佳糖維®

25 毫克膜衣錠、50 毫克膜衣錠、100 毫克膜衣錠

JANUVIA®

25 mg F.C. Tablet, 50 mg F.C. Tablet, 100 mg F.C. Tablet (sitagliptin phosphate)

本藥須由醫師處方使用

25 毫克 衛署藥輸字第 024669 號

50 毫克 衛署藥輸字第 024667 號

100 毫克 衛署藥輸字第 024668 號

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活性成分

每顆JANUVIA膜衣錠含有32.13、64.25或128.5毫克的sitagliptin phosphate monohydrate，分別相當於25、50或100毫克的游離態藥物成分。

治療分類

JANUVIA (sitagliptin phosphate)為一具高度選擇性的口服用強效二肽基肽酶4 (dipeptidyl peptidase 4；DPP-4)酵素抑制劑，適用於治療第二型糖尿病。DPP-4抑制劑乃是一種腸泌素(incretin)增強劑類的藥物。透過抑制DPP-4酵素的作用，sitagliptin可提高兩種已知的活性腸泌素激素的濃度，即類胰高血糖激素胜肽-1 (glucagonlike peptide-1；GLP-1)與葡萄糖依賴性胰島素刺激多肽(glucose-dependent insulinotropic polypeptide；GIP)。Incretins乃是葡萄糖體內平衡生理調節機轉之內因系統的一部份。當血糖濃度正常或升高時，GLP-1與GIP會提高胰臟β細胞合成及釋出胰島素(insulin)的作用。GLP-1也會降低胰臟α細胞的胰高血糖激素(glucagon)分泌作用，進而降低肝臟的葡萄糖生成作用。此機轉並不同於在sulfonylureas中所見的機轉；sulfonylureas在葡萄糖濃度偏低的情況下也會刺激胰島素釋出，致使第二型糖尿病患者和正常人發生sulfonylurea誘發性低血糖。Sitagliptin是一種強效且具高度選擇性的DPP-4酵素抑制劑，在治療濃度下並不會抑制DPP-8或DPP-9這些密切相關的酵素。Sitagliptin的化學結構與藥理作用都不同於GLP-1類似物、胰島素、sulfonylureas或meglitinides、biguanides、過氧化小體增生活化接受體(peroxisome proliferator-activated receptor gamma；PPARγ)促動劑、α葡萄糖苷酶抑制劑及amylin類似物。

臨床藥理學

作用機轉

JANUVIA係屬於一種被稱為二肽基肽酶4 (DPP-4)抑制劑的口服抗高血糖藥物，它可提高活性腸泌素激素的濃度，從而改善第二型糖尿患者的血糖控制。腸泌素激素，包括類胰高血糖激素胜肽-1 (GLP-1)與葡萄糖依賴性胰島素刺激多肽(GIP)，會全天候地自小腸釋出，且其濃度會因進食而升高。Incretins乃是葡萄糖體內平衡生理調節機轉之內因系統的一部份。當血糖濃度正常或升高時，GLP-1與GIP會透過細胞內的環AMP(c-AMP)傳訊路徑提高胰臟β細胞合成及釋出胰島素的作用。第二型糖尿病的動物模型研究顯示，使用GLP-1或使用DPP-4抑制劑治療可增進β細胞對葡萄糖的反應性，並可刺激胰島素的生物合成作用與釋出作用。胰島素濃度升高之後，組織的葡萄糖吸收作用便會隨之增強。此外，GLP-1也會降低胰臟α細胞的glucagon分泌作用。Glucagons濃度降低加上胰島素濃度升高的結果，會促使肝臟的葡萄糖生成作用降低，進而降低血糖的濃度。GLP-1與GIP的作用都具有葡萄糖依賴性，以致GLP-1刺激胰島素釋出與抑制glucagon分泌的作用在血糖濃度偏低時並不會出現。當葡萄糖濃度升高超過正常範圍時，GLP-1與GIP的胰島素釋出刺激作用都會隨之增強。此外，GLP-1並不會減弱身體在低血糖的情況下所產生的正常glucagon反應。GLP-1與GIP的活性會受到DPP-4酵素的限制，此酵素會將腸泌素激素快速水解成不具活性的產物。Sitagliptin可遏阻DPP-4對腸泌素激素的水解作用，從而提高活性形態之GLP-1與GIP的血中濃度。透過提高活性腸泌素之濃度的作用，Sitagliptin可促進胰島素的釋出，並降低glucagon的濃度，且其作用具葡萄糖依賴性。在出現高血糖現象的第二型糖尿病患者中，胰島素與glucagon的濃度變化會促使血紅素A_{1c}(HbA_{1c})及空腹與餐後的血糖濃度降低。這種具葡萄糖依賴性的機轉並不同於在sulfonylureas中所見的機轉；sulfonylureas在葡萄糖濃度偏低的情況下也會刺激胰島素釋出，致使第二型糖尿病患者和正常人出現低血糖的現象。Sitagliptin是一種強效且具高度選擇性的DPP-4酵素抑制劑，因此在治療濃度下並不會抑制DPP-8或DPP-9這些密切相關的酵素。

藥物動力學

Sitagliptin在健康受試者及第二型糖尿病患者體內的藥物動力學特性已有相當廣泛的記述。對健康受試者口服投予一劑100毫克的劑量之後，sitagliptin可迅速為身體所吸收，並可於投藥後1至4小時達到高峰血中濃度(T_{max}中位數)。Sitagliptin的血中AUC值會以和劑量成比例的模式升高。對健康志願者口服投予單劑100毫克的劑量之後，sitagliptin的平均血中AUC值為8.52 μM•hr、C_{max}為950 nM、表面終端半衰期($t_{1/2}$)則為12.4小時。連續投予100毫克的劑量之後，sitagliptin的穩定狀態血中AUC值會比第一劑高出約14%。Sitagliptin的AUC值在受試者本身及受試者間的變異係數很小(分別為5.8%與15.1%)。Sitagliptin在健康受試者與第二型糖尿病患者體內的藥物動力學概況大致相當。

吸收

Sitagliptin的絕對生體可用率約為87%。由於和高脂食物併用並不會影響JANUVIA的藥物動力學，因此，JANUVIA可和食物併用，亦可不和食物併用。

分佈

對健康受試者靜脈注射單劑100毫克的劑量之後，達穩定狀態時的平均分佈體積約為198公升。Sitagliptin和血漿蛋白進行可逆性結合的比例很低(38%)。

代謝

Sitagliptin主要都是以未改變的形式經由尿液排出體外，而代謝則是一個較次要的途徑。約有79%的sitagliptin會以未改變的形式經由尿液排出體外。

口服投予一劑[^{14}C] sitagliptin之後，約有16%的放射活性會以sitagliptin之代謝產物的形式排出體外。其中共檢出六種微量的代謝物，但一般並不認為這些代謝物有助於sitagliptin對血中DPP-4的抑制作用。體外研究顯示，和sitagliptin之有限代謝作用有關的主要酵素為CYP3A4，此外，CYP2C8也涉及其中。

排除

對健康受試者口服投予一劑[^{14}C] sitagliptin之後，幾近100%的放射活性都會在投藥後一週內經由糞便(13%)或尿液(87%)排出體外。口服投予一劑100毫克的sitagliptin之後，表面終端$t_{1/2}$約為12.4小時，腎臟廓清率則為350 mL/min左右。

Sitagliptin的排除主要是透過腎臟的排泄作用，並涉及腎小管的主動分泌作用。Sitagliptin乃是人類有機陰離子載運體-3 (human organic anion transporter-3; hOAT-3)的作用受質，hOAT-3可能和腎臟排除sitagliptin的作用有關，但hOAT-3和sitagliptin之體內運輸的臨床關聯性目前尚未確立。Sitagliptin也是P糖蛋白(p-glycoprotein)的作用受質，P糖蛋白可能也會媒介腎臟排除sitagliptin的作用。不過，Cyclosporine (一種P糖蛋白抑制劑)並不會降低腎臟對sitagliptin的廓清作用。

病患特性

腎功能不全：有一項單一劑量開放研究曾評估過JANUVIA (50毫克)在不同程度之慢性腎功能不全患者體內的藥物動力學，並和正常的健康對照受試者進行比較。這項研究收錄了依據肌酸酐廓清率分類呈現輕度(50至<80 mL/min)、中度(30至<50 mL/min)及重度(<30 mL/min)腎功能不全的患者，以及接受血液透析的末期腎病(end-stage renal disease; ESRD)患者。肌酸酐廓清率的評估係依據24小時尿液肌酸酐廓清率檢測的結果，或是依據Cockcroft-Gault公式由血清肌酸酐濃度推算而得：

$$CrCl = \frac{[140 - 年齡(歲)] \times 體重(公斤)}{[72 \times 血清肌酸酐濃度(mg/dL)]} \{女性患者 \times 0.85\}$$

和正常的健康對照受試者相比較，輕度腎功能不全患者的血中sitagliptin濃度並未出現具臨床意義的升高現象。在中度腎功能不全的患者中，sitagliptin的血中AUC值較正常的健康對照受試者升高了2倍左右，而重度腎功能不全患者與接受血液透析的ESRD患者則升高了4倍左右。血液透析可移除部份的sitagliptin (投藥後4小時開始進行血液透析，3至4小時內可移除13.5%)。對中度和重度腎功能不全的患者，以及必須接受血液透析的ESRD患者，若要達到和腎功能正常之患者相當的血中sitagliptin濃度，建議採用較低的劑量。(參見**劑量與用法**欄中的*腎功能不全患者*)

肝功能不全：對中度肝功能不全(Child-Pugh分數為7至9分)的患者投予單劑100毫克的JANUVIA之後，sitagliptin的平均AUC與C_{max}要比健康的相應對照組分別高出約21%與13%。一般並不認為這些差異具有臨床上的意義。因此，對輕或中度肝功能不全的患者，並不須調整JANUVIA的劑量。在重度肝功能不全(Child-Pugh分數>9)患者方面，目前尚無任何臨床經驗。不過，由於sitagliptin主要乃是透過腎臟排出體外，因此一般並不認為嚴重的肝功能不全會影響sitagliptin的藥物動力學。

老年人：劑量並不須因年齡而進行任何調整。一項針對第I期與第II期研究數據所進行的群體藥物動力學分析顯示，年齡對sitagliptin的藥物動力學並不會造成具臨床意義的影響。老年受試者(65至80歲)的血中sitagliptin濃度要比較年輕的受試者高出19%左右。

小兒：目前並未曾進行過使用JANUVIA治療小兒病患的研究。

性別：劑量並不須因性別而進行任何調整。一項針對第I期藥物動力學研究數據所進行的綜合分析與一項針對第I期與第II期研究數據所進行的群體藥物動力學分析顯示，性別對sitagliptin的藥物動力學並不會造成任何具臨床意義的影響。

種族：劑量並不須因種族而進行任何調整。一項針對第I期藥物動力學研究數據所進行的綜合分析與一項針對涵蓋白人、西班牙人、黑人、亞洲人及其他種族之第I期與第II期研究數據所進行的群體藥物動力學分析顯示，種族對sitagliptin的藥物動力學並不會造成任何具臨床意義的影響。

身體質量指數(Body Mass Index; BMI)：劑量並不須因BMI而進行任何調整。一項針對第I期藥物動力學研究數據所進行的綜合分析與一項針對第I期與第II期研究數據所進行的群體藥物動力學分析顯示，身體質量指數對sitagliptin的藥物動力學並不會造成任何具臨床意義的影響。

第二型糖尿病：Sitagliptin在第二型糖尿病患者體內的藥物動力學和健康受試者大致相當。

臨床研究

在九項評估sitagliptin之血糖控制效果的雙盲安慰劑對照性第III期臨床研究中，約有5200位第二型糖尿病患者接受隨機分組。參與研究的患者普遍都併有其它疾病，包括血脂異常與高血壓，並有50%以上為肥胖患者(BMI≥30 kg/m^2)。大多數的患者(51.6%至65.8%)都符合國家膽固醇教育計劃(National Cholesterol Education Program; NCEP)中的代謝症候群標準。在這些研究中，所收納的患者包括白人、西班牙人、黑人、亞洲人和其他種族，且整體平均年齡約為55歲。

有一項為期52週(包含初期12週雙盲期和40週開放期)的，149位日本第二型糖尿病患者併用JANUVIA和metformin進行隨機安慰劑對照研究。

另外也曾進行過其它的雙盲安慰劑對照性臨床研究，其中一項為針對151位日本第二型糖尿病患者所進行的研究，另一項為針對91位併有中至重度腎功能不全之第二型糖尿病患者所進行的研究。

另有1172位以metformin治療仍無法達到適當血糖控制效果的第二型糖尿病患者參與一項為期52週、以活性藥物(glipizide)對照的研究。另有一項為期24週、針對1050位在飲食控制及運動之治療下，未能達到適當血糖控制效果的第二型糖尿病患者，進行以metformin做為活性對照的研究。

對第二型糖尿病患者，和安慰劑相比較，使用JANUVIA治療可使血紅素A_{1c} (HbA_{1c})、空腹血糖值(FPG)及餐後2小時血糖值(PPG)獲得臨床上明顯的改善。在活性藥物(glipizide)對照研究中，臨床上明顯的血糖控制改善效果可維持達52週。

JANUVIA亦可改善β細胞功能的各項檢測結果(參見**臨床藥理學**欄)。

單一療法臨床研究

共有1,262位第二型糖尿病患者曾參與兩項評估JANUVIA單一療法之療效與安全性的雙盲安慰劑對照研究，其中一項為18週研究，另一項為24週研究。這些血糖控制不良(HbA_{1c}值為7%至10%)的患者經隨機分組後，分別接受每日一次100毫克或200毫克之JANUVIA或安慰劑的治療。

和安慰劑相比較，使用每日100毫克的JANUVIA治療可使HbA_{1c}、FPG及2小時PPG獲得明顯的改善(表1及表2)。在這些研究所收錄的患者中，HbA_{1c}基礎值的分佈範圍相當廣。和安慰劑相比較，HbA_{1c}方面的改善效果並不會因性別、年齡、種族、之前的降血糖治療、BMI基礎值、出現代謝症候群、或胰島素抗性(HOMA-IR)的評估指標而受到影響。在診斷出罹患糖尿病後所經過之時間較短(<3年)或HbA_{1c}基礎值較高的患者中，HbA_{1c}的降低幅度較大。在這兩項18週及24週的研究中，在進入研究時未服用任何降血糖藥物的病患，與基礎值相比，投與JANUVIA者的HbA_{1c}降幅分別為-0.67%及-0.85%；投與安慰劑者的降幅分別為-0.10%及-0.18%。在這兩項研究中，和安慰劑相比較，JANUVIA都可於第3週(檢測FPG的第一個時間點)即達到使FPG明顯降低的效果(在18週研究中的降低程度為-19.3 mg/dL，在24週研究中則為-15.8 mg/dL)。

整體而言，每日200毫克之劑量的降血糖效果並未優於每日100毫克的劑量。JANUVIA對血脂經點評估指標的影響和安慰劑相當。在這兩項研究中，使用JANUVIA治療之患者的體重皆未較基礎值增加，而使用安慰劑的患者則有小幅減輕的現象(表2)。使用JANUVIA治療之患者中的低血糖發生率和使用安慰劑者相當。

表1、針對第二型糖尿病患者†所進行之18週與24週安慰劑對照性JANUVIA研究中的HbA_{1c}相關結果，並依HbA_{1c}的基礎值範圍進行分層分析

	18週研究		24週研究	
	JANUVIA 100毫克	安慰劑	JANUVIA 100毫克	安慰劑
HbA_{1c} (%)	N=193	N=103	N=229	N=244
基礎值(平均值)	8.04	8.05	8.01	8.03
相對於基礎值的變化(校正後平均值‡)	-0.48	0.12	-0.61	0.18
與安慰劑組間的差異(校正後平均值‡)	-0.60§		-0.79§	
達到HbA_{1c}<7%之效果的患者數(%)	69 (35.8)	16 (15.5)	93 (40.6)	41 (16.8)
HbA_{1c}基礎值範圍				
HbA_{1c} (%)基礎值≥9%	N=27	N=20	M=37	N=35
基礎值(平均值)	9.48	9.48	9.59	9.46
相對於基礎值的變化(校正後平均值‡)	-0.83	0.37	-1.27	0.25
與安慰劑組間的差異(校正後平均值‡)	-1.20		-1.52	
HbA_{1c} (%)基礎值≥8%至<9%	N=70	N=25	N=62	N=82

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基礎值(平均值)	8.40	8.38	8.36	8.41
相對於基礎值的變化(校正後平均值‡)	-0.42	0.19	-0.64	0.16
與安慰劑組間的差異(校正後平均值‡)	-0.61		-0.80	
HbA$_{1c}$ (%)基礎值<8%	**N=96**	**N=58**	**N=130**	**N=127**
基礎值(平均值)	7.37	7.41	7.39	7.39
相對於基礎值的變化(校正後平均值‡)	-0.42	0.02	-0.40	0.17
與安慰劑組間的差異(校正後平均值‡)	-0.44		-0.57	

† 所有接受治療的患者(治療意圖分析)。
‡ 依據先前之抗高血糖治療狀態與基礎值加以校正後的最小平方平均值。 § 和安慰劑相比較，p<0.001。

表2、針對第二型糖尿病患者†所進行之18週與24週安慰劑對照性JANUVIA研究中的其它血糖參數及體重相關結果

	18 週研究		24 週研究	
	JANUVIA 100毫克	**安慰劑**	**JANUVIA 100毫克**	**安慰劑**
FPG (mg/dL)	**N=201**	**N=107**	**N=234**	**N=247**
基礎值(平均值)	179.8	183.6	170.2	176.1
相對於基礎值的變化(校正後平均值‡)	-12.7	7.0	-12.4	4.7
與安慰劑組間的差異(校正後平均值‡)	-19.7§		-17.1§	
2 小時 PPG (mg/dL)	‖	‖	**N=201**	**N=204**
基礎值(平均值)			257.2	270.8
相對於基礎值的變化(校正後平均值‡)			-48.9	-2.2
與安慰劑組間的差異(校正後平均值‡)			-46.7§	
體重(公斤)¶	**N=172**	**N=77**	**N=193**	**N=174**
基礎值(平均值)	89.5	91.3	83.9	83.3
相對於基礎值的變化(校正後平均值‡)	-0.6	-0.7	-0.2	-1.1
與安慰劑組間的差異(校正後平均值‡)	0.1#		0.9††	

† 所有接受治療的患者(治療意圖分析)。
‡ 依據先前的抗高血糖治療狀態與基礎值加以校正後的最小平方平均值。
§ 和安慰劑相比較，p<0.001。 ‖ 無資料。
¶ 所有接受治療的患者(APaT)，但不包括接受血糖救援治療的患者。
# 和安慰劑相比較，不具統計意義(P≥0.05)。 ††和安慰劑相比較，p<0.01。

其它單一療法研究

有一項雙盲安慰劑對照研究曾針對日本的第二型糖尿病患者評估每日一次100毫克之JANUVIA的治療效果，並和安慰劑進行比較。此項研究共收錄151位患者(75位使用JANUVIA治療，76位使用安慰劑治療)，患者的平均年齡為55.3歲，BMI基礎值為25.2 kg/m^2，平均HbA$_{1c}$基礎值為7.6%，平均FPG基礎值則為163 mg/dL。經過12週後，JANUVIA組的HbA$_{1c}$值相對於安慰劑組的降低程度為1.05% (JANUVIA組相對於基礎值的變化為-0.65%，安慰劑組則為0.41%，p<0.001)。FPG值相對於安慰劑組的降低程度為31.9 mg/dL (JANUVIA組相對於基礎值的變化為-22.5 mg/dL，安慰劑組則為9.4 mg/dL，p<0.001)。

另有一項多中心、隨機、雙盲、安慰劑對照研究也曾針對91位併有慢性腎功能不全(肌酸酐廓清率<50 mL/min)的第二型糖尿病患者評估JANUVIA的安全性與耐受性。併有中度腎功能不全的患者係接受每日50毫克之JANUVIA的治療，併有重度腎功能不全的患者或接受透析的ESRD患者則是使用每日25毫克的劑量。這項研究顯示，JANUVIA的安全性與耐受性大致和安慰劑相當。此外，JANUVIA組之HbA$_{1c}$值與FPG值相對於安慰劑組的降低程度也和其它單一療法研究中所見者相當。(參見**臨床藥理學**欄中的***藥物動力學***、***病患特性***、**腎功能不全**)

與 Metformin 併用的初始合併治療

共有1,091位在飲食控制及運動之治療下，未能達到適當血糖控制效果的第二型糖尿病患者，參與一項評估合併使用sitagliptin與metformin進行初始治療之安全性與療效的隨機、雙盲、安慰劑對照性階乘研究。人數約略相同的患者在隨機分組後分別使用安慰劑、每日一次100毫克的sitagliptin (JANUVIA)、每日兩次500毫克或1000毫克的metformin、或每日兩次50毫克的sitagliptin合併每日兩次500毫克或1000毫克的metformin進行初始治療。

和安慰劑、單獨使用metformin及單獨使用sitagliptin相比較，合併使用sitagliptin與metformin進行初始治療可使HbA$_{1c}$、FPG及2小時PPG獲得明顯的改善(p<0.001；表3)。FPG方面的改善效果(接近最大FPG降低效果)於第3週評估時間點即可達到(開始治療後的第一個評估時間點)，並可一直維持到24週研究結束。β細胞功能的評估結果(HOMA-β)以及胰島素原和胰島素的比例)也顯示，合併使用sitagliptin與metformin的改善效果要高於其它各種單一藥物療法。脂質影響通常並不明顯。合併使用sitagliptin與metformin之治療組中的體重減輕程度和在metformin單一治療組或安慰劑組中所見者大致相當。在HbA$_{1c}$相對於基礎值之平均降低程度和安慰劑組相比較的差異方面，大致HbA$_{1c}$基礎值越高的患者，差異越大。HbA$_{1c}$方面的改善效果大致不會因性別、年齡、種族或BMI基礎值而受到影響。加入研究時未服用降血糖藥物之病患的HbA$_{1c}$相對於基礎值之平均降低程度為：-1.06%於每日一次100毫克JANUVIA；-1.09%於每日兩次500毫克metformin；-1.24%於每日兩次1000毫克metformin；-1.59%於每日兩次50毫克sitagliptin合併每日兩次500毫克metformin；-1.94%於每日兩次50毫克sitagliptin合併每日兩次1000毫克metformin；及-0.17%於服用安慰劑的病患。

表3、單獨使用及合併使用Sitagliptin與Metformin做為初始治療藥物之患者最後一次回診時(24週研究)的血糖參數及體重相關結果†

	安慰劑	**Sitagliptin (JANUVIA) 100 mg QD**	**Metformin 500 mg bid**	**Sitagliptin 50 mg bid + Metformin 500 mg bid**	**Metformin 1000 mg bid**	**Sitagliptin 50 mg bid + Metformin 1000 mg bid**
HbA$_{1c}$ (%)	**N=165**	**N=175**	**N=178**	**N=183**	**N=177**	**N=178**
基礎值(平均值)	8.68	8.87	8.90	8.79	8.68	8.76
相對於基礎值的變化(校正後平均值‡)	0.17	-0.66	-0.82	-1.40	-1.13	-1.90
與安慰劑組間的差異(校正後平均值‡)	-	-0.83§	-0.99§	-1.57§	-1.30§	-2.07§
達到 HbA$_{1c}$<7%之效果的患者數(%)	15 (9.1)	35 (20.0)	41 (23.0)	79 (43.2)	68 (38.4)	118 (66.3)
FPG (mg/dL)	**N=169**	**N=178**	**N=179**	**N=183**	**N=179**	**N=180**
基礎值(平均值)	196.3	201.4	205.2	203.9	197.0	196.7
相對於基礎值的變化(校正後平均值‡)	5.8	-17.5	-27.3	-47.1	-29.3	-63.9
與安慰劑組間的差異(校正後平均值‡)	-	-23.9§	-33.1§	-52.9§	-35.1§	-69.7§
2 小時 PPG (mg/dL)	**N=129**	**N=136**	**N=141**	**N=147**	**N=138**	**N=152**
基礎值(平均值)	276.8	285.4	292.7	291.8	283.4	286.9
相對於基礎值的變化(校正後平均值‡)	0.3	-51.9	-53.4	-92.5	-78.0	-116.6
與安慰劑組間的差異(校正後平均值‡)	-	-52.2§	-53.7§	-92.8§	-78.3§	-116.9§
體重(公斤)‖	**N=169**	**N=175**	**N=179**	**N=184**	**N=175**	**N=178**
基礎值(平均值)	90.1	85.9	88.1	90.0	89.4	88.2
相對於基礎值的變化(校正後平均值‡)	-0.9	0.0	-0.9	-0.6	-1.1	-1.3
與安慰劑組間的差異(校正後平均值‡)		0.9¶	0.1#	0.4#	-0.1#	-0.3#

† 所有接受治療的患者(治療意圖分析)。
‡ 依據先前的抗高血糖治療狀態與基礎值加以校正後的最小平方平均值。
§ 和安慰劑相比較，p<0.001。 ‖ 所有接受治療的患者(APaT)，但不包括接受血糖救援治療的患者。
¶ 和安慰劑相比較，p=0.005 # 和安慰劑相比較，不具統計意義(P≥0.05)。

此外，這項研究也收錄了患有較為嚴重之高血糖(HbA$_{1c}$ >11%，或血糖濃度>280 mg/dL)的患者(N=117)，並以開放投藥的方式讓他們接受每日兩次sitagliptin 50毫克合併每日兩次metformin 1000毫克的治療。在這組患者中，HbA$_{1c}$、FPG及2小時PPG的基礎值分別為11.15%、314.4 mg/dL與441.0 mg/dL。經過24週之後發現，HbA$_{1c}$、FPG及2小時PPG相對於基礎值的降低程度分別為-2.94%、-126.7 mg/dL與-207.9 mg/dL。在這個開放治療組中，治療24週後的體重有略為增加的現象(1.3公斤)。

初始合併治療或合併治療之維持治療，並不是每一位患者都適合，治療的選擇應由醫師判斷決定。

與 Metformin 合併治療

共有701位第二型糖尿病患者曾參與一項評估JANUVIA與metformin併用之療效的24週、隨機、雙盲、安慰劑對照研究。所有的患者都先接受metformin單一療法的治療，且劑量都提高到至少每日1,500毫克。患者經隨機分組後分別於療程中加入每日一次100毫克的JANUVIA或安慰劑。

和安慰劑加metformin相比較，JANUVIA與metformin併用可使HbA$_{1c}$、FPG及2小時PPG獲得明顯的改善(表4)。與安慰劑相較，HbA$_{1c}$方面的改善效果並不會因HbA$_{1c}$基礎值、先前的抗高血糖治療、性別、年齡、BMI基礎值、診斷出罹患糖尿病後所經過的時間、出現代謝症候群、或胰島素抗性(HOMA-IR)或胰島素分泌(HOMA-β)的評估指標而受到影響。和使用安慰劑的患者相比較，使用JANUVIA之患者的總膽固醇、非HDL膽固醇及三酸甘油脂都有略為降低的現象。兩個治療組的體重都有程度相近的減輕現象。

表4、以添加的方式合併使用JANUVIA與Metformin治療之患者最後一次回診時(24週研究)的血糖參數及體重相關結果†

	JANUVIA 100毫克 + Metformin	**安慰劑 + Metformin**
HbA$_{1c}$ (%)	**N=453**	**N=224**
基礎值(平均值)	7.96	8.03
相對於基礎值的變化(校正後平均值‡)	-0.67	-0.02
與安慰劑+metformin組間的差異(校正後平均值‡)	-0.65§	
達到HbA$_{1c}$<7%之效果的患者數(%)	213 (47.0)	41 (18.3)
FPG (mg/dL)	**N=454**	**N=226**
基礎值(平均值)	170.0	173.5
相對於基礎值的變化(校正後平均值‡)	-16.9	8.5
與安慰劑+metformin組間的差異(校正後平均值‡)	-25.4§	
2 小時 PPG (mg/dL)	**N=387**	**N=182**
基礎值(平均值)	274.5	272.4
相對於基礎值的變化(校正後平均值‡)	-62.0	-11.4
與安慰劑+metformin組間的差異(校正後平均值‡)	-50.6§	
體重(公斤)%	**N=399**	**N=169**
基礎值(平均值)	86.9	87.6
相對於基礎值的變化(校正後平均值‡)	-0.7	-0.6
與安慰劑+metformin組間的差異(校正後平均值‡)	-0.1¶	

† 所有接受治療的患者(治療意圖分析)。
‡ 依據先前的抗高血糖治療狀態與基礎值加以校正後的最小平方平均值。
§ 和安慰劑+metformin相比較，p<0.001。
% 所有接受治療的患者(APaT)，但不包括接受血糖救援治療的患者。
¶ 和安慰劑+metformin相比較，不具統計意義(P≥0.05)。

與 Metformin 合併治療之日本研究

有一項雙盲安慰劑對照研究曾針對日本的第二型糖尿病患者評估每日一次50毫克之JANUVIA併用於metformin的療效。這些患者曾接受metformin單一療法治療，仍無法達到適當血糖控制效果。此項研究共收錄149位患者(77位使用JANUVIA治療，72位使用安慰劑治療)，患者的平均年齡為58.4歲，BMI基礎值為25.1 kg/m^2，平均HbA$_{1c}$基礎值為7.9%，平均FPG基礎值為156 mg/dL，平均PPG基礎值為244 mg/dL。第12週時，每日一次50毫克的JANUVIA併用於metformin治療比安慰劑可顯著地改善HbA$_{1c}$ (分別為-0.39%與0.30%，相對於安慰劑，P<0.001)，FPG (分別為-11.3 mg/dL與6.5 mg/dL，相對於安慰劑，P<0.001)，及2小時PPG (-29.0 mg/dL與17.8 mg/dL，相對於安慰劑，P<0.001)。

以Metformin作為活性藥物對照之研究

JANUVIA與metformin的療效比較，係以一項為期24週、雙盲、metformin作為對照、針對沒有接受降血糖治療(停止治療4個月以上)、且在飲食控制及運動之治療下，未能達到適當血糖控制效果的第二型糖尿病患者的試驗進行評估。在這項研究中，病患經隨機分配分別接受每日一次100毫克JANUVIA(N=528)或metformin(N=522)治療24週。接受metformin的患者，起始劑量為每日500毫克，再由研究人員在5週的期間，依耐受性調整至每日1500至2000毫克的劑量。調整期後的平均metformin劑量約為每日1900毫克。血糖終點評估指標包括HbA$_{1c}$值與空腹血糖值。

相對於基礎值的變化，這兩種療法皆可使血糖控制效果獲得具統計意義的改善。符合計畫書規定之分析族群的平均 HbA$_{1c}$ 基礎值為 7.2%。第 24 週時，HbA$_{1c}$ 相對於基礎值的降低程度在每日 JANUVIA 100 毫克治療組中為-0.43%及在 metformin 治療組為-0.57%。此差異結果符合預設的這兩種藥物的療效彼此相當的結論。

FPG 的降低程度在 JANUVIA 組為-11.5 mg/dL 及在 metformin 組為-19.4 mg/dL。胃腸道不良反應的整體發生率在以 JANUVIA 治療的病患中為 11.6%，而在以 metformin 治療的病患中為 20.7%。設定的胃腸道不良經驗發生率為：下痢(JANUVIA, 3.6%; metformin, 10.9%)、噁心 (1.1%, 3.1%)、腹痛(2.1%, 3.8%)、及嘔吐(0.4%, 1.3%)。兩治療組低血糖的發生率沒有顯著差異(JANUVIA, 1.7%; metformin, 3.4%)。兩治療組比基礎期減少體重(JANUVIA, -0.6 kg; metformin -1.9 kg)。

以Glipizide作為活性藥物對照之研究

研究人員曾在一項為期52週的雙盲glipizide對照試驗中，針對使用劑量≥1500 mg/day之metformin單一療法治療仍無法達到適當血糖控制效果的第二型糖尿病患者，評估治療效果的長期維持表現。在這項研究中，患者經隨機分組後分別以添加每日100毫克之JANUVIA (N=588)或添加glipizide (N=584)的方式治療52週。在glipizide治療組中，患者一開始先接受5 mg/day的劑量，再由研究人員彈性調整劑量，使患者的FPG在後續18週內達到<110 mg/dL的目標值，且未出現明顯的低血糖現象。為達最佳血糖控制效果，最高可使用20 mg/day的劑量。之後即將glipizide的劑量維持固定不變。調整階段結束後的glipizide平均劑量為10.3毫克。

相對於基礎值的變化這兩種療法皆可使血糖控制效果獲得具統計意義的改善。經過52週之後，在每日JANUVIA 100毫克治療組中，HbA$_{1c}$相對於基礎值的降低程度為0.67%，在glipizide治療組中亦為0.67%，由此可見，這兩種藥物的療效彼此相當。在JANUVIA治療組中，FPG的降低程度為10.0 mg/dL，在glipizide治療組中則為7.5 mg/dL。一項事後分析的結果顯示，在這兩個治療組中，HbA$_{1c}$基礎值較高(≥9%)之患者的HbA$_{1c}$相對於基礎值的降低程度都較大(在JANUVIA組中為-1.68%；在glipizide組中為-1.76%)。這項研究顯示，在JANUVIA治療組中，胰島素原和胰島素的比例(胰島素合成與釋出的效率指標)有改善的

現象，在glipizide治療組中則有惡化的現象。JANUVIA治療組中的低血糖發生率(4.9%)要明顯低於glipizide組(32.0%)。使用JANUVIA治療之患者的體重有明顯較基礎值減輕的現象，而使用glipizide治療之患者的體重則有明顯增加的現象(分別為-1.5公斤與+1.1公斤)。

與Pioglitazone併用的初始合併治療

總計 520 位在飲食控制及運動之治療下，未能達到適當血糖控制效果的第二型糖尿病患者參與一項為期 24 週、隨機、雙盲，藉以評估合併使用 JANUVIA 與 pioglitazone 做為初始治療的療效研究。經隨機分配以每日一次 100 毫克 JANUVIA 併用 30 毫克 pioglitazone 或每日一次 30 毫克 pioglitazone 單方做為初始治療的病患數相當。

相較於單獨使用 pioglitazone，合併使用 JANUVIA 與 pioglitazone 進行初始治療可使 HbA_{1c}、FPG 及 2 小時 PPG 獲得明顯的改善(表 5)。在預設的分組分析中，HbA_{1c}基礎值≥10%患者的 HbA_{1c}的降低程度，在 JANUVIA 併用 pioglitazone 組(N=99)為-3.00%，在單獨服用 pioglitazone 組(N=88)為-2.06%。在 HbA_{1c} 基礎值<10%的患者，兩組(併用 N=152、單獨 N=158)分別為-1.99%及-1.14%。不論以性別、年齡、種族、BMI 基礎，或疾病的時間各分組間，HbA_{1c}的改善程度大致相同；JANUVIA 併用 pioglitazone 者的體重稍微增加；血脂參數的變化兩組相似。

表 5、合併使用 JANUVIA 與 Pioglitazone 做為初始治療藥物之患者最後一次回診時(24 週研究)的血糖參數及體重相關結果†

	JANUVIA 100 mg + Pioglitazone	Pioglitazone
HbA_{1c} (%)	**N = 251**	**N = 246**
基礎值(平均值)	9.50	9.44
相對於基礎值的變化(校正後平均值‡)	-2.38	-1.49
與pioglitazone組間的差異(校正後平均值‡)	-0.89§	
達到HbA_{1c}<7%之效果的患者數(%)	151 (60%)	68 (28%)
FPG (mg/dL)	**N = 256**	**N = 253**
基礎值(平均值)	203.3	200.7
相對於基礎值的變化(校正後平均值‡)	-63.0	-40.2
與pioglitazone組間的差異(校正後平均值‡)	-22.8§	
2小時PPG (mg/dL)	**N = 216**	**N = 211**
基礎值(平均值)	282.7	284.1
相對於基礎值的變化(校正後平均值‡)	-113.6	-68.9
與pioglitazone組間的差異(校正後平均值‡)	-44.7§	
體重(公斤)‖	**N = 232**	**N = 218**
基礎值(平均值)	80.4	80.7
相對於基礎值的變化(校正後平均值‡)	3.0	1.9
與pioglitazone組間的差異(校正後平均值‡)	1.1¶	

† 所有接受治療的患者(治療意圖分析)。 ‡依據基礎值加以校正後的最小平方平均值。
§和pioglitazone 相比較，p<0.001。 ‖所有接受治療的患者(APaT)。
¶和pioglitazone 相比較，p<0.01。

與Pioglitazone合併治療

共有353位第二型糖尿病患者曾參與一項評估JANUVIA與pioglitazone併用之療效的24週、隨機、雙盲、安慰劑對照研究。所有的患者都先接受pioglitazone單一療法的治療，劑量為每日30-45毫克。患者經隨機分組後分別於療程中加入每日一次100毫克的JANUVIA或安慰劑。血糖終點評估指標包括HbA_{1c}值與空腹血糖值。

和安慰劑加pioglitazone相比較，JANUVIA與pioglitazone併用可使HbA_{1c}與FPG獲得明顯的改善(表6)。相較於安慰劑，HbA_{1c}方面的改善效果並不會因HbA_{1c}基礎值、先前的抗高血糖治療、性別、年齡、種族、BMI基礎值、診斷出罹患糖尿病後所經過的時間、出現代謝症候群、或胰島素抗性(HOMA-IR)或胰島素分泌(HOMA-β)的評估指標而受到影響。在使用JANUVIA治療的患者中，和使用安慰劑的患者相比較，三酸甘油脂有略為降低的現象。在體重變化方面，JANUVIA治療組與安慰劑組之間並無任何明顯差異。

表6、以添加的方式合併使用JANUVIA與Pioglitazone治療之患者最後一次回診時(24週研究)的血糖參數及體重相關結果†

	JANUVIA 100毫克 + Pioglitazone	安慰劑 + Pioglitazone
HbA_{1c} (%)	**N=163**	**N=174**
基礎值(平均值)	8.05	8.00
相對於基礎值的變化(校正後平均值‡)	-0.85	-0.15
與安慰劑+pioglitazone組間的差異(校正後平均值‡)	-0.70§	
達到HbA_{1c}<7%之效果的患者數(%)	74 (45.4)	40 (23.0)
FPG (mg/dL)	**N=163**	**N=174**
基礎值(平均值)	168.3	165.6
相對於基礎值的變化(校正後平均值‡)	-16.7	1.0
與安慰劑+pioglitazone組間的差異(校正後平均值‡)	-17.7§	
體重(公斤)‖	**N=133**	**N=136**
基礎值(平均值)	90.0	85.6
相對於基礎值的變化(校正後平均值‡)	1.8	1.5
與安慰劑+pioglitazone組間的差異(校正後平均值‡)	0.2¶	

† 所有接受治療的患者(治療意圖分析)。 ‡依據先前的抗高血糖治療狀態與基礎值加以校正後的最小平方平均值。
§和安慰劑+pioglitazone相比較，p<0.001。‖所有接受治療的患者(APaT)，但不包括接受血糖救援治療的患者。
¶和安慰劑+pioglitazone相比較，不具統計意義(P≥0.05)。

與 Glimepiride 或與 Glimepiride 加 Metformin 的合併治療

共有441位第二型糖尿病患者曾參與一項評估JANUVIA與glimepiride (≥每日4毫克)併用或與glimepiride加metformin (≥每日1500毫克)併用之療效的24週、隨機、雙盲、安慰劑對照研究。患者經隨機分組後分別於療程中加入每日一次100毫克的JANUVIA或安慰劑。血糖終點評估指標包括HbA_{1c}與空腹血糖值。

在與glimepiride併用或與glimepiride加metformin併用的情況下，和安慰劑相比較，JANUVIA可使HbA_{1c}與FPG獲得明顯的改善(表7)。在整體研究對象中(包括使用glimepiride治療的患者以及使用glimepiride加metformin治療的患者)，HbA_{1c}相對於基礎值之降低程度和安慰劑相比較的差異為-0.74%，FPG則為-20.1 mg/dL。相較於安慰劑，HbA_{1c}方面的改善效果在預設的性別、年齡、種族、BMI基礎值、診斷出罹患糖尿病後所經過的時間、出現代謝症候群、或胰島素抗性(HOMA-IR)或胰島素分泌(HOMA-β)的評估指標分組間大都一致。和使用安慰劑的患者相比較，使用JANUVIA治療之患者的體重有略為增加的現象。

表7、以添加的方式將JANUVIA與Glimepiride併用或與Glimepiride加Metformin併用之患者最後一次回診時(24週研究)的血糖參數及體重相關結果†

	JANUVIA 100毫克 + Glimepiride	安慰劑 + Glimepiride	JANUVIA 100毫克 + Glimepiride + Metformin	安慰劑 + Glimepiride + Metformin
HbA_{1c} (%)	**N=102**	**N=103**	**N=115**	**N=105**
基礎值(平均值)	8.41	8.46	8.27	8.28
相對於基礎值的變化(校正後平均值‡)	-0.30	0.27	-0.59	0.30
與安慰劑組間的差異(校正後平均值‡)	-0.57§		-0.89§	
達到HbA_{1c}<7%之效果的患者數(%)	11 (10.8)	9 (8.7)	26 (22.6)	1 (1.0)
FPG (mg/dL)	**N=104**	**N=104**	**N=115**	**N=109**
基礎值(平均值)	183.5	184.6	179.3	178.9
相對於基礎值的變化(校正後平均值‡)	-0.9	18.4	-7.8	12.9
與安慰劑組間的差異(校正後平均值‡)	-19.3¶		-20.7§	
體重(公斤)‖	**N=76**	**N=73**	**N=102**	**N=74**
基礎值(平均值)	85.7	81.5	86.5	84.6
相對於基礎值的變化(校正後平均值‡)	1.1	0.0	0.4	-0.7
與安慰劑組間的差異(校正後平均值‡)	-1.1#		1.1††	

† 所有接受治療的患者(治療意圖分析)。 ‡ 依據先前的抗高血糖治療狀態與基礎值加以校正後的最小平方平均值。
§和安慰劑相比較，p<0.001。 ‖所有接受治療的患者(APaT)，但不包括接受血糖救援治療的患者。
¶和安慰劑相比較，p=0.003。 #和安慰劑相比較，p=0.016。 ††和安慰劑相比較，p=0.007。

與Rosiglitazone加Metformin的合併治療

共有262位第二型糖尿病患者曾參與一項評估JANUVIA與metformin和rosiglitazone併用療效的54週、隨機、雙盲、安慰劑對照研究。已接受穩定劑量metformin (每日≥1500毫克)及rosiglitazone (每日≥4毫克)治療仍未能適當控制血糖的患者，經隨機分組後分別於療程中加入每日一次100毫克的JANUVIA或安慰劑。主要血糖參數評估時間點為第18週及第54週。

相較於併用安慰劑與 metformin 和 rosiglitazone，併用 JANUVIA 於 metformin 和 rosiglitazone 在第 18 週時使 HbA_{1c}、FPG 及 2 小時 PPG 獲得明顯的改善(表 8)，併持續至研究結束；血脂方面的效果不顯著；體重的差異在服用 JANUVIA 及安慰劑之間也不顯著。

表 8、以添加的方式將 JANUVIA 與 Metformin 加 Rosiglitazone 併用之患者第 18 週及第 54 週(最後一次回診)的血糖參數及體重相關結果†

	第 18 週		第 54 週	
	JANUVIA 100 毫克 + Metformin + Rosiglitazone	安慰劑 + Metformin + Rosiglitazone	JANUVIA 100 毫克 + Metformin + Rosiglitazone	安慰劑 + Metformin + Rosiglitazone
HbA_{1c} (%)	**N = 168**	**N = 88**	**N = 168**	**N = 88**
基礎值(平均值)	8.81	8.73	8.81	8.73
相對於基礎值的變化(校正後平均值‡)	-1.03	-0.31	-1.05	-0.28
與安慰劑+rosiglitazone+metformin組間的差異 (校正後平均值‡)	-0.72§		-0.77§	
達到HbA_{1c}<7%之效果的患者數(%)	37 (22%)	8 (9%)	44 (26%)	12 (14%)
FPG (mg/dL)	**N = 169**	**N = 89**	**N = 169**	**N = 89**
基礎值(平均值)	182.1	183.5	182.1	183.5
相對於基礎值的變化(校正後平均值‡)	-30.7	-11.7	-28.0	-10.7
與安慰劑+ rosiglitazone + metformin組間的差異 (校正後平均值‡)	-19.0§		-17.4§	
2-小時 PPG (mg/dL)	**N = 142**	**N = 75**	**N = 147**	**N = 77**
基礎值(平均值)	257.8	249.5	256.6	247.7
相對於基礎值的變化(校正後平均值‡)	-59.9	-22.0	-50.7	-16.6
與安慰劑+ rosiglitazone + metformin組間的差異 (校正後平均值‡)	-37.9§		-34.1§	
體重(公斤)‖	**N = 157**	**N = 79**	**N = 115**	**N = 40**
基礎值(平均值)	82.1	87.0	82.0	85.6
相對於基礎值的變化(校正後平均值‡)	0.5	0.2	1.9	1.3
與安慰劑+ rosiglitazone + metformin組間的差異 (校正後平均值‡)	0.3¶		0.6¶	

† 所有接受治療的患者(治療意圖分析)。 ‡ 依據先前的抗高血糖治療狀態與基礎值加以校正後的最小平方平均值。
§和安慰劑+ metformin + rosiglitazone 相比較，p<0.001。
‖ 排除接受血糖救援治療後的所有接受治療的患者(APaT)。
¶和安慰劑+ metformin + rosiglitazone 相比較，不具統計意義(p≥0.05)。

與胰島素(併用或不併用Metformin)的合併治療

共有641位第二型糖尿病患者曾參與一項評估JANUVIA與胰島素(併用或不併用metformin)併用的療效之24週、隨機、雙盲、安慰劑對照研究。已接受預混型、長效、或中效型胰島素併用或不併metformin (每日≥1500毫克)的患者經隨機分組後分別於療程中加入每日一次100毫克的JANUVIA或安慰劑。血糖終點評估指標包括HbA_{1c}、空腹血糖值、和飯後兩小時血糖值。相較於安慰劑，JANUVIA併用胰島素(併用或不併用metformin)，使HbA_{1c}、FPG及2小時PPG獲得明顯的改善(表9)。相較於安慰劑，HbA_{1c}方面的改善效果大致不會因性別、年齡、種族、BMI基礎值、診斷出罹患糖尿病後所經過的時間而受到影響。體重變化在JANUVIA及安慰劑兩組間沒有明顯差異。

表 9、以添加的方式合併使用 JANUVIA 與胰島素或胰島素和 Metformin 治療之患者最後一次回診時(24 週研究)的血糖參數及體重相關結果†

	JANUVIA 100毫克 + 胰島素 (+/-Metformin)	安慰劑 + 胰島素 (+/-Metformin)
HbA_{1c} (%)	**N = 305**	**N = 312**
基礎值(平均值)	8.72	8.64
相對於基礎值的變化(校正後平均值‡)	-0.59	-0.03
與安慰劑+metformin組間的差異(校正後平均值‡)	-0.56‖	
達到HbA_{1c}<7%之效果的患者數(%)	39 (12.8)	16 (5.1)
FPG (mg/dL)	**N = 310**	**N = 313**
基礎值(平均值)	175.8	179.1
相對於基礎值的變化(校正後平均值‡)	-18.5	-3.5
與安慰劑組間的差異(校正後平均值‡)	-15.0‖	
2 小時 PPG (mg/dL)	**N = 240**	**N = 257**
基礎值(平均值)	290.9	292.1
相對於基礎值的變化(校正後平均值‡)	-30.9	5.2
與安慰劑組間的差異(校正後平均值‡)	-36.1‖	
體重(公斤)¶	**N = 266**	**N = 266**
基礎值(平均值)	86.6	87.4
相對於基礎值的變化(校正後平均值‡)	0.1	0.1
與安慰劑組間的差異(校正後平均值‡)	0.0#	

† 所有接受治療的患者(治療意圖分析)。
‡依據第一次回診時使用metformin與否和使用的胰島素(預混型與非預混型[中效型或長效型])與基礎值加以校正後的最小平方平均值。
§ 以metformin分層及胰島素分層，其治療與分層間交互作用均不顯著。
‖和安慰劑相比較，p<0.001。 ¶ 所有接受治療的患者(APaT)，但不包括接受血糖救援治療的患者。
#和安慰劑相比較，不具統計意義(P≥0.05)。

適應症

第二型糖尿病

劑量與用法

JANUVIA的建議劑量為每日一次100毫克，可單獨使用亦可與metformin、sulfonylurea、胰島素(併用或不併用metformin)、PPARγ作用劑(如：thiazolidinedione)、metformin加一種sulfonylurea、或metformin加一種PPARγ作用劑合併使用，做為附加於飲食控制及運動之外的治療藥物，藉以改善第二型糖尿病患的血糖控制效果。

JANUVIA可和食物併用，亦可不和食物併用。

當JANUVIA和sulfonylurea或胰島素併用時，可能必須考慮使用較低劑量的sulfonylurea或胰島素，以降低發生低血糖的風險(參見**注意事項**欄中的*與Sulfonylurea或胰島素併用時的低血糖現象*)。

腎功能不全患者

對輕度腎功能不全(肌酸酐廓清率[CrCl]≥50 mL/min，約相當於男性血清肌酸酐濃度≤1.7 mg/dL，女性≤1.5 mg/dL)的患者，並不須調整JANUVIA的劑量。

對中度腎功能不全(CrCl≥30至<50 mL/min，約相當於男性血清肌酸酐濃度>1.7至≤3.0

mg/dL，女性>1.5至≤2.5 mg/dL)的患者，JANUVIA的劑量為每日一次50毫克。
對重度腎功能不全(CrCl<30 mL/min，約相當於男性血清肌酸酐濃度>3.0 mg/dL，女性>2.5 mg/dL)的患者或必須接受血液透析或腹膜透析的末期腎病(ESRD)患者，JANUVIA的劑量為每日一次25毫克。投予JANUVIA時，可不考慮進行血液透析的時間。
由於必須依腎功能調整劑量，因此，建議在開始使用JANUVIA之前應先評估腎功能，之後亦應定期進行評估。

禁忌

JANUVIA禁用於對本品之任何成分過敏的患者(見**注意事項**欄的*過敏反應*及**副作用**欄的*上市後經驗*)。

注意事項

一般注意事項
JANUVIA不可用於第一型糖尿病患者或用於治療糖尿病酮酸血症。
胰臟炎:曾有服用JANUVIA的病患發生急性胰臟炎的上市後通報，包含致死性及非致死性出血性或壞死性胰臟炎。因此，病患服用JANUVIA後，應密切觀察是否有胰臟炎的徵候。如果有胰臟炎徵候，立即停用JANUVIA，並採取適當處理措施。尚未研究過JANUVIA用於有胰臟炎病史的患者，未知有胰臟炎病史的患者使用JANUVIA是否有較高的胰臟炎發生率。
腎功能不全患者之使用：JANUVIA係透過腎臟排出體外。對中度和重度腎功能不全的患者，以及必須接受血液透析或腹膜透析的ESRD患者，為達到和腎功能正常之患者相近的血中JANUVIA濃度，建議應採用較低的劑量(參見**劑量與用法**欄中的*腎功能不全患者*)。
與Sulfonylurea或胰島素併用時的低血糖現象：在使用JANUVIA做為單一治療用藥或將JANUVIA和已知不會導致低血糖之藥物(如metformin或PPARγ作用劑(thiazolidinedione))合併使用的臨床試驗中，使用JANUVIA之患者中的低血糖發生率和使用安慰劑之患者中的發生率相當。和其它抗高血糖藥物一樣，JANUVIA和已知會導致低血糖的sulfonylurea或胰島素併用時，低血糖的發生率會較安慰劑組升高(參見**副作用**)。因此，為降低低血糖的風險，可能必須考慮使用較低劑量的sulfonylurea或胰島素 (參見**劑量與用法**欄)。
過敏反應: 曾有以JANUVIA治療的患者發生嚴重過敏反應的上市後通報，通報的反應包括全身性過敏、血管水腫、及包括Stevens-Johnson syndrome的皮膚剝落狀況。因為這些不良反應屬於自發性通報，患者總數不詳，通常難以可靠的評估這些不良反應的頻率或確認其與服用藥品之因果關係。這些反應的發生，有些在開始以JANUVIA治療的前三個月內，有些通報在第一次服用就發生。如果懷疑發生過敏，應停用JANUVIA，評估其他可能的導致因素，並以其他的糖尿病治療替代。(見**禁忌**欄及**副作用**欄的*上市後經驗*)

懷孕

在器官生成期間對大鼠口服投予高達250 mg/kg之劑量或對兔子投予高達125 mg/kg之劑量(分別高達成人每日建議劑量100 mg/day下之人類曝藥量的32倍與22倍)的結果顯示，sitagliptin並不具致畸性。針對大鼠所進行的研究發現，在1000 mg/kg/day的口服劑量下(約為成人每日建議劑量100 mg/day下之人類曝藥量的100倍)，致命性肋骨畸形(無肋骨、肋骨發育不全及波浪狀肋骨)的發生率有略為升高的現象。在投予1000 mg/kg/day口服劑量之大鼠的子代中發現，兩種性別的平均斷奶前體重與公鼠的斷奶後新增體重有略為降低的現象。不過，動物生殖研究的結果並不一定能預測人類的反應。
目前並無任何適當且控制良好的孕婦研究；因此，JANUVIA對孕婦的安全性仍然不明。和其它口服降血糖藥物一樣，懷孕期間並不建議使用JANUVIA。

授乳母親

Sitagliptin會移行進入授乳大鼠的乳汁中。但目前尚未知sitagliptin是否會移行進入人類的乳汁。因此，授乳的婦女不可使用JANUVIA。

小兒之使用

JANUVIA對18歲以下小兒病患的安全性及有效性尚未獲得確立。

老年人之使用

在臨床研究中，研究人員曾針對老年病患(≥65歲)與較年輕的病患(<65歲)比較JANUVIA的安全性及有效性。劑量並不須因年齡而進行任何調整。由於老年病患較容易併有腎功能不全的問題，因此，和其他病患一樣，如果出現明顯的腎功能不全現象，可能還是必須調整劑量(參見**劑量與用法**欄中的*腎功能不全患者*)。

藥物交互作用

體外藥物交互作用評估：
Sitagliptin並非CYP3A4、2C8、2C9、2D6、1A2、2C19或2B6等CYP同功酵素的抑制劑，也不是CYP3A4的誘導劑。Sitagliptin是P糖蛋白的作用受質，但並不會抑制由P糖蛋白(p-glycoprotein)所媒介的digoxin輸送機轉。依據這些結果，一般認為sitagliptin不太可能會和其它利用這些途徑的藥物產生交互作用。
Sitagliptin並不會廣泛地和血漿蛋白結合。因此，本品因血漿蛋白結合取代作用而發生具臨床意義之藥物-藥物交互作用的可能性極低。
體內藥物交互作用評估：
Sitagliptin對其它藥物的影響
在臨床研究中(如下所述)，sitagliptin並不會使metformin、glyburide、simvastatin、rosiglitazone、warfarin或口服避孕藥的藥物動力學發生有意義的改變；這些體內研究的證據顯示，其和CYP3A4、CYP2C8、CYP2C9及有機陽離子載運體(OCT)之作用受質發生藥物交互作用的可能性極低。投予多重劑量的sitagliptin會使digoxin的濃度略為升高；不過，一般認為這些升高現象並不具臨床意義，也不會促進特定的作用機轉。
Metformin：對第二型糖尿病患者合併投予多重每日兩劑的sitagliptin與metformin (OCT的作用受質)，並不會使metformin的藥物動力學發生有意義的改變。因此，sitagliptin並非OCT媒介性輸送機轉的抑制劑。
Sulfonylureas：在接受多重劑量之sitagliptin治療的受試者中，單劑glyburide (CYP2C9的作用受質)的藥物動力學並未出現有意義的改變。和其它與glyburide一樣主要都是透過CYP2C9之作用排出體外的sulfonylurea類藥物(如glipizide、tolbutamide及glimepiride)併用時，咸信並不會發生具臨床意義的交互作用。
Simvastatin：在接受多重每日劑量之sitagliptin治療的受試者中，單劑simvastatin (CYP3A4的作用受質)的藥物動力學並未出現有意義的改變。因此，sitagliptin並非CYP3A4媒介性代謝作用的抑制劑。
Thiazolidinediones：在接受多重每日劑量之sitagliptin治療的受試者中，單劑rosiglitazone的藥物動力學並未出現有意義的改變。因此，sitagliptin並非CYP2C8媒介性代謝作用的抑制劑。由於pioglitazone主要都是透過CYP2C8或CYP3A4的作用進行代謝，因此，和pioglitazone併用時，咸信並不會發生具臨床意義的交互作用。
Warfarin：多重每日劑量的sitagliptin並不會使單一劑量之warfarin的藥物動力學(針對S(-)或R(+) warfarin鏡像異構物之檢測值進行評估的結果)或藥效學(針對凝血酶原INR之檢測值進行評估的結果)發生有意義的改變。由於S(-) warfarin主要乃是透過CYP2C9的作用進行代謝，因此，這些數據也印證了sitagliptin並非CYP2C9抑制劑的結論。
口服避孕藥：和sitagliptin併用並不會使norethindrone或ethinyl estradiol的穩定狀態藥物動力學發生有意義的改變。
Digoxin：Sitagliptin會對digoxin的藥物動力學產生極微弱的影響。連續10天每天合併投予0.25毫克的digoxin與100毫克的JANUVIA之後，digoxin的血中AUC會升高11%，血中C_{max}會升高18%，但一般並不認為這些升高現象具有臨床上的意義。服用digoxin者仍應適當監控。
其它藥物對*sitagliptin*的影響
以下的臨床資料顯示，sitagliptin不太容易因與這些藥物併用而發生具臨床意義的交互作用：
Metformin：對第二型糖尿病患者合併投予多重每日兩劑的metformin與sitagliptin，並不會使sitagliptin的藥物動力學發生有意義的改變。
Cyclosporine：有一項研究曾評估過cyclosporine (一種強力的P糖蛋白抑制劑)對sitagliptin之藥物動力學的影響。將單劑100毫克口服劑量的JANUVIA與單劑600毫克口服劑量的cyclosporine合併投予之後，會使sitagliptin的AUC與C_{max}分別升高約29%及68%。一般並不認為sitagliptin的這些小幅藥物動力學變化具有臨床上的意義。此外，sitagliptin的腎臟廓清作用也未發生有意義的改變。因此，和其它的P糖蛋白抑制劑併用時，咸信應該不會發生有意義的交互作用。
群體藥物動力學：研究人員曾針對第二型糖尿病患者進行群體藥物動力學分析。與其它藥物同時投予並不會對sitagliptin的藥物動力學造成具臨床意義的影響。所評估的藥物乃是第二型糖尿病患者常使用到的藥物，包括降膽固醇藥物(如statins、fibrates、ezetimibe)、抗血小板藥物(如clopidogrel)、抗高血壓藥物(如ACE抑制劑、血管收縮素接受體阻斷劑、β阻阻斷劑、鈣離子通道阻斷劑、hydrochlorothiazide)、止痛劑與非類固醇抗發炎藥(如naproxen、diclofenac、celecoxib)、抗憂鬱劑(如bupropion、fluoxetine、sertraline)、抗組織胺劑(如cetirizine)、質子幫浦抑制劑(如omeprazole、lansoprazole)、以及治療勃起功能障礙的藥物(如sildenafil)。

副作用

在對照性的臨床研究中，不論採取單一療法或合併療法，JANUVIA都可表現出良好的耐受性，因出現臨床不良反應而停止治療的病患比例也和安慰劑相當。
在四項分別採取單一藥物療法(一項為18週研究，一項為24週研究)及併用metformin或pioglitazone之合併療法(兩項皆為24週研究)的安慰劑對照研究中，共有1,082位患者使用每日一次100毫克的JANUVIA治療，並有778位患者使用安慰劑治療(在其中兩項研究中還有456位患者使用每日200毫克的JANUVIA治療，此劑量為每日建議劑量的兩倍)。在接受JANUVIA 100毫克治療之患者所通報的藥物相關不良反應中，並無任一不良反應的發生率≥1%。整體而言，每日200毫克之劑量的安全性表現和每日100毫克大致相當。
一項針對上述研究所進行的預設整合分析顯示，使用JANUVIA治療之患者中的整體低血糖相關不良事件發生率和使用安慰劑者相當(分別為1.2%與0.9%)。在使用JANUVIA或安慰劑治療之患者中的特定胃腸道不良反應發生率分別為腹痛(使用JANUVIA治療者，2.3%；使用安慰劑者，2.1%)、噁心(1.4%；0.6%)、嘔吐(0.8%；0.9%)、以及腹瀉(3.0%；2.3%)。
所有的研究中，低血糖相關不良反應係以所有有症狀的低血糖通報為基礎；並不一定要有當時的葡萄糖檢測結果。當JANUVIA與Sulfonylurea或與胰島素合併使用時，低血糖發生率高於對應的安慰劑組。
與Sulfonylurea合併使用：一項將JANUVIA 100毫克與glimepiride併用或與glimepiride加metformin併用的24週安慰劑對照研究(JANUVIA治療組，N=222；安慰劑組，N=219)顯示，在JANUVIA治療組中之通報率≥1%且高於安慰劑組中之通報率的藥物相關不良反應為低血糖(JANUVIA治療組，9.5%；安慰劑組，0.9%)；在整體族群中，低血糖發生率(不論是否具有因果關係者)在JANUVIA治療組為12.2%，而安慰劑組為1.8%。
併用於 Metformin 及一種 PPARγ 作用劑：在一項於原先合併使用 metformin 與rosiglitazone的療程中加入 JANUVIA 每日 100 毫克的安慰劑對照性(JANUVIA N=170；安慰劑 N=92)研究中，至第 18 週的主要時間點，使用 JANUVIA 治療之患者中的通報率≥1%且高於安慰劑組的藥物相關不良反應為頭痛(JANUVIA 2.4%; 安慰劑 0.0%)、下痢(1.8%, 1.1%)、噁心(1.2%, 1.1%)、低血糖(1.2%, 0.0%)、及嘔吐(1.2%, 0.0%). 至第 54 週通報率≥1%且高於安慰劑組的藥物相關不良反應為頭痛(2.4%, 0.0%)、低血糖(2.4%, 0.0%)、上呼吸道感染(1.8%, 0.0%)、噁心(1.2%, 1.1%)、咳嗽(1.2%, 0.0%)、皮膚霉菌感染(1.2%, 0.0%)、周邊水腫(1.2%, 0.0%)、及嘔吐 (1.2%, 0.0%)。
併用於 Metformin：在一項於日本病患原先的 metformin 療程中加入 JANUVIA 50 毫克的安慰劑對照性(JANUVIA N=77；安慰劑 N=72)研究中，在第 12 週時，唯一在 JANUVIA 加 metformin 治療組中之通報率≥1%且高於安慰劑組的藥物相關不良反應為單純性疱疹(JANUVIA，1.3%；安慰劑組，0.0%)。
與Metformin併用的初始合併治療：一項以每日sitagliptin 100毫克加每日metformin 1000毫克或2000毫克之方式(投藥方式為每日兩次sitagliptin 50毫克/metformin 500毫克或1000毫克)進行初始合併治療的24週安慰劑對照性階乘研究顯示，在sitagliptin加metformin治療組(N=372)中之通報率≥1%且高於metformin單一藥物治療組(N=364)中之通報率的藥物相關不良反應為：腹瀉(sitagliptin加metformin治療組，3.5%；metformin治療組，3.3%)、消化不良(1.3%；1.1%)、脹氣(1.3%；0.5%)、嘔吐(1.1%；0.3%)、以及頭痛(1.3%；1.1%)。Sitagliptin加metformin治療組中的低血糖發生率為1.1%，在metformin單一藥物治療組中則為0.5%。
與一種 PPARγ作用劑併用的初始合併治療: 在一項為期 24 週、併用每日 100 毫克JANUVIA 與每日 30 毫克 pioglitazone 做為初始治療的研究中，唯一在併用 JANUVIA 和pioglitazone 治療的患者(N=261)中通報率≥1%，且高於僅用 pioglitazone 治療(N=259)的藥物相關不良反應為血糖降低(無症狀呈現)(JANUVIA 併用 pioglitazone, 1.1%；pioglitazone, 0.0%)。而低血糖(呈現症狀)的發生率在 JANUVIA 併用 pioglitazone 的患者中為 0.4%，在使用 pioglitazone 的患者中為 0.8%，JANUVIA 併用 pioglitazone 組有一位患者發生嚴重低血糖事件。症狀呈現的低血糖不良反應率是基於所有的低血糖通報，不須同時測量血糖。
併用於胰島素：在一項為期24週、安慰劑對照、100毫克JANUVIA併用於胰島素(併用或不併用metformin)的研究中，併用JANUVIA的患者(N=322)中通報率≥1%，且高於併用安慰劑的患者(N=319)的藥物相關不良反應為：低血糖(JANUVIA，9.6%；安慰劑，5.3%)、流行性感冒(1.2%；0.3%)、及頭痛(1.2%；0.0%)。低血糖不良事件，不論是否評估為具有因果關係者，在JANUVIA併用胰島素為15.5%，在安慰劑併用胰島素為7.8%。有三位患者發生嚴重低血糖事件(JANUVIA，0.6%；安慰劑，0.3%)。
在使用JANUVIA治療的患者中，生命徵象或ECG (包括QTc間隔)皆未出現任何具臨床意義的變化。
上市後經驗：
以下為JANUVIA上市後，單方使用或併用其他降血糖藥發生的其他不良反應。因為這些不良反應屬於自發性通報，患者總數不詳，通常難以可靠評估這些不良反應的頻率或確認其與服用藥品之因果關係。
過敏性反應，包括嚴重全身性過敏、血管水腫、皮疹及蕁麻疹、皮膚血管炎、及包括Stevens-Johnson syndrome的剝落性皮膚狀況(見**禁忌**欄及**注意事項**欄的*過敏反應*)；肝生化值上升；急性胰臟炎，包含致死性及非致死性出血性和壞死性胰臟炎(見**注意事項**的*胰臟炎*)；腎功能衰退，包含急性腎衰竭(有時須透析)；上呼吸道感染；鼻咽炎；便秘；嘔吐；頭痛；關節痛；肌痛；肢端疼痛；後背痛。

實驗室檢驗發現

使用JANUVIA 100毫克治療之患者中的實驗室不良反應發生率和使用安慰劑的患者大致相當。在各項臨床研究中，白血球計數都有因嗜中性球增加而小幅升高的現象(WBC和安慰劑組間的差異約為200 cells/microL；WBC的平均基礎值約為6600 cells/microL)。在大部份的研究中(但非所有研究)都可觀察到這種現象。一般並不認為這項實驗室參數變化具有臨床關聯性。

過量

在針對健康受試者所進行的對照性臨床試驗中，單一劑量最高達800毫克的JANUVIA皆可表現出良好的耐受性。在一項使用單劑800毫克之JANUVIA的研究中，受試者曾出現QTc微幅擴大的現象，但一般並不認為此現象具有臨床關聯性(參見**臨床藥理學**欄)。目前並無針對人類使用超過800毫克以上之劑量的經驗。在第I期多重劑量研究中，於使用劑量最高達每日600毫克JANUVIA達十天及每日400毫克之JANUVIA治療達28天的情況下，並未發現任何的劑量相關臨床不良反應。
萬一用藥過量時，可採取一般的支持措施，如移除胃腸道中未被吸收的物質、進行臨床監視(包括心電圖監視)、並於必要時施行支持療法。
透析可移除部份的sitagliptin。臨床研究顯示，經過3至4小時的血液透析之後，約可移除13.5%的劑量。如果臨床狀況允許，或可考慮延長血液透析的時間。目前並不清楚sitagliptin是否可經由腹膜透析排出體外。

貯存

請貯存於溫度最高不超過30°C (86°F)的環境中。

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JANUVIA® 25, 50, and 100 mg Tablets (sitagliptin phosphate)

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ACTIVE INGREDIENTS

Each film-coated tablet of JANUVIA contains 32.13, 64.25, or 128.5 mg of sitagliptin phosphate monohydrate, which is equivalent to 25, 50, or 100 mg, respectively, of free base.

THERAPEUTIC CLASS

JANUVIA®[1] (sitagliptin phosphate) is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. This mechanism is unlike the mechanism seen with sulfonylureas; sulfonylureas cause insulin release even when glucose levels are low, which can lead to sulfonylurea-induced hypoglycemia in patients with type 2 diabetes and in normal subjects. Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4 and does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations. Sitagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulfonylureas or meglitinides, biguanides, peroxisome proliferator-activated receptor gamma (PPARγ) agonists, alpha-glucosidase inhibitors, and amylin analogues.

CLINICAL PHARMACOLOGY

Mechanism of Action

JANUVIA is a member of a class of oral antihyperglycemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors, which improve glycemic control in patients with type 2 diabetes by enhancing the levels of active incretin hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. Treatment with GLP-1 or with DPP-4 inhibitors in animal models of type 2 diabetes has been demonstrated to improve beta cell responsiveness to glucose and stimulate insulin biosynthesis and release. With higher insulin levels, tissue glucose uptake is enhanced. In addition, GLP-1 lowers glucagon secretion from pancreatic alpha cells. Decreased glucagon concentrations, along with higher insulin levels, lead to reduced hepatic glucose production, resulting in a decrease in blood glucose levels. The effects of GLP-1 and GIP are glucose dependent such that when blood glucose concentrations are low, stimulation of insulin release and suppression of glucagon secretion by GLP-1 are not observed. For both GLP-1 and GIP, stimulation of insulin release is enhanced as glucose rises above normal concentrations. Further, GLP-1 does not impair the normal glucagon response to hypoglycemia. The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyzes the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in a glucose-dependent manner. In patients with type 2 diabetes with hyperglycemia, these changes in insulin and glucagon levels lead to lower hemoglobin A_{1c} (HbA_{1c}) and lower fasting and postprandial glucose concentrations. The glucose-dependent mechanism of sitagliptin is distinct from the mechanism of sulfonylureas, which increase insulin secretion even when glucose levels are low and can lead to hypoglycemia in patients with type 2 diabetes and in normal subjects. Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4 and does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations.

Pharmacokinetics

The pharmacokinetics of sitagliptin have been extensively characterized in healthy subjects and patients with type 2 diabetes. After oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose. Plasma AUC of sitagliptin increased in a dose-proportional manner. Following a single oral 100-mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 μM•hr, C_{max} was 950 nM, and apparent terminal half-life ($t_{1/2}$) was 12.4 hours. Plasma AUC of sitagliptin increased approximately 14% following 100-mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for sitagliptin AUC were small (5.8% and 15.1%). The pharmacokinetics of sitagliptin were generally similar in healthy subjects and in patients with type 2 diabetes.

Absorption

The absolute bioavailability of sitagliptin is approximately 87%. Since coadministration of a high-fat meal with JANUVIA had no effect on the pharmacokinetics, JANUVIA may be administered with or without food.

Distribution

The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 liters. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).

Metabolism

Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79% of sitagliptin is excreted unchanged in the urine.

Following a [^{14}C]sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

Elimination

Following administration of an oral [^{14}C]sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing. The apparent terminal $t_{1/2}$ following a 100-mg oral dose of sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min.

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporine, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

Characteristics in Patients

Renal Insufficiency: A single-dose, open-label study was conducted to evaluate the pharmacokinetics of JANUVIA (50-mg dose) in patients with varying degrees of chronic renal insufficiency compared to normal healthy control subjects. The study included patients with renal insufficiency classified on the basis of creatinine clearance as mild (50 to <80 mL/min), moderate (30 to <50 mL/min), and severe (<30 mL/min), as well as patients with end-stage renal disease (ESRD) on hemodialysis. Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula:

$$\text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{[72 \times \text{serum creatinine (mg/dL)}]} \{\times 0.85 \text{ for female patients}\}$$

Patients with mild renal insufficiency did not have a clinically meaningful increase in the plasma concentration of sitagliptin as compared to normal healthy control subjects. An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal insufficiency, and an approximately 4-fold increase was observed in patients with severe renal insufficiency and in patients with ESRD on hemodialysis, as compared to normal healthy control subjects. Sitagliptin was modestly removed by hemodialysis (13.5% over a 3- to 4-hour hemodialysis session starting 4 hours postdose). To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with moderate and severe renal insufficiency, as well as in ESRD patients requiring hemodialysis. (See **DOSAGE AND ADMINISTRATION**, *Patients with Renal Insufficiency.*)

Hepatic Insufficiency: In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), mean AUC and C_{max} of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100-mg dose of JANUVIA. These differences are not considered to be clinically meaningful. No dosage adjustment for JANUVIA is necessary for patients with mild or moderate hepatic insufficiency.

There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score >9). However, because sitagliptin is primarily renally eliminated, severe hepatic insufficiency is not expected to affect the pharmacokinetics of sitagliptin.

Elderly: No dosage adjustment is required based on age. Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

Pediatric: No studies with JANUVIA have been performed in pediatric patients.

Gender: No dosage adjustment is necessary based on gender. Gender had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

Race: No dosage adjustment is necessary based on race. Race had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data, including subjects of white, Hispanic, black, Asian, and other racial groups.

Body Mass Index (BMI): No dosage adjustment is necessary based on BMI. Body mass index had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

Type 2 Diabetes: The pharmacokinetics of sitagliptin in patients with type 2 diabetes are generally similar to those in healthy subjects.

CLINICAL STUDIES

There were approximately 5200 patients with type 2 diabetes randomized in nine double-blind, placebo-controlled Phase III clinical studies conducted to evaluate the effects of sitagliptin on glycemic control. Co-morbid diseases, including dyslipidemia and hypertension, were common in the patients studied and more than 50% were obese (BMI $\geq$30 kg/m^2). The majority of patients met National Cholesterol Education Program (NCEP) criteria for metabolic syndrome. These studies included white, Hispanic, black, Asian, and other racial and ethnic groups, and patients had an overall mean age of approximately 55 years.

A 52-week, placebo-controlled, randomized study (including an initial double-blind period of 12 weeks and an open-label of 40 weeks) of JANUVIA in combination with metformin was conducted in 149 Japanese patients with type 2 diabetes.

Additional double-blind, placebo-controlled clinical studies were conducted, one in 151 Japanese patients with type 2 diabetes and another in 91 patients with type 2 diabetes and moderate to severe renal insufficiency.

An active (glipizide)-controlled study of 52-weeks duration was conducted in 1172 patients with type 2 diabetes who had inadequate glycemic control on metformin. In addition, an active (metformin)-controlled study of 24 weeks was conducted in 1050 patients who were inadequately controlled on diet and exercise alone.

In patients with type 2 diabetes, treatment with JANUVIA produced clinically significant improvements in hemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose (FPG) and 2-hour post-prandial glucose (PPG) compared to placebo. In the active (glipizide)-controlled study, clinically significant improvements in glycemic control were maintained for 52 weeks. JANUVIA provided improvement in measures of beta cell function (see **CLINICAL PHARMACOLOGY**).

Clinical Studies Monotherapy

A total of 1262 patients with type 2 diabetes participated in two double-blind, placebo-controlled studies, one of 18-week and another of 24-week duration, to evaluate the efficacy and safety of JANUVIA monotherapy. Patients with inadequate glycemic control (HbA_{1c} 7% to 10%) were randomized to receive a 100-mg or 200-mg dose of JANUVIA or placebo once daily.

Treatment with JANUVIA at 100 mg daily provided significant improvements in HbA_{1c}, FPG, and 2-hour PPG compared to placebo (Tables 1 and 2). These studies included patients with a wide range of baseline HbA_{1c}. The improvement in HbA_{1c} compared to placebo was not affected by gender, age, race, prior antihyperglycemic therapy, baseline BMI, presence of metabolic syndrome, or a standard index of insulin resistance (HOMA-IR). Patients with a shorter length of time since diagnosis of diabetes (<3 years) or with higher baseline HbA_{1c} had greater reductions in HbA_{1c}. In the 18- and 24-week studies, among patients who were not on an antihyperglycemic agent at study entry, the reduction from baseline in HbA_{1c} was -0.67% and -0.85%, respectively, for those given JANUVIA and -0.10% and -0.18%, respectively, for those given placebo. In both studies, JANUVIA provided a significant reduction compared with placebo in FPG (-19.3 mg/dL in the 18-week study and -15.8 mg/dL in the 24-week study) at 3 weeks, the first time point at which FPG was measured. Overall, the 200-mg daily dose did not provide greater glycemic efficacy than the 100-mg daily dose. The effect of JANUVIA on lipid endpoints was similar to placebo. Body weight did not increase from baseline with JANUVIA therapy in either study, compared to a small reduction in patients given placebo (Table 2). The observed incidence of hypoglycemia in patients treated with JANUVIA was similar to placebo.

Table 1 HbA1c Results in 18- and 24-Week Placebo-Controlled Studies of JANUVIA in Patients with Type 2 Diabetes†, including Stratification by Baseline HbA1c Category

	18-Week Study		24-Week Study	
	JANUVIA 100 mg	**Placebo**	**JANUVIA 100 mg**	**Placebo**
HbA_{1c} (%)	N = 193	N = 103	N = 229	N = 244
Baseline (mean)	8.04	8.05	8.01	8.03
Change from Baseline (adjusted mean‡)	-0.48	0.12	-0.61	0.18
Difference from Placebo (adjusted mean‡)	-0.60§		-0.79§	
Patients (%) achieving HbA_{1c} <7%	69 (35.8)	16 (15.5)	93 (40.6)	41 (16.8)
Baseline HbA_{1c} Category				
HbA_{1c} (%) ≥9% at Baseline	N = 27	N = 20	N = 37	N = 35
Baseline (mean)	9.48	9.48	9.59	9.46
Change from Baseline (adjusted mean‡)	-0.83	0.37	-1.27	0.25
Difference from Placebo (adjusted mean‡)	-1.20		-1.52	
HbA_{1c} (%) ≥8% to <9% at Baseline	N = 70	N = 25	N = 62	N = 82
Baseline (mean)	8.40	8.38	8.36	8.41
Change from Baseline (adjusted mean‡)	-0.42	0.19	-0.64	0.16
Difference from Placebo (adjusted mean‡)	-0.61		-0.80	
HbA_{1c} (%) <8% at Baseline	N = 96	N = 58	N = 130	N = 127
Baseline (mean)	7.37	7.41	7.39	7.39
Change from Baseline (adjusted mean‡)	-0.42	0.02	-0.40	0.17
Difference from Placebo (adjusted mean‡)	-0.44		-0.57	

†All Patients Treated Population (an intention-to-treat analysis).
‡Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
§p<0.001 compared to placebo.

Table 2 Additional Glycemic Parameters and Body Weight in 18- and 24-Week Placebo-Controlled Studies of JANUVIA in Patients with Type 2 Diabetes†

	18-Week Study		24-Week Study	
	JANUVIA 100 mg	**Placebo**	**JANUVIA 100 mg**	**Placebo**
FPG (mg/dL)	N = 201	N = 107	N = 234	N = 247
Baseline (mean)	179.8	183.6	170.2	176.1

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Change from baseline (adjusted mean‡)	-12.7	7.0	-12.4	4.7
Difference from Placebo (adjusted mean‡)	-19.7§		-17.1§	
2-hour PPG (mg/dL)	‖	‖	N = 201	N = 204
Baseline (mean)			257.2	270.8
Change from baseline (adjusted mean‡)			-48.9	-2.2
Difference from Placebo (adjusted mean‡)			-46.7§	
Body Weight (kg)¶	N = 172	N = 77	N = 193	N = 174
Baseline (mean)	89.5	91.3	83.9	83.3
Change from baseline (adjusted mean‡)	-0.6	-0.7	-0.2	-1.1
Difference from Placebo (adjusted mean‡)	0.1#		0.9††	

† All Patients Treated Population (an intention-to-treat analysis).
‡ Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
§ p<0.001 compared to placebo.
‖ Data not available.
¶ All Patients as Treated (APaT) population, excluding patients given glycemic rescue therapy.
# Not statistically significant (p≥0.05) compared to placebo.
†† p<0.01 compared to placebo.

Additional Monotherapy Studies

A double-blind, placebo-controlled study in Japanese patients with type 2 diabetes was performed to examine the efficacy of treatment with JANUVIA 100 mg once daily compared to placebo. This study included 151 patients (75 treated with JANUVIA, 76 treated with placebo) with mean age of 55.3 years, baseline BMI of 25.2 kg/m^2, mean baseline HbA_{1C} of 7.6%, and mean baseline FPG of 163 mg/dL. After 12 weeks, JANUVIA provided a -1.05% decrease in HbA_{1C} relative to placebo (JANUVIA -0.65% change from baseline, placebo 0.41%, p<0.001). FPG decreased by -31.9 mg/dL relative to placebo (JANUVIA -22.5 mg/dL change from baseline, placebo 9.4 mg/dL, p<0.001).

A multinational, randomized, double-blind, placebo-controlled study was also conducted to assess the safety and tolerability of JANUVIA in 91 patients with type 2 diabetes and chronic renal insufficiency (creatinine clearance <50 mL/min). Patients with moderate renal insufficiency received 50 mg daily of JANUVIA and those with severe renal insufficiency or with ESRD on hemodialysis or peritoneal dialysis received 25 mg daily. In this study, the safety and tolerability of JANUVIA were generally similar to placebo. In addition, the reductions in HbA_{1C} and FPG with JANUVIA compared to placebo were generally similar to those observed in other monotherapy studies. (See **CLINICAL PHARMACOLOGY**, ***Pharmacokinetics***, ***Characteristics in Patients***, **Renal Insufficiency**.)

Initial Combination Therapy with Metformin

A total of 1091 patients with type 2 diabetes and inadequate glycemic control on diet and exercise participated in a 24-week, randomized, double-blind, placebo-controlled factorial study designed to assess the safety and efficacy of initial therapy with the combination of sitagliptin and metformin. Approximately equal numbers of patients were randomized to receive initial therapy with placebo, 100 mg of sitagliptin (JANUVIA) once daily, 500 mg or 1000 mg of metformin twice daily, or 50 mg of sitagliptin twice daily in combination with 500 mg or 1000 mg of metformin twice daily.

Initial therapy with the combination of sitagliptin and metformin provided significant improvements in HbA_{1c}, FPG, and 2-hour PPG compared to placebo, to metformin alone, and to sitagliptin alone (p<0.001; Table 3). An improvement in FPG, with near maximal FPG reduction, was achieved by the 3-week time point (the first point assessed after initiation of therapy) and sustained throughout the 24-week study. Measures of beta cell function, HOMA-β and the proinsulin to insulin ratio, also showed greater improvement with the co-administration of sitagliptin and metformin compared with either monotherapy alone. Lipid effects were generally neutral. The decrease in body weight in the groups given sitagliptin in combination with metformin was similar to that in the groups given metformin alone or placebo. Mean reductions from baseline in HbA_{1c} compared with placebo were generally greater for patients with higher baseline HbA_{1c} values. The improvement in HbA_{1c} was generally consistent across subgroups defined by gender, age, race, or baseline BMI. Mean reductions from baseline in HbA_{1c} for patients not on an antihyperglycemic agent at study entry were: JANUVIA 100 mg once daily, -1.06%; metformin 500 mg bid, -1.09%; metformin 1000 mg bid, -1.24%; sitagliptin 50 mg bid with metformin 500 mg bid, -1.59%; and sitagliptin 50 mg bid with metformin 1000 mg bid, -1.94%; and for patients receiving placebo, -0.17%.

Table 3 Glycemic Parameters and Body Weight at Final Visit (24-Week Study) for Sitagliptin and Metformin, Alone and in Combination as Initial Therapy†

	Placebo	Sitagliptin (JANUVIA) 100 mg QD	Metformin 500 mg bid	Sitagliptin 50 mg bid + Metformin 500 mg bid	Metformin 1000 mg bid	Sitagliptin 50 mg bid + Metformin 1000 mg bid
HbA1c (%)	**N = 165**	**N = 175**	**N = 178**	**N = 183**	**N = 177**	**N = 178**
Baseline (mean)	8.68	8.87	8.90	8.79	8.68	8.76
Change from baseline (adjusted mean‡)	0.17	-0.66	-0.82	-1.40	-1.13	-1.90
Difference from placebo (adjusted mean‡)	-	-0.83§	-0.99§	-1.57§	-1.30§	-2.07§
Patients (%) achieving HbA1c <7%	15 (9.1)	35 (20.0)	41 (23.0)	79 (43.2)	68 (38.4)	118 (66.3)
FPG (mg/dL)	**N = 169**	**N = 178**	**N = 179**	**N = 183**	**N = 179**	**N = 180**
Baseline (mean)	196.3	201.4	205.2	203.9	197.0	196.7
Change from baseline (adjusted mean‡)	5.8	-17.5	-27.3	-47.1	-29.3	-63.9
Difference from placebo (adjusted mean‡)	-	-23.3§	-33.1§	-52.9§	-35.1§	-69.7§
2-hour PPG (mg/dL)	**N = 129**	**N = 136**	**N = 141**	**N = 147**	**N = 138**	**N = 152**
Baseline (mean)	276.8	285.4	292.7	291.8	283.4	286.9
Change from baseline (adjusted mean‡)	0.3	-51.9	-53.4	-92.5	-78.0	-116.6
Difference from placebo (adjusted mean‡)		-52.2§	-53.7§	-92.8§	-78.3§	-116.9§
Body Weight (kg)¶	**N = 167**	**N = 175**	**N = 179**	**N = 184**	**N = 175**	**N = 178**
Baseline (mean)	90.1	85.9	88.1	90.0	89.4	88.2
Change from baseline (adjusted mean‡)	-0.9	0.0	-0.9	-0.6	-1.1	-1.3
Difference from placebo (adjusted mean‡)		0.9¶	0.1#	0.4#	-0.1#	-0.3#

† All Patients Treated Population (an intention-to-treat analysis).
‡ Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
§ p<0.001 compared to placebo.
‖ All Patients as Treated (APaT) population, excluding patients given glycemic rescue therapy.
¶ p=0.005 compared to placebo.
# Not statistically significant (p≥0.05) compared to placebo.

In addition, this study included patients (N=117) with more severe hyperglycemia (HbA_{1c} >11% or blood glucose >280 mg/dL) who were treated with open-label sitagliptin at 50 mg and metformin at 1000 mg twice daily. In this group of patients, the baseline HbA_{1c} value was 11.15%, FPG was 314.4 mg/dL, and 2-hour PPG was 441.0 mg/dL. After 24 weeks, decreases from baseline of -2.94% for HbA_{1c}, -126.7 mg/dL for FPG, and -207.9 mg/dL for 2-hour PPG were observed. In this open-label cohort, a modest increase in body weight of 1.3 kg was observed at 24 weeks.

Initial combination therapy or maintenance of combination therapy may not be appropriate for all patients. These management options are left to the discretion of the health care provider.

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 JANUVIA in combination with metformin. All patients were started on metformin monotherapy and the dose increased to at least 1500 mg per day. Patients were randomized to the addition of either 100 mg of JANUVIA or placebo, administered once daily.

In combination with metformin, JANUVIA provided significant improvements in HbA_{1c}, FPG, and 2-hour PPG compared to placebo with metformin (Table 4). The improvement in HbA_{1c} compared to placebo was not affected by baseline HbA_{1c}, prior antihyperglycemic therapy, gender, age, baseline BMI, length of time since diagnosis of diabetes, presence of metabolic syndrome, or standard indices of insulin resistance (HOMA-IR) or insulin secretion (HOMA-β). Compared to patients taking placebo, patients taking JANUVIA demonstrated slight decreases in total cholesterol, non-HDL cholesterol and triglycerides. A similar decrease in body weight was observed for both treatment groups.

Table 4 Glycemic Parameters and Body Weight at Final Visit (24-Week Study) for JANUVIA in Add-on Combination Therapy with Metformin†

	JANUVIA 100 mg + Metformin	Placebo + Metformin
HbA_{1c} (%)	**N = 453**	**N = 224**
Baseline (mean)	7.96	8.03
Change from baseline (adjusted mean‡)	-0.67	-0.02
Difference from placebo + metformin (adjusted mean‡)	-0.65§	
Patients (%) achieving HbA_{1c} <7%	213 (47.0)	41 (18.3)
FPG (mg/dL)	**N = 454**	**N = 226**
Baseline (mean)	170.0	173.5
Change from baseline (adjusted mean‡)	-16.9	8.5
Difference from placebo + metformin (adjusted mean‡)	-25.4§	
2-hour PPG (mg/dL)	**N = 387**	**N = 182**
Baseline (mean)	274.5	272.4
Change from baseline (adjusted mean‡)	-62.0	-11.4
Difference from placebo + metformin (adjusted mean‡)	-50.6§	
Body Weight (kg) ‖	**N = 399**	**N = 169**
Baseline (mean)	86.9	87.6
Change from baseline (adjusted mean‡)	-0.7	-0.6
Difference from placebo + metformin (adjusted mean‡)	-0.1¶	

† All Patients Treated Population (an intention-to-treat analysis).
‡ Least squares means adjusted for prior antihyperglycemic therapy and baseline value.
§ p<0.001 compared to placebo + metformin.
‖ All Patients as Treated (APaT) population, excluding patients given glycemic rescue therapy.
¶ Not statistically significant (p≥0.05) compared to placebo + metformin.

Add-on Combination Therapy with Metformin in Japanese Patients

A double-blind, placebo-controlled study in Japanese patients with type 2 diabetes with inadequate glycemic control on metformin monotherapy was performed to examine the efficacy of treatment with JANUVIA 50 mg once daily in combination with metformin. This study included 149 patients (77 treated with JANUVIA, 72 treated with placebo) with mean age of 58.4 years, baseline BMI of 25.1 kg/m2, mean baseline HbA_{1c} of 7.9%, mean baseline FPG of 156 mg/dL and mean baseline PPG of 244 mg/dL. At 12 weeks, JANUVIA 50 mg once daily in combination therapy with metformin, provided significant improvements in HbA_{1c} (-0.39% and 0.30%, respectively, compared to placebo, p<0.001), FPG (-11.3 mg/dL and 6.5 mg/dL, respectively, compared to placebo, p<0.001) and 2-hour PPG (-29.0 mg/dL and 17.8 mg/dL, respectively, compared to placebo, p<0.001)."

Active-Controlled Study with Metformin

The efficacy of JANUVIA compared to that of metformin was evaluated in a 24-week, double-blind, metformin-controlled trial in patients with type 2 diabetes and inadequate glycemic control on diet and exercise and who were not on antihyperglycemic therapy (off therapy for at least 4 months). In this study, patients were randomized to receive either JANUVIA 100 mg daily (N=528) or metformin (N=522) for 24 weeks. Patients receiving metformin were given an initial dosage of 500 mg/day and then titrated by the investigator to a dose of 1500 to 2000 mg/day over a period of up to 5 weeks based on tolerability. The mean dose of metformin after the titration period was approximately 1900 mg/day. Glycemic endpoints measured included HbA_{1c} and fasting glucose.

Both treatments resulted in a statistically significant improvement in glycemic control from baseline. The mean baseline HbA_{1c} was 7.2% in the per protocol population. At 24 weeks, the reduction from baseline in HbA_{1c} was -0.43% for JANUVIA 100 mg daily and -0.57% for metformin. The difference met the pre-specified criterion for confirming comparable efficacy of the two agents.

The reduction in FPG was -11.5 mg/dL for JANUVIA and -19.4 mg/dL for metformin. The overall incidence of gastrointestinal adverse reactions in patients treated with JANUVIA was 11.6% compared with 20.7% in patients treated with metformin. The incidence of selected gastrointestinal adverse experiences was: diarrhea (JANUVIA, 3.6%; metformin, 10.9%), nausea (1.1%, 3.1%), abdominal pain (2.1%, 3.8%), and vomiting (0.4%, 1.3%). The incidence of hypoglycemia was not significantly different between the treatment groups (JANUVIA, 1.7%; metformin, 3.4%). Body weight decreased from baseline in both treatment groups (JANUVIA, -0.6 kg; metformin -1.9 kg).

Active-Controlled Study with Glipizide

Long-term maintenance of effect was evaluated in a 52-week, double-blind, glipizide-controlled trial in patients with type 2 diabetes and inadequate glycemic control on metformin monotherapy at ≥1500 mg/day. In this study, patients were randomized to the addition of either JANUVIA 100 mg daily (N=588) or glipizide (N=584) for 52 weeks. Patients receiving glipizide were given an initial dosage of 5 mg/day and then electively titrated by the investigator to a target FPG of <110 mg/dL, without significant hypoglycemia, over the next 18 weeks. A maximum dosage of 20 mg/day was allowed to optimize glycemic control. Thereafter, the glipizide dose was to have been kept constant. The mean dose of glipizide after the titration period was 10.3 mg.

Both treatments resulted in a statistically significant improvement in glycemic control from baseline. After 52 weeks, the reduction from baseline in HbA_{1c} was -0.67% for JANUVIA 100 mg daily and -0.67% for glipizide, confirming comparable efficacy of the two agents. The reduction in FPG was -10.0 mg/dL for JANUVIA and -7.5 mg/dL for glipizide. In a post-hoc analysis, patients with higher baseline HbA_{1c} (≥9%) in both groups had greater reductions from baseline in HbA_{1c} (JANUVIA, -1.68%; glipizide, -1.76%). In this study, the proinsulin to insulin ratio, a marker of efficiency of insulin synthesis and release, improved with JANUVIA and deteriorated with glipizide treatment. The incidence of hypoglycemia in the JANUVIA group (4.9%) was significantly lower than that in the glipizide group (32.0%). Patients treated with JANUVIA exhibited a significant mean decrease from baseline in body weight compared to a significant weight gain in patients administered glipizide (-1.5 kg vs. +1.1 kg).

Initial Combination Therapy with Pioglitazone

A total of 520 patients with type 2 diabetes and inadequate glycemic control on diet and exercise participated in a 24-week, randomized, double-blind study designed to assess the efficacy of JANUVIA as initial therapy in combination with pioglitazone. Approximately equal numbers of patients were randomized to receive initial combination therapy with JANUVIA 100 mg and pioglitazone 30 mg once daily or pioglitazone 30 mg once daily as monotherapy.

Initial therapy with the combination of JANUVIA and pioglitazone provided significant improvements in HbA_{1c}, FPG, and 2-hour PPG compared to pioglitazone monotherapy (Table 5). In a pre-defined subgroup analysis, patients with baseline HbA_{1c} ≥10% had reductions in HbA_{1c} of -3.00% in the group given JANUVIA with pioglitazone (N=99) and -2.06% in the group given pioglitazone alone (N=88). In patients with baseline HbA_{1c} <10% the reductions were -1.99% (N=152) and -1.14% (N=158) in the two groups respectively. The improvement in HbA_{1c} was generally consistent across subgroups defined by gender, age, race, baseline BMI, or duration of disease. Patients given JANUVIA with pioglitazone had a modest increase in body weight compared to those given pioglitazone. Changes in lipid parameters were similar in both groups.

Table 5 Glycemic Parameters and Body Weight at Final Visit (24-Week Study) for JANUVIA in Combination with Pioglitazone as Initial Therapy†

	JANUVIA 100 mg + Pioglitazone	Pioglitazone
HbA1c (%)	**N = 251**	**N = 246**
Baseline (mean)	9.50	9.44
Change from baseline (adjusted mean‡)	-2.38	-1.49

Difference from pioglitazone (adjusted mean‡)	-0.89§	
Patients (%) achieving A1c <7%	151 (60%)	68 (28%)
FPG (mg/dL)	**N = 256**	**N = 253**
Baseline (mean)	203.3	200.7
Change from baseline (adjusted mean‡)	-63.0	-40.2
Difference from pioglitazone (adjusted mean‡)	-22.8§	
2-hour PPG (mg/dL)	**N = 216**	**N = 211**
Baseline (mean)	282.7	284.1
Change from baseline (adjusted mean‡)	-113.6	-68.9
Difference from pioglitazone (adjusted mean‡)	-44.7§	
Body Weight (kg) ‖	**N = 232**	**N = 218**
Baseline (mean)	80.4	80.7
Change from baseline (adjusted mean‡)	3.0	1.9
Difference from pioglitazone (adjusted mean‡)	1.1¶	

† All Patients Treated Population (an intention-to-treat analysis).
‡ Least squares means adjusted for baseline value.
§ p<0.001 compared to pioglitazone.
‖ All Patients as Treated (APaT) population.
¶ p<0.01 compared to pioglitazone.

Add-on Combination Therapy with Pioglitazone

A total of 353 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of JANUVIA in combination with pioglitazone. All patients were started on pioglitazone monotherapy at a dose of 30-45 mg per day. Patients were randomized to the addition of either 100 mg of JANUVIA or placebo, administered once daily. Glycemic endpoints measured included HbA_{1c} and fasting glucose.

In combination with pioglitazone, JANUVIA provided significant improvements in HbA_{1c} and FPG compared to placebo with pioglitazone (Table 6). The improvement in HbA_{1c} compared to placebo was not affected by baseline HbA_{1c}, prior antihyperglycemic therapy, gender, age, race, baseline BMI, length of time since diagnosis of diabetes, presence of metabolic syndrome, or standard indices of insulin resistance (HOMA-IR) or insulin secretion (HOMA-β). Compared to patients taking placebo, patients taking JANUVIA demonstrated a slight decrease in triglycerides. There was no significant difference between JANUVIA and placebo in body weight change.

Table 6 Glycemic Parameters and Body Weight at Final Visit (24-Week Study) for JANUVIA as Add-on Combination Therapy with Pioglitazone†

	JANUVIA 100 mg + Pioglitazone	Placebo + Pioglitazone
HbA1c (%)	**N = 163**	**N = 174**
Baseline (mean)	8.05	8.00
Change from baseline (adjusted mean‡)	-0.85	-0.15
Difference from placebo + pioglitazone (adjusted mean‡)	-0.70§	
Patients (%) achieving HbA1c <7%	74 (45.4)	40 (23.0)
FPG (mg/dL)	**N = 163**	**N = 174**
Baseline (mean)	168.3	165.6
Change from baseline (adjusted mean‡)	-16.7	1.0
Difference from placebo + pioglitazone (adjusted mean‡)	-17.7§	
Body Weight (kg)‖	**N = 133**	**N = 136**
Baseline (mean)	90.0	85.6
Change from baseline (adjusted mean‡)	1.8	1.5
Difference from placebo + pioglitazone (adjusted mean‡)	0.2¶	

† All Patients Treated Population (an intention-to-treat analysis).
‡ Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
§ p<0.001 compared to placebo + pioglitazone.
‖ All Patients as Treated (APaT) population, excluding data following glycemic rescue therapy.
¶ Not statistically significant (p≥0.05) compared to placebo + pioglitazone.

Add-on Combination Therapy with Glimepiride or Glimepiride plus Metformin

A total of 441 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of JANUVIA in combination with glimepiride (≥4 mg per day) or glimepiride with metformin (≥1500 mg per day). Patients were randomized to the addition of either 100 mg of JANUVIA or placebo, administered once daily. Glycemic endpoints measured included HbA1c and fasting glucose.

In combination with glimepiride or glimepiride plus metformin, JANUVIA provided significant improvements in HbA_{1c} and FPG compared to placebo (Table 7). In the entire study population (both patients on glimepiride and patients on glimepiride with metformin), a reduction from baseline relative to placebo in HbA_{1c} of -0.74% and in FPG of -20.1 mg/dL was seen. The improvement in HbA_{1c} compared to placebo was generally consistent across subgroups defined by gender, age, race, baseline BMI, length of time since diagnosis of diabetes, presence of metabolic syndrome, or standard indices of insulin resistance (HOMA-IR) or insulin secretion (HOMA-β). Patients treated with JANUVIA had a modest increase in body weight compared to those given placebo.

Table 7 Glycemic Parameters and Body Weight at Final Visit (24-Week Study) for JANUVIA as Add-on Combination Therapy with Glimepiride or Glimepiride plus Metformin†

	JANUVIA 100 mg + Glimepiride	Placebo + Glimepiride	JANUVIA 100 mg + Glimepiride + Metformin	Placebo + Glimepiride + Metformin
HbA_{1c} (%)	**N = 102**	**N = 103**	**N = 115**	**N = 105**
Baseline (mean)	8.41	8.46	8.27	8.28
Change from baseline (adjusted mean‡)	-0.30	0.27	-0.59	0.30
Difference from placebo (adjusted mean‡)	-0.57§		-0.89§	
Patients (%) achieving HbA_{1c} <7%	11 (10.8)	9 (8.7)	26 (22.6)	1 (1.0)
FPG (mg/dL)	**N = 104**	**N = 104**	**N = 115**	**N = 109**
Baseline (mean)	183.5	184.6	179.3	178.9
Change from baseline (adjusted mean‡)	-0.9	18.4	-7.8	12.9
Difference from placebo (adjusted mean‡)	-19.3¶		-20.7§	
Body Weight (kg)‖	**N = 76**	**N = 73**	**N = 102**	**N = 74**
Baseline (mean)	85.7	81.5	86.5	84.6
Change from baseline (adjusted mean‡)	1.1	0.0	0.4	-0.7
Difference from placebo (adjusted mean‡)	1.1#		1.1††	

† All Patients Treated Population (an intention-to-treat analysis).
‡ Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
§ p<0.001 compared to placebo.
‖ All Patients as Treated (APaT) population, excluding data following glycemic rescue therapy.
¶ p=0.003 compared to placebo.
# p=0.016 compared to placebo.
†† p=0.007 compared to placebo.

Add-on Combination Therapy with Metformin plus Rosiglitazone

A total of 262 patients with type 2 diabetes participated in a 54-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of JANUVIA in combination with metformin and rosiglitazone. Patients with inadequate glycemic control on a stable regimen of metformin (≥1500 mg per day) and rosiglitazone (≥4 mg per day) were randomized to the addition of either 100 mg of JANUVIA or placebo, administered once daily. Glycemic parameters were evaluated at the primary time point of Week 18 and at Week 54.

In combination with metformin and rosiglitazone, JANUVIA provided significant improvements in HbA_{1c}, FPG, and 2-hour PPG compared to placebo with metformin and rosiglitazone (Table 8) at Week 18, with improvements sustained through the end of the study. Lipid effects were generally neutral. There was no significant difference between JANUVIA and placebo in body weight change.

Table 8 Glycemic Parameters and Body Weight at Week 18 and Week 54 (Final Visit) for JANUVIA as Add-on Combination Therapy with Metformin and Rosiglitazone†

	Week 18		Week 54	
	JANUVIA 100 mg + Metformin+ Rosiglitazone	Placebo + Metformin + Rosiglitazone	JANUVIA 100 mg + Metformin + Rosiglitazone	Placebo + Metformin + Rosiglitazone
HbA1c (%)	**N = 168**	**N = 88**	**N = 168**	**N = 88**
Baseline (mean)	8.81	8.73	8.81	8.73
Change from baseline (adjusted mean‡)	-1.03	-0.31	-1.05	-0.28
Difference from placebo + rosiglitazone + metformin (adjusted mean‡)	-0.72§		-0.77§	
Patients (%) achieving A1C <7%	37 (22%)	8 (9%)	44 (26%)	12 (14%)
FPG (mg/dL)	**N = 169**	**N = 89**	**N = 169**	**N = 89**
Baseline (mean)	182.1	183.5	182.1	183.5
Change from baseline (adjusted mean‡)	-30.7	-11.7	-28.0	-10.7
Difference from placebo + rosiglitazone + metformin (adjusted mean‡)	-19.0§		-17.4§	
2-hour PPG (mg/dL)	**N = 142**	**N = 75**	**N = 147**	**N = 77**
Baseline (mean)	257.8	249.5	256.6	247.7
Change from baseline (adjusted mean‡)	-59.9	-22.0	-50.7	-16.6
Difference from placebo + rosiglitazone + metformin (adjusted mean‡)	-37.9§		-34.1§	
Body Weight (kg)‖	**N = 157**	**N = 79**	**N = 115**	**N = 40**
Baseline (mean)	82.1	87.0	82.0	85.6
Change from baseline (adjusted mean‡)	0.5	0.2	1.9	1.3
Difference from placebo + metformin + rosiglitazone (adjusted mean‡)	0.3¶		0.6¶	

† All Patients Treated Population (an intention- to-treat analysis).
‡ Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
§ p<0.001 compared to placebo + metformin + rosiglitazone.
‖ All Patients as Treated (APaT) population, excluding data following glycemic rescue therapy.
¶ Not statistically significant (p≥0.05) compared to placebo + metformin + rosiglitazone.

Add-on Combination Therapy with Insulin (with or without Metformin)

A total of 641 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of JANUVIA as add-on combination therapy with insulin (with or without metformin). Patients on pre-mixed, long-acting, or intermediate-acting insulin with or without metformin (≥1500 mg per day) were randomized to the addition of either 100 mg of JANUVIA or placebo, administered once daily. Glycemic endpoints measured included HbA1c, fasting glucose, and 2-hour post-prandial glucose.

In combination with insulin (with or without metformin), JANUVIA provided significant improvements in HbA_{1c}, FPG, and 2-hour PPG compared to placebo (Table 9). The improvement in HbA_{1c} compared to placebo was generally consistent across subgroups defined by gender, age, race, baseline BMI, length of time since diagnosis of diabetes. There was no significant difference between JANUVIA and placebo in body weight change.

Table 9 Glycemic Parameters and Body Weight at Final Visit (24-Week Study) for JANUVIA as Add-on Combination Therapy with Insulin or Insulin plus Metformin†

	JANUVIA 100 mg + Insulin (+/- Metformin)	Placebo + Insulin (+/- Metformin)
HbA1c (%)	**N = 305**	**N = 312**
Baseline (mean)	8.72	8.64
Change from baseline (adjusted mean‡)	-0.59	-0.03
Difference from placebo (adjusted mean‡,§)	-0.56‖	
Patients (%) achieving HbA1c <7%	39 (12.8)	16 (5.1)
FPG (mg/dL)	**N = 310**	**N = 313**
Baseline (mean)	175.8	179.1
Change from baseline (adjusted mean‡)	-18.5	-3.5
Difference from placebo (adjusted mean‡)	-15.0‖	
2-hour PPG (mg/dL)	**N = 240**	**N = 257**
Baseline (mean)	290.9	292.1
Change from baseline (adjusted mean‡)	-30.9	5.2
Difference from placebo (adjusted mean‡)	-36.1‖	
Body Weight (kg)¶	**N = 266**	**N = 266**
Baseline (mean)	86.6	87.4
Change from baseline (adjusted mean‡)	0.1	0.1
Difference from placebo (adjusted mean‡)	0.0#	

† All Patients Treated Population (an intention-to-treat analysis).
‡ Least squares means adjusted for metformin use at Visit 1 (yes/no), insulin use at Visit 1 (pre-mixed vs. non-pre-mixed [intermediate- or long-acting]), and baseline value.
§ Treatment by stratum interaction was not significant (p>0.10) for metformin stratum and for insulin stratum.
‖ p<0.001 compared to placebo.
¶ All Patients as Treated (APaT) population, excluding data following glycemic rescue therapy.
# Not statistically significant (p≥0.05) compared to placebo.

INDICATIONS

Type 2 diabetes mellitus

DOSAGE AND ADMINISTRATION

The recommended dose of JANUVIA is 100 mg once daily as monotherapy or as combination therapy with metformin, a sulfonylurea, insulin (with or without metformin), a PPARγ agonist (i.e., thiazolidinediones), metformin plus a sulfonylurea, or metformin plus a PPARγ agonist as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

JANUVIA can be taken with or without food.

When JANUVIA is used in combination with a sulfonylurea or with insulin, a lower dose of sulfonylurea or insulin may be considered to reduce the risk of hypoglycemia. (See **PRECAUTIONS,** *Hypoglycemia in Combination with a Sulfonylurea or with Insulin.*)

Patients with Renal Insufficiency

For patients with mild renal insufficiency (creatinine clearance [CrCl] ≥50 mL/min, approximately corresponding to serum creatinine levels of ≤1.7 mg/dL in men and ≤1.5 mg/dL in women), no dosage adjustment for JANUVIA is required.

For patients with moderate renal insufficiency (CrCl ≥30 to <50 mL/min, approximately corresponding to serum creatinine levels of >1.7 to ≤3.0 mg/dL in men and >1.5 to ≤2.5 mg/dL in women), the dose of JANUVIA is 50 mg once daily.

For patients with severe renal insufficiency (CrCl <30 mL/min, approximately corresponding to serum creatinine levels of >3.0 mg/dL in men and >2.5 mg/dL in women) or with end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis, the dose of JANUVIA is 25 mg once daily. JANUVIA may be administered without regard to the timing of dialysis.

Because there is a dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of JANUVIA and periodically thereafter.

CONTRAINDICATIONS

JANUVIA is contraindicated in patients who are hypersensitive to any components of this product. (See **PRECAUTIONS**, *Hypersensitivity Reactions* and **SIDE EFFECTS**, *Postmarketing Experience*.)

PRECAUTIONS

General

JANUVIA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Pancreatitis: There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking JANUVIA. After initiation of JANUVIA, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, JANUVIA should promptly be discontinued and appropriate management should be initiated. JANUVIA has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using JANUVIA.

Use in Patients with Renal Insufficiency: JANUVIA is renally excreted. To achieve plasma concentrations of JANUVIA similar to those in patients with normal renal function, lower dosages are recommended in patients with moderate and severe renal insufficiency, as well as in ESRD patients requiring hemodialysis or peritoneal dialysis. (See DOSAGE AND ADMINISTRATION, Patients with Renal Insufficiency.)

Hypoglycemia in Combination with a Sulfonylurea or with Insulin: In clinical trials of JANUVIA as monotherapy and as part of combination therapy with agents not known to cause hypoglycemia (i.e. metformin or PPARγ agonist (thiazolidinedione)), rates of hypoglycemia reported with JANUVIA were similar to rates in patients taking placebo. As is typical with other antihyperglycemic agents, when JANUVIA was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo (see **SIDE EFFECTS**). Therefore, to reduce the risk of hypoglycemia, a lower dose of sulfonylurea or insulin may be considered (see **DOSAGE AND ADMINISTRATION**).

Hypersensitivity Reactions: There have been postmarketing reports of serious hypersensitivity reactions in patients treated with JANUVIA. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. 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. Onset of these reactions occurred within the first 3 months after initiation of treatment with JANUVIA, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUVIA, assess for other potential causes for the event, and institute alternative treatment for diabetes. (See **CONTRAINDICATIONS** and **SIDE EFFECTS**, *Postmarketing Experience*.)

PREGNANCY

Sitagliptin was not teratogenic in rats at oral doses up to 250 mg/kg or in rabbits given up to 125 mg/kg during organogenesis (up to 32 and 22 times, respectively, the human exposure based on the recommended daily adult human dose of 100 mg/day). In rats, a slight increase in the incidence of fetal rib malformations (absent, hypoplastic and wavy ribs) was observed at oral doses of 1000 mg/kg/day (approximately 100 times the human exposure based on the recommended daily adult human dose of 100 mg/day). Slight decreases in mean preweaning body weights of both sexes and postweaning body weight gains of males were observed in the offspring of rats given oral dose of 1000 mg/kg/day. However, animal reproduction studies are not always predictive of the human response.

There are no adequate and well-controlled studies in pregnant women; therefore, the safety of JANUVIA in pregnant women is not known. JANUVIA, like other oral antihyperglycemic agents, is not recommended for use in pregnancy.

NURSING MOTHERS

Sitagliptin is secreted in the milk of lactating rats. It is not known whether sitagliptin is secreted in human milk. Therefore, JANUVIA should not be used by a woman who is nursing.

PEDIATRIC USE

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

USE IN THE ELDERLY

In clinical studies, the safety and effectiveness of JANUVIA in the elderly (≥65 years) were comparable to those seen in younger patients (<65 years). No dosage adjustment is required based on age. Elderly patients are more likely to have renal insufficiency; as with other patients, dosage adjustment may be required in the presence of significant renal insufficiency (see **DOSAGE AND ADMINISTRATION**, *Patients with Renal Insufficiency*).

DRUG INTERACTIONS

***In Vitro* Assessment of Drug Interactions:**

Sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4. Sitagliptin is a p-glycoprotein substrate, but does not inhibit p-glycoprotein mediated transport of digoxin. Based on these results, sitagliptin is considered unlikely to cause interactions with other drugs that utilize these pathways.

Sitagliptin is not extensively bound to plasma proteins. Therefore, the propensity of sitagliptin to be involved in clinically meaningful drug-drug interactions mediated by plasma protein binding displacement is very low.

***In Vivo* Assessment of Drug Interactions:**

Effects of Sitagliptin on Other Drugs

In clinical studies, as described below, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing *in vivo* evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT). Multiple doses of sitagliptin slightly increased digoxin concentrations; however, these increases are not considered likely to be clinically meaningful and are not attributed to a specific mechanism.

Metformin: Co-administration of multiple twice-daily doses of sitagliptin with metformin, an OCT substrate, did not meaningfully alter the pharmacokinetics of metformin in patients with type 2 diabetes. Therefore, sitagliptin is not an inhibitor of OCT-mediated transport.

Sulfonylureas: Single-dose pharmacokinetics of glyburide, a CYP2C9 substrate, were not meaningfully altered in subjects receiving multiple doses of sitagliptin. Clinically meaningful interactions would not be expected with other sulfonylureas (e.g., glipizide, tolbutamide, and glimepiride) which, like glyburide, are primarily eliminated by CYP2C9.

Simvastatin: Single-dose pharmacokinetics of simvastatin, a CYP3A4 substrate, were not meaningfully altered in subjects receiving multiple daily doses of sitagliptin. Therefore, sitagliptin is not an inhibitor of CYP3A4-mediated metabolism.

Thiazolidinediones: Single-dose pharmacokinetics of rosiglitazone were not meaningfully altered in subjects receiving multiple daily doses of sitagliptin. Therefore, sitagliptin is not an inhibitor of CYP2C8-mediated metabolism. Clinically meaningful interactions with pioglitazone are not expected because pioglitazone predominantly undergoes CYP2C8- or CYP3A4-mediated metabolism.

Warfarin: Multiple daily doses of sitagliptin did not meaningfully alter the pharmacokinetics, as assessed by measurement of S(-) or R(+) warfarin enantiomers, or pharmacodynamics (as assessed by measurement of prothrombin INR) of a single dose of warfarin. Since S(-) warfarin is primarily metabolized by CYP2C9, these data also support the conclusion that sitagliptin is not a CYP2C9 inhibitor.

Oral Contraceptives: Co-administration with sitagliptin did not meaningfully alter the steady-state pharmacokinetics of norethindrone or ethinyl estradiol.

Digoxin: Sitagliptin had a minimal effect on the pharmacokinetics of digoxin. Following administration of 0.25 mg digoxin concomitantly with 100 mg of JANUVIA daily for 10 days, the plasma AUC of digoxin was increased by 11%, and the plasma C_{max} by 18%. These increases are not considered to be clinically meaningful. Patients receiving digoxin should be monitored appropriately.

Effects of Other Drugs on Sitagliptin

Clinical data described below suggest that sitagliptin is not susceptible to clinically meaningful interactions by co-administered medications:

Metformin: Co-administration of multiple twice-daily doses of metformin with sitagliptin did not meaningfully alter the pharmacokinetics of sitagliptin in patients with type 2 diabetes.

Cyclosporine: A study was conducted to assess the effect of cyclosporine, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Coadministration of a single 100-mg oral dose of JANUVIA and a single 600-mg oral dose of cyclosporine increased the AUC and C_{max} of sitagliptin by approximately 29% and 68%, respectively. These modest changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was also not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

Population Pharmacokinetics: Population pharmacokinetic analyses have been conducted in patients with type 2 diabetes. Concomitant medications did not have a clinically meaningful effect on the pharmacokinetics of sitagliptin. Medications assessed were those that are commonly administered to patients with type 2 diabetes including cholesterol-lowering agents (e.g., statins, fibrates, ezetimibe), anti-platelet agents (e.g., clopidogrel), antihypertensives (e.g., ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, hydrochlorothiazide), analgesics and non-steroidal anti-inflammatory agents (e.g., naproxen, diclofenac, celecoxib), anti-depressants (e.g., bupropion, fluoxetine, sertraline), antihistamines (e.g., cetirizine), proton-pump inhibitors (e.g., omeprazole, lansoprazole), and medications for erectile dysfunction (e.g., sildenafil).

SIDE EFFECTS

JANUVIA was generally well tolerated in controlled clinical studies as both monotherapy and combination therapy, with discontinuation of therapy due to clinical adverse experiences similar to placebo.

In four placebo-controlled clinical studies as both monotherapy (one study of 18- and one of 24-week duration) and add-on combination therapy with metformin or pioglitazone (both of 24-week duration), there were 1082 patients treated with JANUVIA 100 mg once daily and 778 patients given placebo. (Two of these studies also included 456 patients treated with JANUVIA 200 mg daily, two times the recommended daily dose.) There were no drug-related adverse reactions reported that occurred with an incidence of ≥1% in patients receiving JANUVIA 100 mg. Overall, the safety profile of the 200-mg daily dose was similar to that of the 100-mg daily dose.

In a prespecified pooled analysis of the above studies, the overall incidence of adverse experiences of hypoglycemia in patients treated with JANUVIA 100 mg was similar to placebo (1.2% vs. 0.9%). The incidences of selected gastrointestinal adverse experiences in patients treated with JANUVIA or placebo were: abdominal pain (JANUVIA, 2.3%; placebo, 2.1%), nausea (1.4%, 0.6%), vomiting (0.8%, 0.9%), and diarrhea (3.0%, 2.3%).

In all studies, adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required. When JANUVIA was used in combination with a sulfonylurea or with insulin, the incidence of sulfonylurea- or insulin-induced hypoglycemia was increased over that of placebo.

Add-on Combination with a Sulfonylurea: In a 24-week placebo-controlled study of JANUVIA 100 mg in combination with glimepiride or with glimepiride and metformin (JANUVIA, N=222; placebo, N=219), the drug-related adverse reaction reported in ≥1% of patients treated with JANUVIA and more commonly than in patients treated with placebo was hypoglycemia (JANUVIA, 9.5%; placebo, 0.9%). The overall incidence of hypoglycemia reported regardless of assessment of causality was 12.2% in patients treated with JANUVIA and 1.8% in patients given placebo.

Add-on Combination with Metformin and a PPARγ Agonist: In a placebo-controlled study of JANUVIA 100 mg in combination with metformin and rosiglitazone (JANUVIA, N=170; placebo, N=92), the drug-related adverse reactions reported through the primary time point at Week 18 in ≥1% of patients treated with JANUVIA and more commonly than in patients treated with placebo were: headache (JANUVIA, 2.4%; placebo, 0.0%), diarrhea (1.8%, 1.1%), nausea (1.2%, 1.1%), hypoglycemia (1.2%, 0.0%), and vomiting (1.2%, 0.0%). Through Week 54, the drug-related adverse reactions reported in ≥1% of patients treated with JANUVIA and more commonly than in patients treated with placebo were: headache (2.4%, 0.0%), hypoglycemia (2.4%, 0.0%), upper respiratory tract infection (1.8%, 0.0%), nausea (1.2%, 1.1%), cough (1.2%, 0.0%), fungal skin infection (1.2%, 0.0%), peripheral edema (1.2%, 0.0%), and vomiting (1.2%, 0.0%).

Add-on Combination with Metformin: In a placebo-controlled study in Japanese patients of JANUVIA 50 mg in combination with metformin (JANUVIA, N=77; placebo, N=72), the only drug-related adverse reaction reported at Week 12 in ≥1% of patients treated with JANUVIA and more commonly than in patients treated with placebo was herpes simplex (JANUVIA, 1.3%; placebo, 0.0%).

Initial Combination Therapy with Metformin: In a 24-week placebo-controlled factorial study of initial therapy with sitagliptin 100 mg in combination with metformin at 1000 mg or 2000 mg per day (administered as sitagliptin 50 mg/metformin 500 mg or 1000 mg twice daily), the drug-related adverse reactions reported in ≥1% of patients treated with sitagliptin plus metformin (N=372) and more commonly than in patients treated with metformin alone (N=364) were: diarrhea (sitagliptin plus metformin, 3.5%; metformin, 3.3%), dyspepsia (1.3%; 1.1%), flatulence (1.3%; 0.5%), vomiting (1.1%; 0.3%), and headache (1.3%; 1.1%). The incidence of hypoglycemia was 1.1% in patients given sitagliptin in combination with metformin and 0.5% in patients given metformin alone.

Initial Combination Therapy with a PPARγ Agonist: In a 24-week study of initial therapy with JANUVIA at 100 mg/day in combination with pioglitazone at 30 mg/day, the only drug-related adverse reaction reported in ≥1% of patients treated with JANUVIA with pioglitazone (N=261) and more commonly than in patients treated with pioglitazone alone (N=259) was (asymptomatic) decreased blood glucose (JANUVIA with pioglitazone, 1.1%; pioglitazone, 0.0%). The incidence of (symptomatic) hypoglycemia was 0.4% in patients given JANUVIA in combination with pioglitazone and 0.8% in patients given pioglitazone. One patient taking JANUVIA and pioglitazone experienced a severe episode of hypoglycemia.

Add-on Combination with Insulin: In a 24-week placebo-controlled study of JANUVIA 100 mg in combination with insulin (with or without metformin), the drug-related adverse reactions reported in ≥1% of patients treated with JANUVIA (N=322) and more commonly than in patients treated with placebo (N=319) were: hypoglycemia (JANUVIA, 9.6%; placebo, 5.3%), influenza (1.2%, 0.3%), and headache (1.2%, 0.0%). The incidence of hypoglycemia reported regardless of assessment of causality in patients treated with JANUVIA was 15.5%, and with placebo was 7.8%. Three patients experienced a severe episode of hypoglycemia (JANUVIA, 0.6%; placebo, 0.3%).

No clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed in patients treated with JANUVIA.

Postmarketing Experience:

Additional adverse reactions have been identified during postmarketing use of JANUVIA as monotherapy and/or in combination with other antihyperglycemic agents. 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.

Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions, including Stevens-Johnson syndrome (see **CONTRAINDICATIONS** and **PRECAUTIONS**, *Hypersensitivity Reactions*); hepatic enzyme elevations; acute pancreatitis; including fatal and non-fatal hemorrhagic and necrotizing pancreatitis worsening (see **PRECAUTIONS,** *Pancreatitis*); renal function, including acute renal failure (sometimes requiring dialysis); upper respiratory tract infection; nasopharyngitis; constipation; vomiting; headache; arthralgia; myalgia; pain in extremity; back pain.

LABORATORY TEST FINDINGS

The incidence of laboratory adverse experiences was similar in patients treated with JANUVIA 100 mg compared to patients treated with placebo. Across clinical studies, a small increase in white blood cell count (approximately 200 cells/microL difference in WBC vs placebo; mean baseline WBC approximately 6600 cells/microL) was observed due to an increase in neutrophils. This observation was seen in most but not all studies. This change in laboratory parameters is not considered to be clinically relevant.

OVERDOSAGE

During controlled clinical trials in healthy subjects, single doses of up to 800 mg JANUVIA were generally well tolerated. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg JANUVIA (see **CLINICAL PHARMACOLOGY)**. There is no experience with doses above 800 mg in humans. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with JANUVIA with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

Sitagliptin is modestly dialyzable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

STORAGE

Store up to 30°C (86°F).

AVAILABILITY

To be filled in locally.