Skip to main content

Kazano (Alogliptin and Metformin HCl Tablets)

Zuletzt aktualisiert: 30. November 2017

Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Alogliptin and Metformin hydrochloride

Over 2700 patients with type 2 diabetes have received alogliptin coadministered with metformin in four large randomized, double-blind controlled clinical trials. The mean exposure to KAZANO was 58 weeks with more than 1400 subjects treated for more than one year. These included two 26-week placebo controlled studies, one 52-week active control study and an interim analysis of a 104-week active control study. In the KAZANO arm, the mean duration of diabetes was approximately 6 years, the mean body mass index (BMI) was 31 kg/m² (56% of patients had a BMI ? 30 kg/m²), and the mean age was 55 years (18% of patients ? 65 years of age).

In a pooled analysis of these four controlled clinical studies, the overall incidence of adverse reactions was 74% in patients treated with KAZANO compared to 76% treated with placebo. Overall discontinuation of therapy due to adverse events was 6.2% with KAZANO compared to 1.9% in placebo, 6.4% in metformin, and 5.0% in alogliptin.

Adverse reactions reported in ? 4% of patients treated with KAZANO and more frequently than in patients who received alogliptin, metformin or placebo are summarized in Table 1.

Table 1: Adverse Reactions Reported in ? 4% of Patients Treated with KAZANO and More Frequently Than in Patients Receiving Either Alogliptin, Metformin or Placebo

	Number of Patients (%)			
	Placebo N=106	Metformin‡ N=1592	Alogliptin† N=222	KAZANO* N=2794
Upper respiratory tract infection	3 (2.8)	105 (6.6)	6 (2.7)	224 (8.0)
Nasopharyngitis	2 (1.9)	93 (5.8)	7 (3.2)	191 (6.8)
Diarrhea	3 (2.8)	105 (6.6)	4 (1.8)	155 (5.5)
Hypertension	6 (5.7)	96 (6.0)	5 (2.3)	154 (5.5)
Headache	3 (2.8)	74 (4.6)	11 (5.0)	149 (5.3)
Back pain	1 (0.9)	72 (4.5)	1 (0.5)	119 (4.3)
Urinary tract infection	2 (1.9)	59 (3.7)	4 (1.8)	116 (4.2)

*KAZANO - includes data pooled for patients receiving alogliptin 25 and 12.5 mg combined with various dose of metformin
† Alogliptin - includes data pooled for patients receiving alogliptin 25 and 12.5 mg
‡Metformin - includes data pooled for patients receiving various doses of metformin

Hypoglycemia

In a 26-week, double-blind, active-controlled study, of alogliptin in combination with metformin, the number of patients reporting hypoglycemia was 1.9% in the alogliptin 12.5 mg with metformin HCl 500 mg, 5.3% in the alogliptin 12.5 mg with metformin HCl 1000 mg, 1.8% in the metformin HCl 500 mg, and 6.3% in the metformin HCl 1000 mg treatment groups.

In a 26-week placebo-controlled study of alogliptin 25 mg administered once daily as add-on to metformin regimen, the number of patients reporting hypoglycemic events was 0.9% in the alogliptin with metformin and 2.9% in the placebo treatment groups.

In a 52-week, active-controlled, double-blind study of alogliptin once daily as add-on therapy to the combination of pioglitazone 30 mg and metformin compared to the titration of pioglitazone 30 mg to 45 mg and metformin, the number of patients reporting hypoglycemia was 4.5% in the alogliptin 25 mg with pioglitazone 30 mg and metformin group versus 1.5% in the pioglitazone 45 mg with metformin group.

In an interim analysis conducted in a 104-week, double-blind, active controlled study, of alogliptin 25 mg in combination with metformin, the number of patients reporting hypoglycemia was 1.4% in the alogliptin 25 mg with metformin group versus 23.8% in the glipizide with metformin group.

Alogliptin

Approximately 8500 patients with type 2 diabetes have been treated with alogliptin in 14 randomized, double-blind, controlled clinical trials with approximately 2900 subjects randomized to placebo and approximately 2200 to an active comparator. The mean exposure to alogliptin was 40 weeks with more than 2400 subjects treated for more than one year. Among these patients, 63% had a history of hypertension, 51% had a history of dyslipidemia, 25% had a history of myocardial infarction, 8% had a history of unstable angina, and 7% had a history of congestive heart failure. The mean duration of diabetes was 7 years, the mean body mass index (BMI) was 31 kg/m² (51% of patients had a BMI ? 30 kg/m²), and the mean age was 57 years (24% of patients ? 65 years of age).

Two placebo-controlled monotherapy trials of 12 and 26 weeks of duration were conducted in patients treated with alogliptin 12.5 mg daily, alogliptin 25 mg daily and placebo. Four placebo-controlled add-on combination therapy trials of 26 weeks duration were also conducted: with metformin, with a sulfonylurea, with a thiazolidinedione, and with insulin.

Five placebo-controlled trials of 16 weeks up through two years in duration were conducted in combination with metformin, in combination with pioglitazone and with pioglitazone added to a background of metformin therapy.

Three active-controlled trials of 52 weeks in duration were conducted in patients treated with pioglitazone and metformin, in combination with metformin and as monotherapy compared to glipizide.

In a pooled analysis of these 14 controlled clinical trials, the overall incidence of adverse events was 66% in patients treated with alogliptin 25 mg compared to 62% with placebo and 70% with active comparator. Overall discontinuation of therapy due to adverse events was 4.7% with alogliptin 25 mg compared to 4.5% with placebo or 6.2% with active comparator.

Adverse reactions reported in ? 4% of patients treated with alogliptin 25 mg and more frequently than in patients who received placebo are summarized in Table 2.

Table 2: Adverse Reactions Reported in ? 4% Patients Treated with Alogliptin 25 mg and More Frequently Than in Patients Given Placebo in Pooled Studies

Number of Patients (%)			
Active Comparator N=2257	Placebo N=2926	Alogliptin 25 mg N=5902	
113 (5.0)	89 (3.0)	257 (4.4)	Nasopharyngitis
121 (5.4)	72 (2.5)	247 (4.2)	Headache
113 (5.0)	61 (2.1)	247 (4.2)	Upper respiratory tract infection

Pancreatitis

In the clinical trial program, pancreatitis was reported in 11 of 5902 (0.2%) patients receiving alogliptin 25 mg daily compared to 5 of 5183 (< 0.1%) patients receiving all comparators.

Hypersensitivity Reactions

In a pooled analysis, the overall incidence of hypersensitivity reactions was 0.6% with alogliptin 25 mg compared to 0.8% with all comparators. A single event of serum sickness was reported in a patient treated with alogliptin 25 mg.

Hypoglycemia

Hypoglycemic events were documented based upon a blood glucose value and/or clinical signs and symptoms of hypoglycemia.

In the monotherapy study, the incidence of hypoglycemia was 1.5% in patients treated with alogliptin compared to 1.6% with placebo. The use of alogliptin as add-on therapy to glyburide or insulin did not increase the incidence of hypoglycemia compared to placebo. In a monotherapy study comparing alogliptin to a sulfonylurea in elderly patients, the incidence of hypoglycemia was 5.4% with alogliptin as compared to 26% with glipizide.

Metformin hydrochloride

Table 3: Most Common Adverse Reactions (? 5%) in a Placebo-Controlled Clinical Study of Metformin Monotherapy*

Placebo	Metformin	

(n=145)	Monotherapy (n=141)	
% of Patients		
11.7	53.2	Diarrhea
8.3	25.5	Nausea/Vomiting
5.5	12.1	Flatulence
5.5	9.2	Asthenia
4.1	7.1	Indigestion
4.8	6.4	Abdominal Discomfort
4.8	5.7	Headache
*Reactions that were more common in metformin than placebo-treated patients		

Laboratory Abnormalities

Alogliptin and Metformin hydrochloride

No clinically meaningful differences were observed among treatment groups regarding hematology, serum chemistry, or urinalysis results.

Alogliptin

No clinically meaningful changes in hematology, serum chemistry, or urinalysis were observed in patients treated with alogliptin.

Metformin hydrochloride

Metformin may lower serum Vitamin B12 concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on KAZANO and any].**WARNINGS AND PRECAUTIONS**apparent abnormalities should be appropriately investigated and managed [see

Postmarketing Experience

Alogliptin

The following adverse reactions have been identified during the postmarketing use of alogliptin outside the United States. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions including analphylaxis, angioedema, rash, urticaria, and severe cutaneous adverse reactions including Stevens-Johnson syndrome; hepatic enzyme elevations; fulminant hepatic failure; and acute pancreatitis.