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Teneligliptin: DPP-4 inhibitor in the treatment of type II Diabetes Mellitus

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Abstract

The collective review of teneligliptin as an antidibetic drug concerning about the mechanisms of action, pharmacokinetic study, pharmacodynamic study, toxicological study and dose and its contraindication. Teneligliptin is used in the treatment of type II diabetes mellitus. Teneligliptin, a third generation DPP-4 inhibitor, teneligliptin was approved by the US Food and Drug Administration on 2012 based on a large development program. Teneligliptin, a novel DPP-4 inhibitor, exhibits a unique structure characterized by five consecutive rings, which produce a potent and long-lasting effect. Teneligliptin is currently used in cases showing insufficient improvement in glycemic control even after diet control and exercise or a combination of diet control, exercise, and sulfonylurea or thiazolidine-class drugs. In adults, teneligliptin is orally administered at a dosage of 20 mg once daily, which can be increased up to 40 mg per day. Due to the metabolites of this drug are eliminated via renal and hepatic excretion so, adjustable dose is not required to renal impairment patient. In this review, all the clinical data is described. Teneligliptin shows promise in stabilizing glycemic fluctuations throughout the day and consequently suppressing the progression of diabetic complications.

Keywords: Teneligliptin, DPP-4 inhibitor, hypoglycaemic, toxicity.

1. Introduction

Teneligliptin is a pharmaceutical drug for the treatment of type 2 diabetes mellitus. It belongs to the class of anti-diabetic drugs known as dipeptidyl peptidase-4 inhibitors or "gliptins", Teneligliptin is a third generation DPP-4 inhibitor approved for treatment of type 2 diabetes [1,2]. It is currently available in Japan, South Korea, Argentina and India. It is under pre-registration in Indonesia & under Phase I trials in US & Phase II trials in Denmark, Germany, Hungary, Lithuania, Poland, Romania & UK [5,6]. The aim of this paper is to provide a comprehensive datum analysis of Teneligliptin in the management of type II diabetes. This paper summarizes the unique pharmacodynamic & pharmacokinetic advantages of Teneligliptin [3]. It provides a concise summary of all clinical trials till the date with Teneligliptin monotherapy & combination with other antidiabetic drugs. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released from enteroendocrine cells and enhance insulin secretion [4]. Incretins are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4), and have a very short half-life ($t_{1/2}$) as a result. DPP-4 inhibitors increase the levels of active GLP-1 and GIP by inhibiting DPP-4 enzymatic activity; thus, in patients with diabetes, these inhibitors improve hyperglycemia in a glucose-dependent manner by increasing serum insulin levels and decreasing serum glucagon levels [5]. Therefore, incretin-related agents such as DPP-4 inhibitors are promising drugs that can decrease glucose fluctuations in diabetic patients and have emerged as a new class of antidiabetic [6-8]. The effect of these inhibitors on glycemic control when administered as monotherapy or in combination with other drugs has been investigated in multiple trials. Moreover, DPP-4 inhibitors have shown favorable results in improving glycemic control with a minimal risk of hypoglycemia and weight gain [9].

2. Mechanism of action

The mechanism of Teneligliptin is to increase incretin levels (GLP-1 and GIP), which inhibit glucagon release, which in turn increases insulin secretion, decreases gastric emptying, and decreases blood glucose levels[10-12].

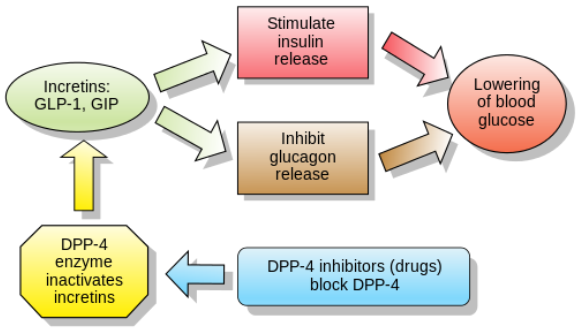
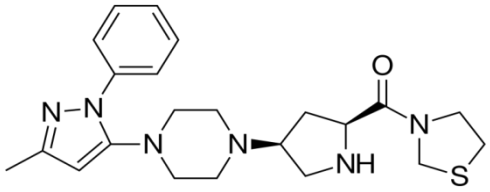


Figure 1: Mechanisms of action of teneligliptin

3. Chemical structure

Teneligliptin, {(2S,4S)-4-[4-(3-methyl-1-phenyl-1H- pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl} (1,3-thiazolidin-3-yl) methanone hemipenta exhibits a unique structure that is characterized by five consecutive rings and is peptidomimetic. An X-ray co-crystal structure of teneligliptin with DPP-4 demonstrates that the key interaction occurs between the phenyl ring on the pyrazole and the S_2 extensive subsite of DPP-4, which not only enhances the potency of the drug but also increases its selectivity [13-15].



[(2S,4S)-4-[4-(3-methyl-1-phenyl-1H- pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl] (1,3-thiazolidin-3-yl) methanone hemipenta

Figure 2: chemical structure and IUPAC Name of teneligliptin

4. Pharmacokinetic study

Teneligliptin is priorly metabolized by cytochrome P450 (CYP) 3A4 & flavin monooxygenases (FMO) [16]. Teneligliptin does not induce CYP3A4 or CYP1A2 [17]. There were no clinically relevant drug-drug interactions when Teneligliptin was co-administered with Ketoconazole (a potent CYP3A4 and P-glycoprotein inhibitor), Metformin or Canagliflozin in healthy volunteers. No clinically relevant effects on the pharmacokinetics of Teneligliptin were observed when it was co-administered with Glimepiride or Pioglitazone [18]. Teneligliptin follows dual mode of excretion *i.e.* renal & hepatic. At least 90% of the radiolabeled dose of Teneligliptin was excreted within 216 h, with 45.4% excreted in the urine and 46.5% excreted in the faeces [19]. Teneligliptin is excreted in the urine as unchanged drug aproximately 20%. Teneligliptin has long half-life of 26.9 hours which offers convenient once a day administration. The plasma concentrations of teneligliptin after the administration of teneligliptin at dosages of 10 or 20 mg once daily for 4 weeks revealed a median time to maximum concentration (C_{max}) of 1.0 hour in both groups and a mean $t_{1/2}$ of 20.8 and 18.9 hours, respectively [20].

4.1 Renal Impairment

20 mg of teneligliptin in patients with renal impairment revealed not shown changes at Cmax and $t_{1/2}$. area under curve shown comparatively mild cretinine clearance shown 80 ml/min., moderate renal impairment cretinine clearance shown 50 ml/min.and severe renal impairment cretinine clearance shown 30 ml/min.was approximately 1.25 times, 1.68 times, and 1.49 times higher than that of healthy adult subjects, respectively [21-23].

4.2 Hepatic Impairment

20 mg of teneligliptin in patients with hepatic impairment revealed that the C_{max} of mild hepatic impairment and moderate hepatic impairment was approximately 1.25 times and 1.38 times that of healthy adult subjects, respectively. Compared to healthy adult subjects, the area under curve of teneligliptin shown with mild and moderate hepatic impairments was approximately 1.46 times and 1.59 times higher than that of healthy adult subjects, respectively [24-25].

5. Pharmacodynamics

Teneligliptin inhibits concentration-dependent human plasma DPP-4 activity, and its IC50 value (95% CI) was 1.75 (1.62 - 1.89) nmol/L [26]. In the glucose tolerance test using Zucker Fatty rat, an obesity model showing insulin resistance and abnormal glucose tolerance, teneligliptin increased plasma active form GLP-1 concentration and plasma insulin concentration by its single-dose administration. In patients having type 2 diabetes mellitus, the administration of 20 mg teneligliptin once daily inhibited the plasma DPP-4 activity and increased the plasma active form GLP-1 concentration [27-30].

5.1 Glucose tolerance improvement action:

1. In the glucose tolerance test using Zucker Fatty rat, an obesity model showing insulin resistance and abnormal glucose tolerance, teneligliptin controlled an increase in the blood sugar level by its single-dose administration
2. In patients having type 2 diabetes mellitus, the administration of 20 mg teneligliptin once daily improved

the blood sugar after breakfast, lunch, and dinner and the fasting blood sugar

6. Clinical approach of teneligliptin

The efficacy of Teneligliptin has been evaluated both as monotherapy and combination with other antihyperglycemic agents in patients with type 2 diabetes. Studies evaluating the efficacy of Teneligliptin in patients with Type 2 diabetes and end-stage renal disease (ESRD) who were on haemodialysis are reported. In combination trials with Glimepiride & Pioglitazone, patients from 12 weeks double blind study were switched to 40 weeks open label study [31]. In respective studies, patients were switched from add-on placebo to add-on Teneligliptin (P/T group) or had received add-on Teneligliptin throughout 52 weeks (12 weeks double blind + 40 weeks open label extension) study [32]. Teneligliptin in combination with Glimepiride showed significant improvement in glycaemic control at 12 weeks compared with add-on placebo, in terms of mean changes in HbA1c, FPG and 2-h PPG. At 12 weeks, add-on Teneligliptin also improved several other parameters significantly ($p < 0.01$) including changes in PPG AUC2, the proinsulin/insulin ratio, HOMA-β. And postprandial glucagon AUC2. There were no significant between-group differences (BGDs) for changes from baseline in HOMA-R, fasting insulin, fasting glucagon or postprandial insulin AUC2. Teneligliptin in combination with Pioglitazone significantly ($p < 0.001$) improved glycaemic control compared with placebo plus Pioglitazone [33]. Several other parameters including changes in PPG AUC2, the proinsulin/insulin ratio, HOMA-β and postprandial glucagon AUC2 were also improved significantly ($p < 0.001$). There were no significant BGDs for changes from baseline in HOMA-R, fasting insulin, fasting glucagon or postprandial insulin AUC2 [34-35].

6.1 Monotherapy

Table 1: Mono-therapy of teneligliptin dose

Therapy	Dose	Duration (week)	No. of patient	Placebo-subtracted LSM change from BL to study end (mean BL value)		
				HbA1c (%)	FPG (mg/dL)	2hPPG (mg/dL)
Teneligliptin	10 mg	04	33		169	Breakfast-272 Lunch-248 Dinner-255
Teneligliptin	20 mg		34			
placebo	-		32		163	Breakfast-261 Lunch-244 Dinner-245

6.2 Combination therapy

Table 2: Combination therapy of teneligliptin dose

Therapy	Dose	Duration (week)	No. of patient	Placebo-subtracted LSM change from BL to study end (mean BL value)		
				HbA1c (%)	FPG (mg/dL)	2hPPG(mg/dL)
Teneligliptin + Glimepride	20 mg/day	12	96	8	165	258
Placebo + glimepride	4 mg/day		98	8	163	256
Teneligliptin + pioglitazone	20 mg/day	12	103	8	150	230
Placebo + pioglitazone	30 mg/day		101	7	145	221

Therapy	Dose	Duration (days)	No. of patient	Glucose Level	Before Treatment	After Treatment
Teneligliptin + insulin	20 mg + 60 unit	07	26	Mean glucose level (mg/dL) 0:00 - 7:00 h 7:00 - 24:00 h	148.8 ± 25.7 126.0 ± 7.5	131.3 ± 17.0b 119.0 ± 4.2b
				SD over 24 h (mg/dL)	159.1 ± 9.8	138.0 ± 9.1b
				MAGE (mg/dL)	32.0 ± 16.2	26.9 ± 10.9b
				Proportion (%) of time in Hypoglycemia (<70 mg/dL)	90.1 ± 46.7 1.0 ± 2.4	85.5 ± 34.3a 1.6 ± 2.6
				Hyperglycemia (>140 mg/dL)	59.8 ± 24.7	37.6 ± 22.4b

6.3 Overdose

In the course of an overdose of teneligliptin, it is vital to employ the usual supportive measures, like remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and hospitality supportive therapy if required [36-37].

6.4 Safety

The dose of Teneligliptin administrates 10 and 20 mg respectively. There was not any significant adverse effect observed in Teneligliptin and placebo doses like hypoglycemic symptoms. Nasopharyngitis, ketonuria, glucosuria and proteinuria were reported in ≥5% of patients in any group. Combination of Teneligliptin with Glimepiride involving 195 patients, hypoglycemic symptoms were reported by 2.1% in the Teneligliptin group and 3.1% in the placebo group during the combined dose, showing no significant difference between the two groups. All of the events were classified as mild and did not result in study discontinuation.

Combination of Teneligliptin with Pioglitazone involving 200 patients, the incidence of pioglitazone monotherapy shown effect peripheral edema at 12 weeks in the present study. In addition, there was not observed symptoms to increase in the incidence of peripheral edema, even if the drug was administered for a long time and the concomitant administration of Teneligliptin and Pioglitazone doesn't an increase in the incidence of edema [38-39].

7. Non-clinical toxicology

7.1 Reproductive, carcinogenicity and genetoxicity study

Teneligliptin toxicology studies focus on reproductive, carcinogenicity, genotoxicity, all are done the *vivo* studies. Teneligliptin (30, 100, 200 mg/kg/day) was administered orally to female Wistar rats. Teneligliptin had no effect on estrous cycle, copulation rate, conception rate, or days required for copulation. The effects on reproductive function observed were low number of vaginal plugs, low number of implantation, low epididymal weight, and low number of sperms in the epididymal tail, and high percentage of abnormal sperms. Teneligliptin (10, 25, 75 mg/kg/day in males) and (10, 30, 100 mg/kg/day in females) was administered to Wistar rats, 55 male and female per group respectively for 104 weeks. For this studies did not cause any increase in neoplastic lesion. The genotoxicity studies of oral administration of teneligliptin was show negative result in bacterial reverse mutation tests, in bone marrow micronucleus tests in rats , and in unscheduled DNA synthesis test in liver cells. In a chromosomal aberration test after treatment with 2250 and 2500 μg/mL of teneligliptin for 6 hours in the absence of metabolic activation system. However, since the cell growth index at these concentrations was only 29% and 19%, respectively, from these results, determined that teneligliptin is not genotoxic [40].

7.2 Drug interactions

Table 3: drug interaction of teneligliptin with other medicinal drug

Drug name	Clinical condition/ Measures	Mechanism / risk factors
Sulfonylurea fast-acting insulin secretagogue α-glucosidase inhibitor Biguanide Thiazolidinediones GLP-1 analog preparation SGLT2 inhibitor Insulin preparation	Since hypoglycemia might occur, these drugs should be administered while carefully observing the patient's Condition. Particularly, when co administered with sulfonylurea or insulin formulation, there is a possibility Of higher risk of hypoglycemia. In order to reduce the risk of hypoglycemia caused by sulfonylurea or insulin formulation, consider decreasing the quantity of sulfonylurea or insulin formulation. When hypoglycemia is observed, usually, cane sugar should be given, and when co-administered with α - glucosidase inhibitor, glucose should be given.	Hypoglycemic action is Increased.
β-blocking agents Salicylic acid Monoamine oxidase inhibitor	Since the blood sugar may further decrease, these drugs should be administered while carefully observing the Patient's condition in addition to blood sugar level.	Hypoglycemic action is Increased.
Adrenalin adrenocortical hormone	Since the blood sugar may increase, these drugs should be administered while carefully observing the Patient's condition in addition to blood sugar level.	Hypoglycemic action is Decreased.
Class IA antiarrhythmic drug Quinidine sulfate hydrate, procainamide hydrochloride **Class III antiarrhythmic drugs** amiodarone hydrochloride, sotalol hydrochloride	QT prolongation might occur	QT prolongation is seen with single administration of these drugs.

8. Dosage and contraindication

The dosage of 20 mg teneligliptin tablet, for adults, at a time, once a day. If the effect is insufficient, the dose may be increased up to 2 tablets (40 mg) at a time, once a day. Strictly follow the instructions. If you miss a dose, take a dose as soon as possible. If it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule. You should never take two doses at one time. If you accidentally take more than your prescribed dose, consult with your doctor or pharmacist. Do not stop taking this medicine unless your doctor instructs you to do so. Teneligliptin Tablets are contraindicated in patients with Hypersensitivity to the drug or any of its components, severe ketosis, diabetic coma or pre-coma and also for immediate remedy in type 1 diabetes and severe trauma, before and after surgery and when the blood glucose has to be controlled with insulin injection [41-42].

9. Conclusions

After clinical trial, noted that DPP-4 inhibitors provide effective and consistent glycemic control with a good tolerability profile, including no severe hypoglycemia and weight gain. Although different DPP-4 inhibitors are distinctive in their metabolic properties, excretion, recommended dosage, and daily dosage and the available data regarding indirect comparisons suggest that all available DPP-4 inhibitors have nearly the same efficacy and safety profile. The suitable approach towards management of diabetes should include not only glycemic control but also early preservation of islet function, a strategy currently correct to delay progression of a disease which cannot be indicative. Thus, we may expect a similar efficacy and safety with the novel DPP-4 inhibitor, teneligliptin, although this drug requires careful long-term post marketing surveillance and additional clinical trials to evaluate its efficacy and safety as well as to gain additional indications for its clinical use.

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