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Amturnide (Aliskiren, Amlodipine and Hydrochlorothiazide Tablets)

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Clinical Studies Experience

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- **WARNINGS AND PRECAUTIONS** Risk of fetal/neonatal morbidity and mortality [see]
- **WARNINGS AND PRECAUTIONS** Head and neck angioedema [see]
- **WARNINGS AND PRECAUTIONS** Hypotension [see]

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 clinical trials of another drug and may not reflect the rates observed in practice.

Amturnide

Amturnide has been evaluated for safety in 1155 patients treated with Amturnide, including 182 patients for over 1 year.

In a short-term controlled trial, there were 60.5% males, 84.1% Caucasians, 10% Blacks, 6.4% Hispanics, and 19.1% who were ? 65 years of age. In this study, the overall incidence of adverse events on therapy with Amturnide was similar to that observed with the individual components. The overall frequency of adverse events was similar between men and women and Black and White patients. Discontinuation of therapy because of a clinical adverse event in this study occurred in 3.6% of patients treated with Amturnide versus 2.4% in aliskiren/amlodipine, 0.7% in aliskiren/HCTZ, and 2.7% in amlodipine/HCTZ.

Table 1: Adverse events in a short-term controlled trial that occurred in at least 2% of patients treated with Amturnide

Amlo/HCTZ	Ali/HCTZ	Ali/amlo	Amturnide	
4.1%	2.0%	8.0%	7.1%	Edema peripheral
1.7%	3.4%	2.4%	3.6%	Dizziness
5.1%	4.0%	3.1%	3.6%	Headache
3.4%	2.0%	0.7%	2.6%	Nasopharyngitis

In a long-term safety trial, the safety profile was similar to that seen in the short-term controlled trial.

Aliskiren

Aliskiren has been evaluated for safety in 6460 patients, including 1740 treated for longer than 6 months, and 1250 for longer than 1 year. In placebo-controlled clinical trials, discontinuation of therapy because of a clinical adverse event, including uncontrolled hypertension, occurred in 2.2% of patients treated with aliskiren, versus 3.5% of patients given placebo.

Two cases of angioedema with respiratory symptoms were reported with aliskiren use in the clinical studies. Two other cases of periorbital edema without respiratory symptoms were reported as possible angioedema and resulted in discontinuation. The rate of these angioedema cases in the completed studies was 0.06%.

In addition, 26 other cases of edema involving the face, hands, or whole body were reported with aliskiren use, including 4 leading to discontinuation.

In the placebo-controlled studies, however, the incidence of edema involving the face, hands, or whole body was 0.4% with aliskiren compared with 0.5% with placebo. In a long-term active-controlled study with aliskiren and HCTZ arms, the incidence of edema involving the face, hands, or whole body was 0.4% in both treatment arms.

Aliskiren produces dose-related gastrointestinal (GI) adverse reactions. Diarrhea was reported by 2.3% of patients at 300 mg, compared to 1.2% in placebo patients. In women and the elderly (age ? 65) increases in diarrhea rates were evident starting at a dose of 150 mg daily, with rates for these subgroups at 150 mg similar to

those seen at 300 mg for men or younger patients (all rates about 2%). Other GI symptoms included abdominal pain, dyspepsia, and gastroesophageal reflux, although increased rates for abdominal pain and dyspepsia were distinguished from placebo only at 600 mg daily. Diarrhea and other GI symptoms were typically mild and rarely led to discontinuation.

Aliskiren was associated with a slight increase in cough in the placebo-controlled studies (1.1% for any aliskiren use versus 0.6% for placebo). In active-controlled trials with ACE inhibitor (ramipril, lisinopril) arms, the rates of cough for the aliskiren arms were about one-third to one-half the rates in the ACE inhibitor arms.

Other adverse reactions with increased rates for aliskiren compared to placebo included rash (1% versus 0.3%), elevated uric acid (0.4% versus 0.1%), gout (0.2% versus 0.1%), and renal stones (0.2% versus 0%).

Single episodes of tonic-clonic seizures with loss of consciousness were reported in 2 patients treated with aliskiren in the clinical trials. One patient had predisposing causes for seizures and had a negative electroencephalogram (EEG) and cerebral imaging following the seizures; for the other patient, EEG and imaging results were not reported. Aliskiren was discontinued and there was no re-challenge in either case.

No clinically meaningful changes in vital signs or in ECG (including QTc interval) were observed in patients treated with aliskiren.

Amlodipine

Amlodipine (Norvasc®) has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. Other adverse events that have been reported at < 1% but > 0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain were:

arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, peripheral ischemia, syncope, postural hypotension, **Cardiovascular:** vasculitis

neuropathy peripheral, paresthesia, tremor, vertigo **Central and Peripheral Nervous System:**

anorexia, constipation, dyspepsia,** dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia **Gastrointestinal:**

allergic reaction, asthenia,** back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease **General:**

arthralgia, arthrosis, muscle cramps,** myalgia **Musculoskeletal System:**

sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization **Psychiatric:**

dyspnea, epistaxis **Respiratory System:**

angioedema, erythema multiforme, pruritus,** rash,** rash erythematous, rash maculopapular **Skin and Appendages:**

**These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus **Special Senses:**

micturition frequency, micturition disorder, nocturia **Urinary System:**

dry mouth, sweating increased **Autonomic Nervous System:**

hyperglycemia, thirst **Metabolic and Nutritional:**

leukopenia, purpura, thrombocytopenia **Hemopoietic:**

Other events reported with amlodipine at a frequency of ? 0.1% of patients include: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia. Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

HCTZ

Other adverse reactions not listed above that have been reported with HCTZ, without regard to causality, are listed below:

weakness **Body as a Whole:**

pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation **Digestive:**

aplastic anemia, agranulocytosis, hemolytic anemia **Hematologic:**

photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary **Hypersensitivity:** edema, anaphylactic reactions

glycosuria, hyperuricemia **Metabolic:**

muscle spasm **Musculoskeletal:**

restlessness **Nervous System/Psychiatric:**

renal failure, renal dysfunction, interstitial nephritis **Renal:**

erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis **Skin:**

transient blurred vision, xanthopsia **Special Senses:**

Clinical Laboratory Test Abnormalities

Clinical laboratory findings for Amturnide were obtained in a controlled trial of Amturnide administered at the maximal dose of 300/10/25 mg compared to maximal doses of dual therapies, i.e., aliskiren/amlodipine 300/10 mg, aliskiren/HCTZ 300/25 mg and amlodipine/HCTZ 10/25 mg.

RBC Count, Hemoglobin and Hematocrit

Small mean changes from baseline were seen in RBC count, hemoglobin and hematocrit in patients treated with Amturnide. This effect is also seen with other agents acting on the renin angiotensin system. In aliskiren monotherapy trials these decreases led to slight increases in rates of anemia compared to placebo (0.1% for any aliskiren use, 0.3% for aliskiren 600 mg daily, versus 0% for placebo). No patients discontinued Amturnide because of anemia.

Blood Urea Nitrogen (BUN)/Creatinine

No patients treated with Amturnide had elevations in BUN > 40 mg/dL or creatinine > 2.0 mg/dL.

Liver Function Tests

Occasional elevations (greater than 150% from baseline) in ALT (SGPT) were observed in 2.7% of patients treated with Amturnide, compared with 1.7-2.7% in patients treated with the dual combinations. No patients were discontinued due to abnormal liver function tests.

Serum Uric Acid

Uric acid increase > 50% from baseline was more commonly observed in patients treated with Amturnide (4.7%) compared with the dual combinations (0.4-2.8%). Gout was less commonly observed (0.3% in Amturnide-treated patients) and renal stones were not reported.

Serum Electrolytes

]**WARNINGS AND PRECAUTIONS** [See

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of either aliskiren or amlodipine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure:

angioedema requiring airway management and hospitalization **:*Hypersensitivity***

peripheral edema, Blood creatinine increased **:*Aliskiren***

The following postmarketing event has been reported infrequently where a causal relationship is uncertain: gynecomastia. In postmarketing experience,**:*Amlodipine*** jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine.