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WHAT'S NEW WITH GABAPENTIN?

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In 1993 Parke-Davis received FDA approval to market gabapentin as an adjunct therapy for partial seizures under the brand name Neurontin®.[1] In the following years further data emerged suggesting gabapentin may help alleviate pain of a neuropathic origin.[2] This eventually led to a second FDA approved indication in 2002 for postherpetic neuralgia (PHN). Despite these FDA-approved indications a large portion of gabapentin prescriptions are attributed to off-label prescribing. Analgesia associated with diabetic peripheral neuropathy is perhaps the most common use of gabapentin, but it can also be given prophylactically for migraines and to treat hot flashes in postmenopausal women.

With over 23,000 prescriptions written in 2009 gabapentin is a widely used drug in modern medicine.[3] Today, gabapentin is available in strengths ranging from 100 mg to 800 mg and in a variety of oral dosage forms. Gralise® and Horizant® are two new extended release gabapentin formulations that were introduced to the market in 2011. This article will review these two new formulations as well as discuss the medical literature behind immediate release (IR) gabapentin's approved indications and most common off-label uses.

Pharmacology

The mechanism of action of gabapentin is unknown. Structurally, it is similar to the neurotransmitter gamma-aminobutyric acid (GABA), but gabapentin does not mimic or alter the inhibitory actions of endogenous GABA. *In vitro* studies conducted in rats suggest that gabapentin binds to calcium channels in the brain; however, the significance of this data remains unknown.[1]

The bioavailability of IR gabapentin decreases with increasing dosages. A 900 mg daily dose given in three divided doses has a bioavailability of approximately 60% whereas a 4,800 mg daily dose given in three divided doses has a bioavailability of approximately 27%. If taken with food, the rate and extent of absorption can be increased by as much as 14%.[1]

Gabapentin undergoes minimal metabolism and hepatic dysfunction is not a dosing concern. The drug is primarily excreted unchanged in the urine. In patients with a creatinine clearance (CrCL) ≥ 60 mL/min, gabapentin's half-life typically ranges from 5-7 hours. In diminished CrCL (≤ 30 mL/min), the half-life can be extended beyond 50 hours. Dose adjustments are typically required in patients with renal dysfunction including geriatric patients with age related renal decline.[1]

Dosing

When given for PHN, recommended dosing of IR gabapentin consists of a single 300 mg dose on day 1, 300 mg twice a day on day 2, and 300 mg three times a

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Table 1 | Immediate Release Gabapentin Dosage Based on Renal Function [1]

CrCL (mL/min)	Daily Dose (mg/day)	Potential Dosing Regimens (mg)				
≥60	900-3600	300 TID	400 TID	600 TID	800 TID	1200 TID
30-59	400-1400	200 BID	300 BID	400 BID	500 BID	700 BID
15-29	200-700	200 QD	300 QD	400 QD	500 QD	700 QD

BID = Twice daily, CrCL = Creatinine Clearance , min = minutes, QD = Daily, TID = Three times daily

day on day 3. The dose can be continuously up-titrated to achieve a maximum 1,800 mg/day dose given in three divided doses.[1]

If used for epilepsy, the recommended dose of gabapentin for patients 12 years and older is 300 mg three times a day that may be up-titrated to 1,800 mg/day. Doses of 2,400 mg/day have also been well tolerated for extended use, and doses of 3,600 mg/day have been well tolerated in short-term clinical trials. The starting dose for patients 3-12 years old is 10-15 mg/kg/day in three divided doses. Patients 3 or 4 years old should be titrated to a dose of 40 mg/kg/day in three divided doses over the course of three days. Patients 5 to 12 years of age should be titrated to a dose of 25-35 mg/kg/day also in three divided doses over the course of three days. As gabapentin is excreted unchanged in the urine, dose adjustments are necessary for diminished CrCL calculated by the Cockcroft and Gault method (**Table 1**).

Adverse Effects

Adverse effects in clinical trials were mild (**Table 2**). Somnolence and dizziness occurred with the greatest frequency and were also among the most frequent causes for discontinuation of the drug.[1] Fatigue and ataxia occurred at a rate greater than 10%. In patients aged 3 to 12 years old, fever and viral infections were both noted at rates higher than 10%. Although occurring at a much lower rate, emotional liability, hostility and hyperkinesias were the side effects most likely to cause discontinuation of gabapentin therapy in pediatric patients. Post-marketing analysis suggest about a dozen additional side effects may be associated with gabapentin that range in severity from fever to Stevens-Johnson syndrome. Abrupt discontinuation of gabapentin may result in adverse events such as anxiety, insomnia, nausea, pain, and swelling. If gabapentin is to be discontinued, it is recommended to gradually decrease the dose over the course of at least a week.[1]

Gabapentin is fairly benign in regard to drug interactions. Over-the-counter antacids may result in decreased gabapentin bioavailability by as much as 20%. For this reason, it is recommended to take gabapentin two-hours after antacids.[1]

Clinical Use of Gabapentin

Partial Seizure Adjunctive Therapy

Gabapentin's role as adjunct therapy for partial seizures was evaluated in double-blinded and placebo-controlled studies. Efficacy was measured using percent change in seizure frequency (PCH), responder rate (RR), and response ratio (RRatio). A negative PCH indicates a reduction in seizure frequency and a positive PCH indicates an increase in seizure frequency. RR was defined as the number of patients that experienced a decrease of at least 50% in number of partial seizures from baseline. Negative RRatios indicate a decreased number of seizures while positive values indicate an increased number of seizures.[4-7]

The first study recruited 127 patients (113 completed) aged 14 to 73 years that experienced at least one partial seizure a week while on one or two other antiepileptic drugs (AEDs).[4] In addition to their AEDs, patients were randomized to receive gabapentin 200 mg three times a day (TID) or placebo for 2 weeks. After this initial phase, the dose was doubled for the remaining 12 weeks of the study. Primary outcomes measured were RR and RRatio. Intention-to-treat (ITT) analysis demonstrated a 23% RR in the gabapentin group vs. a 9% RR for placebo ($p = 0.049$). The RRatio was -0.192 for the gabapentin group and -0.060 for the placebo group ($p=0.0056$) (**Table 3**). A reduction in seizures was noted 2 weeks into the study and maintained until the trial's conclusion. Efficacy was also shown to increase with higher doses.[4]

The second study enrolled 306 patients ≥ 16 years old who suffered from at least 4 partial seizures each month despite taking 1-2 other AEDs.[5] Patients were randomized to receive gabapentin or placebo in addition to existing AEDs for 12 weeks. The gabapentin group was given either 300 mg/day or 600 mg/day initially, then titrated to 600 mg/day, 1,200 mg/day, or 1,800 mg/day over the course of 2-3 days. The results of the trial favored gabapentin therapy (**Table 3**). The authors noted that a dose response was evident and gabapentin was particularly helpful in controlling secondarily generalized seizures.[5]

The third study enrolled 272 (245 completed) patients ≥ 12 years old with a body weight between 40 and 110 kg.[6] Patients averaged 4 partial seizures each

Table 2 | Incidence of Adverse Events Observed in Clinical Trials [a,b]

	Epilepsy Trials		Postherpetic Neuralgia Trials	
Adverse event	Gabapentin, % (N = 543)	Placebo, % (N=378)	Gabapentin, % (N = 336)	Placebo, % (N=227)
Abdominal Pain	-	-	2.7	2.6
Accidental injury	-	-	3.3	1.3
Amblyopia	4.2	1.1	2.7	0.4
Amnesia	2.2	0.0	-	-
Asthenia	-	-	5.7	4.8
Ataxia	12.5	5.6	3.3	0.0
Constipation	1.5	0.8	3.9	1.8
Diarrhea	-	-	5.7	3.1
Diplopia	5.9	1.9	1.2	0.0
Dizziness	17.1	6.9	28.0	7.5
Dry mouth/throat	1.7	0.5	4.8	3.1
Dysarthria	2.4	0.5	-	-
Dyspepsia	2.2	0.5	-	-
Fatigue	11.0	5.0	-	-
Flatulence	-	-	2.1	1.8
Headache	-	-	3.3	3.1
Infection	-	-	5.1	3.5
Myalgia	2.0	1.9	-	-
Nausea	-	-	3.9	1.8
Nervousness	2.4	1.9	-	-
Nystagmus	8.3	4.0	-	-
Peripheral edema	1.7	0.5	8.3	2.2
Pharyngitis	2.8	1.6	1.2	0.4
Rhinitis	4.1	3.7	-	-
Somnolence	19.3	8.7	21.4	5.3
Thinking abnormal	1.7	1.3	2.7	0.0
Tremor	6.8	3.2	-	-
Vomiting	-	-	3.3	1.8
Weight increase	2.9	1.6	1.8	0.0

[a]Patients older than 12 years of age
[b]Only side effects that occurred at rates ≥2% are reported in this table

month while on 1-2 other AEDs. Medications were given in addition to current AED medications in 3 divided doses and titrated to the intended dose over 2 days. The results favored gabapentin therapy and demonstrated greater efficacy at higher doses (**Table 3**). A particular increase in benefits was shown in patients suffering from complex partial seizures.[6]

The final study was a pediatric study. Patients (n=247) were required to be ≤ 12 years old and weigh between 17 kg and 72 kg.[7] Patients were taking between 1-3 AEDs and still experiencing at least 4 seizures during a 6-week baseline phase of the study. Patients were randomized to placebo or gabapentin 23.2 to 35.3 mg/kg/day (600-1,800 mg/day) in 3 divided doses, titrated over the course of 3 days. The modified intention-to-treat (MITT) group (n=233) received study medication and had data collected for at least 28 days both during the baseline and the double-blind phases. RRatio was -0.161 for the gabapentin group and -0.072 for the placebo group (p=0.0407). RR was higher in the gabapentin group, but did not achieve statistical significance. Median PCH in the gabapentin group was -17.0% compared with -6.5% in the placebo group. The PCH also indicated greater efficacy in complex partial seizures and secondarily generalized seizures.[7]

These studies consistently show that gabapentin is an effective adjunct therapy for partial seizures, but do not clearly identify an ideal dose. The trials that studied multiple gabapentin doses did not have comparable numbers of patients in each arm of the trial. The studies suggest increased efficacy with higher doses, but were not designed to determine the most effective dose. Also, gabapentin as an antiepileptic is a medication likely to be started at an early age to be used for extended durations. These trials were all 12 weeks in length and do not prove efficacy with extended use.

Postherpetic Neuralgia

Herpes zoster (also known as shingles) is associated with a skin rash and neuropathic pain.[8-9] Two randomized, double blind, placebo controlled trials were used as supportive evidence for gabapentin's use in PHN (**Table 4**).

The first trial was an 8-week trial in 229 adults ≥18 years of age with pain 3 months after a herpes zoster rash had healed.[2] Patients also needed to have a pain score of 40 mm on the 100-mm Visual Analog Scale (VAS) on the Short-Form McGill Pain Questionaire (SF-MPQ) and an average daily pain score of 4 on an 11 point Likert scale (with 0 meaning no pain and a 10 meaning worst pain imaginable). Patients were started at gabapentin 300 mg/day and titrated to 3,600 mg/day or the maximum tolerated dose regardless of pain relief. Daily doses were divided into 3 equal doses. Titration took place between weeks 1 and 4 and the dose remained consistent thereafter. At conclusion, the average daily pain score for the gabapentin group was reduced 33% from 6.3 to 4.2 compared with a 7.7% decrease from 6.5 to 6.0 in the placebo group (p<0.001). Pain relief was noted at week 2 and peaked at the end of titration in week 4.[2]

In the second study, 334 adults ≥ 18 years of age with pain lasting 3 months after healing of a herpes zoster rash that had an average baseline pain score of 4 (0-10 scale) were randomized to gabapentin 1,800 mg/day, 2,400 mg/day or placebo.[8] Patients were titrated over the course of 9 to 16 days and received medication in 3 divided doses throughout the 7 week trial. The primary efficacy endpoint was change in average daily pain score from baseline. At conclusion, average daily pain scores were reduced by 15.7% in the placebo group, 34.5% in the gabapentin 1,800 mg/day group and 34.4% in the gabapentin 2,400 mg/day group (p<0.01). The study discussion mentioned that 1,800 mg/day appears to be the most effective dose,

Table 3 | Summary of Epilepsy Trials

Trial	Intervention	Results
UK Gabapentin Study Group[4]	Gabapentin 1,200 mg/day or Placebo	RR: 23% gabapentin vs. 9% placebo (p=0.049) RRatio: -0.192 gabapentin vs. -0.060 placebo (p=0.0056)
The US Gabapentin Study Group No. 5[5]	Gabapentin 1,200 mg/day or placebo[a]	RR: 17.6% gabapentin vs. 8.4% placebo (p=0.080) RRatio: -0.188 gabapentin vs. -0.025 placebo (p=0.023) PCH: -20.0% gabapentin vs. -5.9% placebo
Anhut et al.[6]	Gabapentin 900 mg/day or placebo[b]	RR: 22.9% gabapentin vs. 10.1% placebo (p=0.020) RRatio: -0.126 gabapentin vs. -0.025 placebo (p=0.0046) PCH: -21.8% gabapentin vs. -0.3 placebo
Appleton et al.[7]	Gabapentin 23.3 – 35.5 mg/kg/day or placebo	RR: 21.2% gabapentin vs. 17.5% placebo (p > 0.05) RRatio: -0.161 gabapentin vs. -0.072 placebo (p=0.0407) PCH: -17.0% gabapentin vs. -6.5% placebo

PCH = Median Percent Change in Seizure Frequency, RR= Responder Rate, RRatio = Response Ratio

[a]Two other smaller groups of gabapentin 600 mg/day and 1,800 mg/day were also included to analyze dose response

[b]One other smaller group of gabapentin 1.200 mg/day was also included to analyze dose response

Table 4 | Summary of Postherpetic Neuralgia Trials

Trial	Intervention	Results
Rowbotham et al.[2]	Gabapentin 3,600 mg/day or placebo	ADPS reduced 33% in gabapentin group and 7.7% in placebo group ($p < 0.001$)
Rice et al.[8]	Gabapentin 1,800 mg/day, 2,400 mg/day or placebo	ADPS reduced 34.5% in 1,800 mg/day group, 34.4% in 2,400 mg/day group and 15.7% in placebo group ($p < 0.01$)

ADPS = Average Daily Pain Score

although the study was not formally designed to determine this.[8]

Diabetic Neuropathy

Although gabapentin does not have an FDA approved indication for relieving pain caused by diabetic neuropathy, it is frequently used to treat this condition.

One 8 week trial randomized 165 patients to receive placebo or gabapentin titrated over 4 weeks to 3,600 mg/day in 3 divided doses.[9] Inclusion criteria consisted of diabetic neuropathy for 1 to 5 years, a pain score of at least 40 mm on the 100-mm VAS of the SF-MPQ, and an average pain score of 4 on the Likert pain scale. To avoid dose adjustments, patients with a CrCL < 60 mL/min were excluded. At the end of the study, patients receiving gabapentin had a pain score reduction of 39% compared to a 21% reduction in the placebo group ($p<0.001$) (**Table 5**). A benefit from gabapentin therapy was noted at week 2 and continued throughout the 8 week study.[9]

A small, randomized, double-blinded study compared the efficacy of gabapentin with amitriptyline in 28 patients (19 completed) with controlled diabetes, neuropathic pain for at least 3 months and a CrCL of at least 30 mL/min.[10] The crossover trial involved two 6-week treatment phases with a 1 week washout period between the two phases. Gabapentin was titrated to 1,800 mg/day in 3 divided doses over the course of 2 days and amitriptyline was titrated to 75 mg/day. Active amitriptyline was given once a day with two other placebo doses to maintain blinding. To measure efficacy, patients were asked to describe their pain on a 13-word scale that ranged from "none" to "extremely intense." Data were quantified on The Pain Scale Rating System and Global Rating Scale. The study found a 67% reduction in pain from baseline with amitriptyline and a 52% reduction with gabapentin. Both treatments were statistically significant from baseline, but the difference between therapies did not reach significance (**Table 5**). This is likely due to the small size of the trial.[10]

An open label Korean trial compared gabapentin to tramadol 37.5 mg /acetaminophen 325 mg (T/A).[11] The study enrolled 163 adult patients with painful diabetic neuropathy for at least 3 months and an average daily pain score of ≥4 on a VAS. Patients were randomized to gabapentin, titrated over 2 weeks to a maximum dose of 3,600 mg/day in 3 divided doses or T/A titrated from 1 tablet a day to a maximum of 8 tablets a day over the course of 2 weeks. At the end of the trial, the average dose was 1,575 mg/day or gabapentin and 4.22 tablets/day of T/A. Average daily pain score reduction from baseline in the gabapentin group was 42.9% ($p<0.0001$) and 46.5% in the T/A group ($p<0.0001$). There was no statistical difference in pain reduction between groups (**Table 5**). Additionally, both treatment groups noted a comparable improvement in sleep.[11]

Table 5 | Summary of Diabetic Peripheral Neuropathy Trials

Trial	Intervention	Results
Backonja et al.[9]	Gabapentin 3,600 mg/day or placebo	ADPS reduced 39% in gabapentin group and 21% in placebo group ($p < 0.001$)
Morello et al.[10]	Gabapentin 1,800 mg/day or amitriptyline 75 mg/day	PSRS/GRS decreased 52% from baseline with gabapentin and decreased 67% from baseline with amitriptyline. Gabapentin vs. amitriptyline ($p > 0.1$)
Ko et al.[11]	Gabapentin 3,600 mg/day or T/A	ADPS reduced 42.9% from baseline with gabapentin ($p < 0.0001$) ADPS reduced 46.5% from baseline with T/A ($p < 0.0001$) Gabapentin vs. T/A ($p = 0.744$)

ADPS = Average Daily Pain Score, PSRS/GRS = Pain Scale Rating System and Global Rating Scale,
T/A = Tramadol 37.5 mg/Acetaminophen 325 mg,

Hot Flashes

In a 2008 randomized, double-blind, placebo-controlled trial, gabapentin was studied in women 45-65 years of age with natural cessation of menses that experienced 14 hot flashes a week.[12] Patients with CrCL < 30 mL/min or those taking AEDs or other medications known to affect hot flashes were excluded. Number and severity of hot flashes at baseline and at 4 weeks were used to measure efficacy. Caucasian women (n=197) were randomized to receive gabapentin 900 mg/day in 3 divided doses titrated over 3 days or placebo. Hot flash intensity was reduced by 51% in the gabapentin group vs. a 26% reduction in the placebo group (p<0.001). Hot flash frequency decreased by 45.7% in the gabapentin group vs. 24.7% in the placebo group (p<0.001). These results are comparable with other trials that measured hot flashes in patients treated with non-hormone therapy medications.[12]

Migraine Prophylaxis

A randomized, double-blinded, placebo control study enrolled 143 patients, aged 16 to 75 years, suffering from migraines with or without auras for at least 6 months.[13] Patients had to have 3-8 migraines per month during the 3 months immediately prior to the study. Patients taking other medications that may interfere with the study, suffering from other types of headaches, or those with severely decreased liver or kidney function were excluded. The first 4 weeks consisted of a single-blinded phase in which all 143 patients received placebo. During the second 12-week double-blinded phase, 45 patients received placebo and 98 patients received gabapentin titrated to 2,400 mg/day or maximum tolerated dose over the course of 4 weeks. Efficacy was measured as migraine rate during the four weeks after the titration period. The study had a dropout rate of 24% and used a MITT analysis for its results. The median 4 week headache rate in the gabapentin group decreased from 4.2 to 2.7 compared with 4.1 to 3.5 in the placebo group (p=0.006). The study concluded that gabapentin is an effective and well tolerated prophylactic treatment for migraines.[13]

New Formulations

In 2011, the FDA approved two new extended release formulations of gabapentin: Gralise® by Depomed, Inc. and Horizant® by GlaxoSmithKline.

Gralise® is approved for use in PHN and is available in 300 mg and 600 mg tablets.[14] Since Gralise® is an extended release formulation, it's once daily dosing frequency is not interchangeable with other IR gabapentin products. When a patient first begins taking Gralise®, a starter package may be prescribed that provides easy-to-follow instructions for the 15 day titration period. At the recommended 1,800 mg/day maintenance dose, patients should take three 600 mg tablets as a single dose with the evening meal. In trials conducted with IR gabapentin, dizziness and somnolence were the two adverse effects consistently reported with incidence rates near or greater than 20%. However, the only appreciable adverse effect seen with Gralise® was dizziness at an incidence rate of 10.9%.[14]

Horizant® (gabapentin enacarbil [GEn]) is available in 300 mg and 600 mg tablets.[15] The product is FDA approved for both PHN and moderate to severe restless leg syndrome (RLS). When used for PHN, a 600 mg tablet in the morning and evening is recommended after titrating over the course of 4 days. In clinical trials, side effects worsened at higher doses but additional efficacy was not seen.[15]

The RLS indication for GEn makes it unique among the gabapentin products.[15] RLS dosing consists of a single 600 mg tablet taken daily at 5pm with food. This recommendation comes from two 12 week clinical trials that enrolled adult patients with frequent restless leg symptoms and scored ≥15 on the International Rest-less Legs Scale (IRLS).

The first study randomized 222 patients to GEn 1,200 mg at 5pm with food vs. placebo.[16] At week 12, GEn was found to reduce IRLS score by 13.2 points compared to 8.8 points with placebo (p=0.0003). The Clinical Global Impression-Improvement scale (CGI-I) was also used to classify the percentage of patients that responded to GEn therapy. CGI-I scores were 76.1% with GEn and 38.9% with placebo (p<0.0001).[16]

The second study randomized 325 patients to receive GEn 600 mg, 1,200 mg or placebo taken at 5pm with food.[17] At the end of the study, IRLS score was significantly reduced by 13.8 points with GEn 600 mg, 13.0 points with GEn 1,200 mg and by 9.8 points with placebo. CGI-I scores were 73% with GEn 600 mg, 77% with 1,200 mg and 39% with placebo.[17]

Results from these trials showed that gabapentin enacarbil therapy provided a significant benefit compared with placebo, but there appeared to be no additional benefit at doses higher than 600 mg/day.[15]

Cost

The average monthly cost of gabapentin therapy is difficult to assess due to the variety of conditions it is used in, wide range of recommended doses, and its multiple dosage forms, strengths, and formulations. **Table 6** reflects the average monthly cost of the most commonly used gabapentin maintenance regimens as

well as the price variance associated with each regimen. These data come from four major chain pharmacies found throughout the state of Florida.

Summary

Gabapentin is a commonly used medication that has FDA approval for use in partial seizures, postherpetic neuralgia, and in certain formulations, restless leg syndrome. However, there is an appreciable amount of evidence supporting gabapentin's off-label use as an analgesic in diabetic neuropathy. Evidence also suggests that gabapentin can be used as an alternative therapy for postmenopausal hot flashes and as a prophylactic treatment for migraines. Gabapentin's pharmacokinetic profile is altered at different doses or when taken with food. Overall, gabapentin remains a well-tolerated prescription medication known to frequently cause only dizziness and somnolence and is generally free of drug interactions.

Table 6 | Average Monthly Retail Cost of Gabapentin Products at Maintenance Doses

	Average Cost	Price Range
Gabapentin 300mg (90 capsules)	$83.37	$43.49 - $99.99
Gabapentin 400mg (90 capsules)	$110.68	$86.78 - $129.99
Gabapentin 600mg (90 tablets)	$147.61	$85.46 - $190.99
Gabapentin 800mg (90 tablets)	$180.83	$73.78 - $227.99
Gralise® 600mg (90 tablets)	$245.41	$225.72 - $257.95
Horizant® 600mg (30 tablets)	$132.68	$116.78 - $140.99
Horizant® 600mg (60 tablets)	$258.14	$232.62 - $281.99

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Clinical Trial Update

Aliskiren combination therapy in type 2 diabetes— Dual blockade of the renin-angiotension-aldosterone system (RAAS) with an angiotension converting enzyme inhibitor (ACEi) and an angiotension receptor blocker (ARB) was not shown to reduce cardiovascular (CV) outcomes in high risk patients in the ONTARGET trial compared to monotherapy; however, the risk for adverse events such as hypotension, hyperkalemia, and worsening renal function was increased with combination therapy.[1] One proposed mechanism for the lack of efficacy is a compensatory increase in plasma renin due to the dual RAAS blockade. Therefore, the ALTITUDE trial investigated whether the direct renin inhibitor, aliskiren, when added to baseline ACEi or ARB therapy would reduce cardiorenal endpoints in subjects with type 2 diabetes (T2DM) and chronic kidney disease (CKD), CV disease, or both.[2]

Subjects were randomized to aliskiren (n=4274) or placebo (n=4287) in addition to baseline therapy with an ACEi or ARB; aliskiren was initated at 150 mg daily and titrated at 4 weeks to 300 mg daily if there was no safety concerns; 84% of subjects were successfully titrated up to 300 mg daily. At baseline, the mean age was approximately 65 years, 32% were female, and the mean blood pressure was 137/74 mmHg. The mean estimated glomerular filtration rate (GFR) was 57 mL/min and 98% and 84% had CKD and proteinuria, respectively; 82% had T2DM for at least 5 years and 42.3% had known CV disease other than hypertension.

The primary outcome was the time to the first of a composite of 9 CV and renal endpoints, ranging from a doubling of the baseline serum creatinine that was sustained for at least one month to death from CV causes . Analysis was by intention-to-treat and events were adjudicated by a central adjudication committee.

At the second planned interim efficacy analysis and seventh interim safety analysis the data safety and monitoring committee recommended the study be terminated prematurely as the increased risk for adverse events associated with aliskiren would not be offset by a reduction in the primary outcome.

After a median follow-up of 32.9 months the primary outcome occurred in 18.3% of subjects receiving aliskiren compared to 17.1% receiving placebo (hazard ratio [HR] 1.8, 95% confidence interval [CI] 0.98-1.20, p=0.12). Treatment effect was consistent across all subgroups except subjects with an elevated baseline serum potassium (5 mEq/L or higher) receiving aliskiren had a higher risk for the primary outcome. Secondary CV and renal outcomes also showed no difference between aliskiren and placebo.

Blood pressure increased in both groups during follow-up but increased less in the aliskiren group (between-group difference, 1.3/0.6 mmHg, favoring aliksiren). The urinary albumin-to-creatinine ratio also decreased more with aliskiren (between-group difference of 14%, 95% CI 11-17%). Conversely, the decline in GFR at 6 months was greater for aliskiren than for placebo (-2.45 mL/min vs. -1.29 mL/min, respectively, p<0.001); differences between groups at later time points were not provided.

Mores subjects discontinued aliskiren permanently than placebo (p=0.001) and more discontinued aliskiren due to adverse events than placebo (13.2% vs. 10.2%, p<0.001). Hyperkalemia was the most common adverse event and also the most common reason cited for study drug discontinuation. A potassium between 5.5 and 6 mEq/L occurred in 21.2% of subjects receiving aliskiren compared to 16.9% receiving placebo; potassium levels > 6 mEq/L occurred in 11.2% and 7.2% of aliskiren and placebo subjects, respectively (p<0.001 for both comparisons). Renal impairment and hypotension were the second and third most common reasons for study drug discontinuation and occurred more frequently in the aliskiren group than the placebo group.

In subjects with T2DM or CKD, or in those with CV disease, the addition of aliskiren to baseline ACEi or ARB therapy did not reduce cardiorenal endpoints but increased the incidence of adverse events such as hyperkalemia, hypotension, and renal impairment and therefore should be avoided.

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