HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRADJENTA safely and effectively. See full prescribing information for TRADJENTA.

Tradjenta™ (linagliptin) tablets
Initial U.S. Approval: 2011

----------INDICATIONS AND USAGE----------

TRADJENTA is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1.1)

Important limitations of use:

- Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis (1.2)
- Has not been studied in combination with insulin (1.2)

----------DOSAGE AND ADMINISTRATION----------

- The recommended dose of TRADJENTA is 5 mg once daily. TRADJENTA can be taken with or without food. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 5 mg (3)

----------CONTRAINDICATIONS----------

History of hypersensitivity reaction to linagliptin, such as urticaria, angioedema, or bronchial hyperreactivity (4)

----------WARNINGS AND PRECAUTIONS----------

- When used with an insulin secretagogue (e.g., sulfonylurea), consider lowering the dose of the insulin secretagogue to reduce the risk of hypoglycemia (5.1)
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with TRADJENTA or any other antidiabetic drug (5.2)

----------ADVERSE REACTIONS----------

- Adverse reactions reported in ≥5% of patients treated with TRADJENTA and more commonly than in patients treated with placebo included nasopharyngitis (6.1)
- Hypoglycemia was more commonly reported in patients treated with the combination of TRADJENTA and sulfonylurea compared with those treated with the combination of placebo and sulfonylurea (6.1)
- Pancreatitis was reported more often in patients randomized to linagliptin (1 per 538 person years versus zero in 433 person years for comparator) (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or 1-800-459-9906 TTY, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

P-glycoprotein/CYP 3A4 inducer: The efficacy of TRADJENTA may be reduced when administered in combination (e.g., with rifampin). Use of alternative treatments is strongly recommended. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: There are no adequate and well-controlled studies in pregnant women. TRADJENTA tablets should be used during pregnancy only if clearly needed. (8.1)
- Nursing mothers: Caution should be exercised when TRADJENTA is administered to a nursing woman (8.3)
- Pediatric patients: Safety and effectiveness of TRADJENTA in patients below the age of 18 have not been established (8.4)
- Renal or hepatic impairment: No dose adjustment recommended (8.6, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 5/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Monotherapy and Combination Therapy

TRADJENTA tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus *[see Clinical Studies (14.1)]*.

1.2 Important Limitations of Use

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

TRADJENTA has not been studied in combination with insulin.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of TRADJENTA is 5 mg once daily.

TRADJENTA tablets can be taken with or without food.

2.2 Concomitant Use with a Sulfonylurea

When TRADJENTA is used in combination with an insulin secretagogue (e.g., sulfonylurea), a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

TRADJENTA is contraindicated in patients with a history of a hypersensitivity reaction to linagliptin, such as urticaria, angioedema, or bronchial hyperreactivity *[see Adverse Reactions 6.1]*.

5 WARNINGS AND PRECAUTIONS

5.1 Use with Medications Known to Cause Hypoglycemia

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

5.2 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with TRADJENTA tablets or any other antidiabetic drug.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

The safety of linagliptin has been evaluated in over 4000 patients with type 2 diabetes in clinical trials, including 12 placebo-controlled studies and 1 active-controlled study with glimepiride.

TRADJENTA 5 mg once daily was studied as monotherapy in two placebo-controlled trials of 18- and 24-weeks duration. Five placebo-controlled trials investigated linagliptin in combination with other oral anti-glycemic agents: two with metformin (12- and 24-weeks treatment duration); one with a sulfonylurea (18-weeks treatment duration); one with metformin and sulfonylurea (24-week treatment duration); and one with pioglitazone (24-week treatment duration). In placebo-controlled clinical trials, adverse reactions that occurred in ≥5% of patients receiving TRADJENTA (n = 2566) and more commonly than in patients given placebo (n = 1183) included nasopharyngitis (5.8% vs 5.5%). Adverse reactions reported in ≥2% of patients treated with TRADJENTA 5 mg daily as monotherapy or in combination with pioglitazone, sulfonylurea, or metformin and at least 2-fold more commonly than in patients treated with placebo are shown in Table 1.

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

	Monotherapy* n (%)		Combination with Metformin# n (%)		Combination with SU n (%)		Combination with Metformin + SU n (%)		Combination with Pioglitazone n (%)	
	TRADJENTA n = 765	Placebo n = 458	TRADJENTA n = 590	Placebo n = 248	TRADJENTA n = 161	Placebo n = 84	TRADJENTA n = 791	Placebo n = 263	TRADJENTA n = 259	Placebo n = 130
Nasopharyngitis	--	--	--	--	7 (4.3)	1 (1.2)	--	--	--	--
Hyperlipidemia	--	--	--	--	--	--	--	--	7 (2.7)	1 (0.8)
Cough	--	--	--	--	--	--	19 (2.4)	3 (1.1)	--	--
Hypertriglyceridemia†	--	--	--	--	4 (2.4)	0 (0.0)	--	--	--	--
Weight increased	--	--	--	--	--	--	--	--	6 (2.3)	1 (0.8)

SU = sulfonylurea
* Pooled data from 7 studies
# Pooled data from 2 studies
† Includes reports of hypertriglyceridemia (n = 2; 1.2%) and blood triglycerides increased (n = 2; 1.2%)

Following 52 weeks treatment in a controlled study comparing linagliptin with glimepiride in which all patients were also receiving metformin, adverse reactions reported in ≥5% patients treated with linagliptin (n = 776) and more frequently than in patients treated with a sulfonylurea (n = 775) were arthralgia (5.7% vs 3.5%), back pain (6.4% vs 5.2%), and headache (5.7% vs 4.2%).

Other adverse reactions reported in clinical studies with treatment of TRADJENTA were hypersensitivity (e.g., urticaria, angioedema, localized skin exfoliation, or bronchial hyperreactivity), and myalgia. In the clinical trial program, pancreatitis was reported in 8 of 4687 patients (4311 patient years of exposure) while being treated with TRADJENTA compared with 0 of 1183 patients (433 patient years of exposure) treated with placebo. Three additional cases of pancreatitis were reported following the last administered dose of linagliptin.

Hypoglycemia
In the placebo-controlled studies, 195 (7.6%) of the total 2566 patients treated with TRADJENTA 5 mg reported hypoglycemia compared to 49 patients (4.1%) of 1183 placebo treated patients. The incidence of hypoglycemia was similar to placebo when linagliptin was administered as monotherapy or in combination with metformin, or with pioglitazone. When linagliptin was administered in combination with metformin and a sulfonylurea, 181 of 791 (22.9%) of patients reported hypoglycemia compared with 39 of 263 (14.8%) of patients administered placebo in combination with metformin and a sulfonylurea.

Laboratory Tests
Changes in laboratory findings were similar in patients treated with TRADJENTA 5 mg compared to patients treated with placebo. Changes in laboratory values that occurred more frequently in the TRADJENTA group and ≥1% more than in the placebo group were increases in uric acid (1.3% in the placebo group, 2.7 % in the TRADJENTA group).

No clinically meaningful changes in vital signs were observed in patients treated with TRADJENTA.

7 DRUG INTERACTIONS

7.1 Inducers of P-glycoprotein or CYP3A4 Enzymes
Rifampin decreased linagliptin exposure suggesting that the efficacy of TRADJENTA may be reduced when administered in combination with a strong P-gp or CYP 3A4 inducer. Therefore, use of alternative treatments is strongly recommended when linagliptin is to be administered with P-gp or CYP 3A4 inducer *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category B
Reproduction studies have been performed in rats and rabbits. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Linagliptin administered during the period of organogenesis was not teratogenic at doses up to 30 mg/kg in the rat and 150 mg/kg in the rabbit, or approximately 49 and 1943 times the clinical dose based on AUC exposure. Doses of linagliptin causing maternal toxicity in the rat and the rabbit also caused developmental delays in skeletal ossification and slightly increased embryofetal loss in rat (1000 times the clinical dose) and increased fetal resorptions and visceral and skeletal variations in the rabbit (1943 times the clinical dose).

Linagliptin administered to female rats from gestation day 6 to lactation day 21 resulted in decreased body weight and delays in physical and behavioral development in male and female offspring at maternally toxic doses (exposures >1000 times the clinical dose). No functional, behavioral, or reproductive toxicity was observed in offspring of rats exposed to 49 times the clinical dose.

Linagliptin crossed the placenta into the fetus following oral dosing in pregnant rats and rabbits.

8.3 Nursing Mothers
Available animal data have shown excretion of linagliptin in milk at a milk-to-plasma ratio of 4:1. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRADJENTA is administered to a nursing woman.

8.4 Pediatric Use
Safety and effectiveness of TRADJENTA in pediatric patients have not been established.

8.5 Geriatric Use
Of the total number of patients (n= 4040) in clinical studies of TRADJENTA, 1085 patients were 65 years and over, while 131 patients were 75 years and over. No overall differences in safety or effectiveness were observed between patients 65 years and over and younger patients. While this and other reported clinical experience have not identified differences in response between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out. No dose adjustment is recommended in this population.

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

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

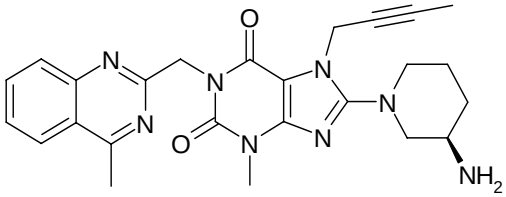
10 OVERDOSAGE
During controlled clinical trials in healthy subjects, with single doses of up to 600 mg of TRADJENTA (equivalent to 120 times the recommended daily dose) there were no dose related clinical adverse drug reactions. There is no experience with doses above 600 mg in humans.

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Linagliptin is not expected to be eliminated to a therapeutically significant degree by hemodialysis or peritoneal dialysis.

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

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

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



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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

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

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

Absorption

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

Distribution

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

Metabolism

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

Excretion

Following administration of an oral [^{14}C]-linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated via the enterohepatic system (80%) or urine (5%) within 4 days of dosing. Renal clearance at steady state was approximately 70 mL/min.

Specific Populations

Renal Impairment

An open-label pharmacokinetic study evaluated the pharmacokinetics of linagliptin 5 mg in male and female patients with varying degrees of chronic renal impairment. The study included 6 healthy subjects with normal renal function (creatinine clearance [CrCl] ≥80 mL/min), 6 patients with mild renal impairment (CrCl 50 to <80

mL/min), 6 patients with moderate renal impairment (CrCl 30 to <50 mL/min), 10 patients with type 2 diabetes mellitus and severe renal impairment (CrCl <30 mL/min), and 11 patients with type 2 diabetes mellitus and normal renal function. Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula.

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

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

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

Results of this study, supported by results of population pharmacokinetic analyses, indicate that no dose adjustment is recommended in patients with renal impairment.

Hepatic Impairment
In patients with mild hepatic impairment (Child-Pugh class A) steady-state exposure ($AUC_{\tau,ss}$) of linagliptin was approximately 25% lower and $C_{max,ss}$ was approximately 36% lower than in healthy subjects. In patients with moderate hepatic impairment (Child-Pugh class B), AUC_{ss} of linagliptin was about 14% lower and $C_{max,ss}$ was approximately 8% lower than in healthy subjects. Patients with severe hepatic impairment (Child-Pugh class C) had comparable exposure of linagliptin in terms of AUC_{0-24} and approximately 23% lower C_{max} compared with healthy subjects. Reductions in the pharmacokinetic parameters seen in patients with hepatic impairment did not result in reductions in DPP-4 inhibition. No dose adjustment of linagliptin is necessary in patients with hepatic impairment.

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

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

Geriatric
No dose adjustment is recommended based on age, as age did not have a clinically meaningful impact on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis.

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

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

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

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

In vivo Assessment of Drug Interactions
Inducers of CYP3A4 or P-gp (e.g., rifampin) decrease exposure to linagliptin to subtherapeutic and likely ineffective concentrations. For patients requiring use of such drugs, an alternative to linagliptin is strongly recommended. *In vivo* studies indicated evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-gp and organic cationic transporter (OCT). No dose adjustment of TRADJENTA is recommended based on results of the described pharmacokinetic studies.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.