Taiwan Food and Drug Administration

Assessment Report

Trade Name：Galvus Tablets 50 mg

Active Ingredient：Vildagliptin

License Number： 衛署藥輸字第 025306 號

Applicant：台灣諾華股份有限公司

Approval Date： 2010/12/07

Indication： Type 2 diabetes mellitus. As dual oral therapy in combination with metformin or sulphonylurea or thiazolidinedione in patients with insufficient glycemic control despite monotherapy with metformin or sulphonylurea or thiazolidinedione.

1. Background Information

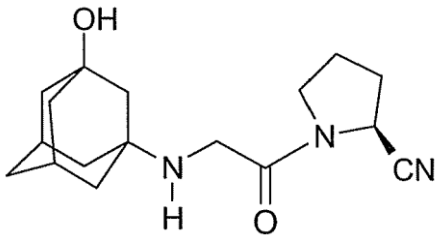
Trade Name	Galvus Tablets 50 mg
Active Ingredient(s)	Vildagliptin
Applicant	台灣諾華股份有限公司
Dosage Form & Strengths	Tablets / 50 mg
Indication	Type 2 diabetes mellitus
Posology	As dual oral therapy in combination with metformin or sulphonylurea or thiazolidinedione in patients with insufficient glycemic control despite monotherapy with metformin or sulphonylurea or thiazolidinedione. Adults: When used in dual combination with metformin or a thiazolidinedione, the recommended daily dose of vildagliptin is 100 mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening. When used in dual combination with a sulphonylurea, the recommended dose of vildagliptin is 50 mg once daily administered in the morning. In this patient population, vildagliptin 100 mg daily was no more effective than vildagliptin 50 mg once daily. Doses higher than 100 mg are not recommended. The safety and efficacy of vildagliptin as triple oral therapy in combination with metformin and a thiazolidinedione or with metformin and a sulphonylurea has not been established. Galvus can be administered with or without a meal.
Pharmacological Category **ATC Code**	DPP-IV inhibitor ATC code: A10BH02

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, vildagliptin, is chemically designated as (S)-1-[2-(3-hydroxyadamantan-1-ylamino)acetyl]pyrrolidine-2-carbonitrile and has the following structure:



It is a white to slightly yellowish or slightly greyish crystalline powder. The molecular formula and the molecular weight are $C_{17}H_{25}N_3O_2$ and 303.40, respectively. The structure has one chiral center. Chiral starting material containing the correct stereochemical configuration ensures the formation of the correct isomer. No other polymorphic form or solvate is found. It is a non-hygroscopic, high solubility and permeability compound.

Adequate information on characterization of the drug substance has been provided. The structure of vildagliptin is confirmed by UV, IR, mass and nuclear magnetic resonance spectrum (^{1}H-NMR, ^{13}C-NMR). The spectrum assignations were consistent with the declared chemical structure

The specification includes tests for appearance, color and clarity of solution, identity, assay, structural related substances, residual solvents, heavy metals, loss on drying, sulphated ash, particle size and microbial limit. A rationale of the acceptance criteria is provided and based on analytical data from the release and stability studies of drug substance batches manufactured during development, and toxicological safety assessment.

2.1.2 Drug product

Vildagliptin drug product (Galvus®) in 50 mg is a tablet dosage from packaged in aluminum blister. The excipients used in the drug product formulation comply with the compendial monographs. Only one excipient is of animal origin, but it is derived from healthy animals and under the same conditions for human consumption. During the process development of Galvus® tablets, optimal process conditions were defined and parameters were established. A robust process is further confirmed by three consecutive batches of process validation.

Adequate release and shelf-life specification have been presented for the Galvus® tablets and test items include description, identification, assay, degradation products, content uniformity, dissolution, water content and microbial purity. The results of batch analysis are all complied with the specification. For non-pharmacopoeia methods, validations are performed and accepted in terms of specificity, linearity, accuracy, repeatability, intermediate precision, LOD/LOQ and robustness.

Stability studies under long-term (25°C/60% RH and 30°C/70% RH) and accelerated conditions (40°C/75% RH) have been carried out on three production-scale batches. The products are packaged in the container closure system intended for marketing. The parameters evaluated during the stability study are appearance, assay, degradation products, dissolution, water content and microbiological purity. Up to 12 months of long-term and 6

months of accelerated stability data are submitted. The available results showed that no significant changes were observed at both conditions. The shelf life of Galvus® 50 mg can be tentatively granted for 24 months under the storage condition of 30°C.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Galvus (vildagliptin) inhibits DPP-4 by binding to the catalytic site of the enzyme, competing with the binding of substrates such as GLP-1 (glucagon-like peptide). In vitro and in vivo pharmacological studies demonstrated that vildagliptin is a potent, high selective, competitive and fully reversible inhibitor of human DPP-4. The pharmacological rationale of vildagliptin for treating type 2 diabetes is acceptable. In safety pharmacological studies, findings of note occurred only in relation to the cardiovascular system. These effects of vildagliptin in animals were considered not to represent a significant risk for human treated with vildagliptin at the recommended clinical doses, based on the exposure margins (~6X) relative to the animal findings and the absence of any similar effects in clinical trials to date.

2.2.2 Toxicological Studies

In toxicological studies, all of the major toxicity findings are either considered expected, due to the pharmacological effect of vildagliptin (i.e. alveolar macrophages), or not to represent a significant risk to humans, based on one or more of the following: an adequate systemic exposure ratio (~150X) and lack of relevance to human (i.e. increased hemangiosarcoma and mammary tumor incidences in mice), lack of a corresponding demonstrable effects (i.e. GI effects in dogs, cardiac arrhythmia in dogs, heart rate/blood pressure changes in dogs and monkeys) in large populations or high-dose studies in humans. However, the clinical relevance of drug-related skin lesions found in monkey is uncertain and the safety margin cannot be determined. The findings in monkey should be stated in the labeling.

In conclusion, the technical data submitted by sponsor is acceptable. This NDA is suggested to be approved from preclinical pharmacological and toxicological point of view.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Vildagliptin was absorbed rapidly with a mean t_{max} of about 2 hrs. Vildagliptin has slightly over dose-proportional property in the range of 25 mg to 200 mg after a single oral dose administration. The absolute bioavailability was approximately 85.3%. Following multiple dosing, a minimal accumulation was observed. Patients with type II DM had comparable pharmacokinetic profile with that of healthy subjects. The co-administration of high-fat meal decreased the C_{max} by 19% and delayed t_{max} by 0.75 hrs. Therefore, vildagliptin can be administered with or without food. The volume of distribution of vildagliptin was

approximately 70.5 L. Vildagliptin was a low plasma protein binding drug. Studies of radiolabeled vildagliptin in animals showed that radioactivity was not detectable in brain tissue, but was found in fetus, indicating drug-related radioactivity may transfer across placenta. Vildagliptin was secreted into the milk in rat. The appropriate information was described in labeling. DPP-4 is responsible for the hydrolysis of vildagliptin, however, oxidation is not a predominant pathway in the metabolism of vildagliptin. The major metabolite was LAY151, inactive metabolite. Following oral administration, approximately 85.4% and 14.8% of radioactivity dose were recovered from urine and feces within 168 hrs, respectively. The total clearance (CL_T) and renal clearance (CL_R) of vildagliptin after a single IV infusion was 40.6 L/hr and 13.0 L/hr, respectively. Vildagliptin has a short half-life (2-3 hr).

2.3.2 Interaction Studies

Based on results of *in vitro* studies, vildagliptin does not inhibit the activity of CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and CYP3A4/5. Vildagliptin is not an inducer of CYP1A2, 2C8, 2B6, 2C9, 2C19 and 3A, UGT1A1, ABCB1 (MDR1) and ABCC2 (MRP2). It is a substrate of P-gp but not an inhibitor of P-gp.

The combinations of vildagliptin and metformin, SU (glyburide), TZD (pioglitazone) and glyburide were evaluated. No dosage adjustment is recommended when vildagliptin is co-administered with three drugs above, ramipril, digoxin, warfarin, simvastatin, amlodipine and valsartan.

2.3.3 Special Populations

The pharmacokinetic parameters of vildagliptin are not affected by food, gender, age, BMI and varied degrees of hepatic impairment (Child-Pugh A to C).

Compared to healthy subjects, the trend of changes of pharmacokinetic parameters of vildagliptin in subjects with mild, moderate and severe renal impairment and ESRD subjects was not consistent. Mild and severe renal impaired subjects had about 2-fold higher exposure than healthy subjects. However, subjects with moderate and ESRD subjects had comparable profiles as compared to healthy subjects. Exposure to LAY151, the inactive metabolite, increased in subjects with mild, moderate, severe renal impairment and ESRD subjects by 65%, 121%, 516% and 577%, respectively. Although LAY151 is considered to be an inactive metabolite, the clinical impact of the increase of LAY151 up to 6 folds is not clear. The comparison of PK data of vildagliptin and LAY151 indicated that hemodialysis removed only few dose of vildagliptin from plasma.

Due to limited clinical experience in patients with moderate to severe renal impairment, and end-stage renal disease patients, it is not recommended vildagliptin to be used in these patients. Based on safety reason, it is not recommended to be used in patients with liver disease.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The efficacy of Galvus® used as monotherapy was assessed in 4 Phase III double-blind, placebo- or active-controlled (metformin or rosiglitazone) pivotal studies (Studies [2301], [2309], [2327], and [2384]), and 3 Phase III double-blind, placebo- or active-controlled (voglibose or acarbose) studies (Studies [1301], [1303], and [2323]) conducted in Asian patients. That used in combination with commonly prescribed anti-diabetic agents (metformin,pioglitazone, glimepiride, or insulin) was evaluated in 4 pivotal studies (Studies [2303], [2304], [2305] and [2311]) as well as 2 Asian studies (Studies [1302],and [23140]). Treatment duration was 24 weeks for all pivotal studies except for Study [2309] (52 weeks). In 3 Japanese studies (Studies [1301], [1302], and [1303]), the treatment duration was 12 weeks, and it was 24 weeks in 2 studies performed in China (Studies [2323], and [23140]). The primary efficacy endpoint for all studies was the change from baseline in HbA1c at the end of double-blind treatment. In pivotal studies, treatment comparisons were performed using the ANCOVA model with treatment and pooled center as the classification variables and baseline HbA_{1C} (centered by subtracting the overall mean baseline HbA_{1C} of all treatment groups) as the covariate. Treatment differences were estimated from the adjusted mean (least square mean) changes from baseline for each treatment group, as derived from the ANCOVA. If there were more than one primary comparison, the Hochberg's multiple comparison procedure was used to protect the overall two-sided significance level of 5%.

The primary results of the 8 pivotal studies are summarized in Table 1. Two monotherapy studies of Galvus® at daily dose of 50 mg or 100 mg showed significant greater reductions in HbA_{1C} as compared to placebo in drug-naïve T2DM patients (Studies [2301] and [2384]). Non-inferiority (margin: 0.4%) of Galvus® 50 mg bid to rosiglitazone 8 mg qd was not well established in Study [2327]. Galvus® 50 mg bid failed to show non-inferiority (margin: 0.4%) to metformin 1000 mg bid in Study [2309]. The combining use of Galvus® (50 mg or 100 mg daily) with metformin, glimepiride, or pioglitazone was shown efficacious in improving the glycemic control in patients who had failed previous OAD monotherapy (Studies [2303], [2304] and [2305]). Regarding combination with insulin, Galvus (50 mg bid) demonstrated statistically significantly greater HbA_{1C} reduction compared to insulin alone when added to existing insulin therapy (Study [2311]).

Table 1 The primary results of the 8 pivotal studies

	Change from baseline in HbA1c at the end of double-blind treatment			
	***Galvus*® 50 mg qd**	***Galvus*® 50 mg bid**	***Galvus*® 100 mg qd**	**Control**
Monotherapy				
Study [2301] (ITT)				**Placebo**
N	104	90	92	94

LS mean change (SE)	-0.78(0.12)	-0.79 (0.13)	-0.88 (0.13)	-0.30 (0.13)
LS mean difference vs. control (95% CI)	-0.48 (-0.82, -0.14)	-0.49 (-0.84, -0.14)	-0.58 (-0.93, -0.23)	
P value vs. control	0.006	0.006	0.001	
Study [2309] (ITT)				**Met 1000 mg bid**
N		511		249
LS mean change (SE)		-0.96 (0.07)		-1.44 (0.09)
LS mean difference vs. control (95% CI)		0.48 (0.28, 0.67)		
Study [2309] (PP)				
N		404		193
LS mean change (SE)		-1.02 (0.07)		-1.60 (0.10)
LS mean difference vs. control (95% CI)		0.58 (0.36, 0.80)		
Study [2327] (ITT)				**Rosiglitazone 8 mg qd**
N		459		249
LS mean change (SE)		-1.13 (0.06)		-1.32 (0.09)
LS mean difference vs. control (95% CI)		0.19 (-0.01, 0.39)		
Study [2327] (PP)				
N		420		207
LS mean change (SE)		-1.20 (0.07)		-1.48 (0.09)
LS mean difference vs. control (95% CI)		0.28 (0.07, 0.49)		
Study [2384] (ITT)				**Placebo**
N	84	79	89	88
LS mean change (SE)	-0.47 (0.14)	-0.72 (0.14)	-0.84 (0.13)	0.01 (0.13)
LS mean difference vs. control (95% CI)	-0.48 (-0.86, -0.11)	-0.73 (-1.11, -0.35)	-0.85 (-1.22, -0.49)	
P value vs. control	0.011	<0.001	< 0.001	
Add-on combination therapy				
Study [2303] (ITT)	**+metformin**	**+metformin**		**PL+metformin**
N	143	143		130
LS mean change (SE)	-0.51 (0.10)	-0.88 (0.10)		0.23 (0.10)
LS mean difference vs. control (95% CI)	-0.73(-1.00, -0.47)	-1.10(-1.37, -0.84)		
P value vs. control	<0.001	<0.001		

Study [2304] (ITT)	**+pioglitazone**	**+pioglitazone**		**PL+pilglitazone**
N	124	136		138
LS mean change (SE)	-0.76 (0.10)	-0.97 (0.10)		-0.30 (0.10)
LS mean difference vs. control (95% CI)	-0.46 (-0.7, -0.19)	-0.67 (-0.94, -0.4)		
P value vs. control	0.001	<0.001		
Study [2305] (ITT)	**+glimepiride**	**+glimepiride**		**PL+ glimepiride**
N	132	132		144
LS mean change (SE)	-0.58 (0.10)	-0.63 (0.09)		0.07 (0.09)
LS mean difference vs. control (95% CI)	-0.64 (-0.90, -0.39)	-0.70 (-0.95, -0.44)		
P value vs. control	<0.001	<0.001		
Study [2311] (ITT)		**+insulin**		**PL+insulin**
N		125		131
LS mean change (SE)		-0.51 (0.09)		-0.24 (0.09)
LS mean difference vs. control (95% CI)		-0.27 (-0.51, -0.04)		
P value vs. control		0.022		

Met: Metformin; PL: placebo

The primary results of 5 Asian studies are summarized in Table 2. Two monotherapy studies showed Galvuls® at daily dose of 100 mg was significantly superior to placebo (Study[1303]) and voglibose 0.2 mg tid (Study[1301] in reducing HBA1c in drug-naïve T2DM patients. In addition, Galvus® 50 mg bid was non-inferior to acarbose up to 100 mg tid (margin: 0.3%) in improving glycemic control in study [2323]. Two combination studies showed the addition of Galvus 50 mg bid to metformin (Study [23140]) or glimepiride (Study[1302]) resulted in significantly greater HbA1c reduction compared to OAD monotherapy in T2DM patients.

Table 2 The primary results of 5 Asian studies

Study No.	**Change from baseline in HbA1c at the end of double-blind treatment**			
	***Galvus*® 50 mg qd**	***Galvus*® 50 mg bid**	***Galvus*® 100 mg qd**	**Control**
Monotherapy				
Study [1301] (ITT)				**Voglibose 0.2 mg tid**
N		188		192
LS mean change (SE)		-0.95(0.04)		-0.38 (0.04)
LS mean difference vs. control (95% CI)		-0.57(-0.68, -0.46)		

P value vs. control		< 0.001		
Study [1303] (ITT)				**Placebo**
N	58	63	56	59
LS mean change (SE)	-0.78 (0.07)	-0.86 (0.07)	-0.86 (0.07)	0.13 (0.07)
LS mean difference vs. control (95% CI)	-0.91(-1.11, -0.71)	-0.99(-1.19, -0.79)	-0.99(-1.19, -0.78)	
P value vs. control	< 0.001	< 0.001	< 0.001	
Study [2323] (ITT)				**Acarbose up to 100 mg tid**
N		431		216
LS mean change (SE)		-1.40 (0.07)		-1.29 (0.09)
LS mean difference vs. control (95% CI)		-0.11(-0.32, 0.10)		
Study [2323] (PP)				
N		405		199
LS mean change (SE)		-1.45 (0.07)		-1.35(0.09)
LS mean difference vs. control (95% CI)		-0.09(-0.32, 0.13)		
Add-on combination therapy				
Study [23140] (ITT)	**+metformin**	**+metformin**		**PL+metformin**
N		147		144
LS mean change (SE)		-0.92 (0.079)		0.54 (0.079)
LS mean difference vs. control (95% CI)		-0.38(-0.60, -0.16)		
P value vs. control		<0.001		
Study [1302] (ITT)		**+glimepiride**		**PL+ glimepiride**
N		102		100
LS mean change (SE)		-1.00 (0.06)		0.06 (0.06)
LS mean difference vs. control (95% CI)		-0.95 (-1.11, -0.79)		
P value vs. control		<0.001		

In summary, two monotherapy studies of Galvus® at daily dose of 50 mg or 100 mg showed significant greater reductions in HbA1C as compared to placebo in drug-naïve T2DM patients (Studies [2301] and [2384]). The combining use of Galvus® (50 mg or 100 mg daily) with metformin, glimepiride, or pioglitazone was shown efficacious in improving the glycemic control in patients who had failed previous OAD monotherapy (Studies [2303], [2304] and [2305]). Regarding combination with insulin, Galvus (50 mg bid) demonstrated

statistically significantly greater HbA1C reduction compared to insulin alone when added to existing insulin therapy (Study [2311]), however, the treatment effect of Galvus® 50mg bid combined with insulin is limited(the treatment effect is about 0.27%).

2.4.2 Safety Results

Safety data were obtained from a total of 11500 patients (including about 1211 Asian patients) exposed to Galvus® on controlled trials of at least 12 weeks duration. The majority of adverse reactions were mild and transient, not requiring treatment discontinuations.

Rare cases of hepatic dysfunction (including hepatitis) have been reported. The patients were generally asymptomatic without clinical sequelae and liver function returned to normal after discontinuation of treatment. Some hepatic dysfunction (including hepatitis) occurred after having taken Galvus® for several months.

The incidence of hypoglycemia in patients receiving Galvus® 50mg bid combined with metformin is 1% compared with 0.4% in patients receiving placebo combined with metformin. The incidence of hypoglycemia in patients receiving Galvus® 50mg qd combined with sulphonylurea is 1.2% compared with 0.6% in patients receiving placebo combined with sulphonylurea. The incidence of hypoglycemia in patients receiving Galvus® 50mg bid combined with thiazolidinedione is 0.6% compared with 1.9% in patients receiving placebo combined with thiazolidinedione.

2.5 Bridging Study Evaluation

Vildagliptin has slightly over dose-proportional property in the range of 25 mg to 200 mg after a single oral dose administration. The pharmacodynamic curve for safety and efficacy is not steep. It is not a narrow therapeutic range drug. Vildagliptin was metabolized via varied metabolic pathways. There are no evidences to show enzymes involved metabolism may be different between ethnicities. Vildagliptin is not a prodrug. The bioavailability is 85% with low to moderate variation. Food may slightly affect the PK parameters but not clinical relevant.

Healthy Japanese appears to have approximately 30% higher systemic exposure than healthy non-Japanese. Based on E_{max} modeling results, the E_{max} and IC_{50} values between Japanese and non-Japanese are similar.

Either used as monotherapy or combined with other antidiabetic agents, Galvus® 50mg qd or 50mg bid is efficacious in Caucasian and Asian type 2 DM patients. The safety profiles are acceptable. The bridging study is waived.

2.6 Conclusion

The proposed indication is an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus as monotherapy or in dual combination with Metformin, a sulphonylurea (SU), a thiazolidinedione (TZD) or insulin when diet, exercise

and a single anti-diabetic agent do not result in adequate glycaemic control. Based on the submitted clinical study reports and PSUR, the benefit/risk of Galvus® is favorable. Nonetheless, based on study 2305, the HbA1c improvement in treatment arm of Galvus® 50mg bid combined with sulphonylurea was not better than in the treatment arm of Galvus® 50mg qd combined with sulphonylurea. Based on study 2311, the HbA1c improvement in treatment arm of Galvus® 50mg bid combined with insulin is limited. Due to rare cases of hepatic dysfunction (including hepatitis) has been reported, liver function tests (ALT and AST) should be performed prior to the initiation of treatment of Galvus® . If the baseline values of liver function tests are above 2.5X ULN, Galvus® is not recommended. Liver function should be monitored during treatment with Galvus® at three-month interval during the first year and periodically thereafter. ALT should be tested if the patients suffer from nausea, vomiting, fatigue, epigastric discomfort or jaundice. Hence the approved indication is type 2 diabetes mellitus. The approved posology and method of administration is as follows:
As dual therapy in combination with metformin or sulphonylurea or thiazolidinedione in patients with insufficient glycaemic control despite monotherapy with metformin or sulphonylurea or thiazolidinedione. In combination with metformin or thiazolidinedione, the recommended maximal daily dose is 50mg bid. In combination with sulphonylurea, the recommended daily dose is 50mg qd.

3. Post-Marketing Requirements

Routine post-marketing surveillance as required by department of health is adequate. No additional risk management plan is required.