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs *[see Warnings and Precautions (5.4)].*

Bullous Pemphigoid

Inform patients that bullous pemphigoid has been reported during use of TRAJENTA. Instruct patients to seek medical advice if blisters or erosions occur *[see Warnings and Precautions (5.5)].*

Missed Dose

Instruct patients to take TRAJENTA only as prescribed. If a dose is missed, advise patients not to double their next dose.

Blood Glucose and A1C Monitoring

Inform patients that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and A1C levels, with a goal of decreasing these levels toward the normal range. A1C monitoring is especially useful for evaluating long-term glycemic control.

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