

Exforge[®] (amlodipine and valsartan) and Exforge HCT[®] (amlodipine, valsartan, hydrochlorothiazide) Tablets for High Blood Pressure

Effective and Convenient Combination Treatments to Help Get Patients to Blood Pressure Goals

Exforge (amlodipine and valsartan) tablets are a once-a-day medication indicated to treat high blood pressure in adults. It is the first single pill that contains the angiotensin II receptor blocker (ARB) valsartan and the calcium channel blocker (CCB) amlodipine besylate – the number one prescribed medications in their classes. Exforge may be used when one medicine to lower your blood pressure is not enough. It may also be used as the first medicine to lower high blood pressure if your doctor decides you are likely to need more than one medicine to get to blood pressure goal.

- In clinical trials involving more than 5,000 patients, Exforge has been shown to lower blood pressure significantly greater than valsartan or amlodipine monotherapy.
- A clinical study in patients with stage 2 hypertension showed Exforge 10/160 mg lowered systolic blood pressure by 30 mmHg, compared to 24 mmHg with amlodipine 10 mg. In a subanalysis of patients with a systolic blood pressure greater or equal to 180 mmHg (severe hypertension), those taking Exforge 10/160 mg achieved a mean systolic blood pressure reduction of 40 mmHg, compared to 32 mmHg with amlodipine 10 mg. Comparable results were observed in a similar trial of African American patients with hypertension.
- In patients previously uncontrolled on either an ARB or a CCB, Exforge demonstrated additional double digit systolic blood pressure reductions.

Exforge HCT (amlodipine, valsartan, hydrochlorothiazide) tablets are newly FDA-approved and the only high blood pressure treatment to combine three medications in a single pill. Exforge HCT combines the number one prescribed calcium channel blocker, angiotensin receptor blocker and diuretic in one pill, and is an important new option for patients who have tried taking dual combinations of these classes of blood pressure medications without success. Exforge HCT is not indicated for the initial therapy of hypertension.

- In a clinical trial, the maximum dose of Exforge HCT (amlodipine/valsartan/hydrochlorothiazide 10 mg/320 mg/25 mg) demonstrated significantly greater reductions in systolic and diastolic blood pressures when compared to all dual combinations of its components at the same doses (valsartan/hydrochlorothiazide 320 mg/25 mg, amlodipine/valsartan 10 mg/320 mg, and amlodipine/hydrochlorothiazide 10 mg/25 mg), providing additional reductions of 18-29% in systolic blood pressure and 19- 32% in diastolic blood pressure.
- The reductions in systolic/diastolic blood pressure with Exforge HCT were 7.6/5.0 mmHg greater than with valsartan/hydrochlorothiazide, 6.2/3.3 mmHg greater than with amlodipine/valsartan, and 8.2/5.3 mmHg greater than with amlodipine/hydrochlorothiazide. These results also include a placebo effect of unknown size. Ambulatory blood pressure monitoring showed that the blood pressure lowering effect of Exforge HCT was maintained throughout the 24-hour period.
- The full blood pressure lowering effect was achieved two weeks after being on the maximal dose of Exforge HCT.

Combination Therapy for Effective Blood Pressure Lowering

- Exforge HCT is the only blood pressure treatment to combine three medications in a single pill (amlodipine, valsartan and hydrochlorothiazide).
- The two medicines in Exforge and the three medicines in Exforge HCT each work in different ways to help lower blood pressure.
- Research suggests that up to 85% of patients may need multiple medications to help control their blood pressure and many need three or more.

Significant Blood Pressure Reductions in Difficult-to-Treat Patients

- In a clinical trial, Exforge 10/160-320 mg lowered high blood pressure significantly more than amlodipine alone in African-American patients with systolic blood pressure greater or equal to 160 mmHg, a group that traditionally has great difficulty getting to goal.
 - In these patients, Exforge lowered blood pressure by 33 mmHg , on average, compared to 27 mmHg reductions with amlodipine monotherapy.
 - In a subset of these patients with systolic blood pressure greater or equal to 180 mmHg (severe hypertension), Exforge lowered blood pressure by 44 mmHg on average, compared to 37 mmHg reductions with amlodipine monotherapy.
 - Comparable results were observed in a similar trial of patients with hypertension.
- Ambulatory blood pressure monitoring showed that the blood pressure lowering effect of Exforge HCT was maintained throughout the 24-hour period.

Cost and Convenience

- Exforge and Exforge HCT will be offered at the same price in the US on a dose-equivalent basis, essentially providing the added diuretic in Exforge HCT at no additional cost.
- Exforge and Exforge HCT can help appropriate patients reach their blood pressure treatment goals, while offering convenience and potential cost savings by reducing multiple co-payments to one.
- Patients needing multiple blood pressure medications may find treatment more convenient with one single pill rather than separate pills.

Various Dosing Options

- Exforge and Exforge HCT are available in various dosage strengths to fit individual patient needs.

About High Blood Pressure

- High blood pressure affects approximately 74 million adults in the US and one in four adults worldwide.
- If high blood pressure is not treated, it can lead to heart attack and stroke. Exforge and Exforge HCT are not indicated for the treatment or prevention of heart attack or stroke.

Indications and Important Safety Information

EXFORGE® is indicated for the treatment of hypertension in patients not adequately controlled on monotherapy and as initial therapy in patients likely to need multiple drugs to reach their blood pressure goals.

The decision to use a combination as initial therapy should be individualized and should be shaped by considerations such as baseline blood pressure, the target goal, and the incremental likelihood of achieving goal with a combination product compared to monotherapy.

EXFORGE HCT® is indicated for the treatment of hypertension. This fixed combination drug is not indicated for the initial therapy of hypertension.

IMPORTANT CONSIDERATIONS

WARNING: AVOID USE IN PREGNANCY: When pregnancy is detected, discontinue EXFORGE or EXFORGE HCT as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury or death to the developing fetus. [See Warnings and Precautions (5.1)]

Because of the hydrochlorothiazide component, EXFORGE HCT is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

Excessive hypotension was seen in 0.4% of patients treated with EXFORGE and in 1.7% of patients treated with EXFORGE HCT 10/320/25 mg. Correct volume- or salt-depletion before administering EXFORGE or EXFORGE HCT or symptomatic hypotension may occur. Caution should be observed when initiating therapy with EXFORGE in patients with heart failure or recent myocardial infarction and in patients undergoing surgery or dialysis. Do not initiate treatment with EXFORGE HCT in patients with aortic or mitral stenosis or obstructive hypertrophic cardiomyopathy.

Rarely, increased frequency, duration, or severity of angina or acute myocardial infarction have developed in patients treated with calcium channel blockers; particularly patients with severe obstructive coronary artery disease.

EXFORGE should be used with caution in patients with severe hepatic impairment and should be used with care in patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, because of lower valsartan clearance.

Avoid use of EXFORGE HCT in patients with severe hepatic impairment. In patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, monitor for worsening of hepatic or renal function, including fluid status and electrolytes, and adverse reactions.

In patients with renal artery stenosis or severe renal impairment, care should be exercised with dosing of EXFORGE. Avoid use of EXFORGE HCT in severe renal disease (creatinine clearance \leq 30 mL/min). The usual regimens of therapy with EXFORGE HCT may be followed if the patient's creatinine clearance is $>$ 30 mL/min.

In patients with severe heart failure, decline in renal function and rarely, acute renal failure and/or death has been associated with inhibiting the renin-angiotensin system. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function. Dosage reduction and/or discontinuation of the diuretic and/or valsartan may be required.

Important considerations due to the hydrochlorothiazide component of EXFORGE HCT: Thiazides have been reported to cause exacerbation or activation of systemic lupus erythematosus. Lithium generally should not be given with thiazides.

Monitor serum electrolytes periodically based on EXFORGE HCT use and other factors such as renal function, other medications, or history of prior electrolyte imbalances.

The most common adverse reactions that occurred more frequently with EXFORGE than placebo were peripheral edema (5% vs 3%), nasopharyngitis (4% vs 2%), upper respiratory tract infection (3% vs 2%), and dizziness (2% vs 1%).

The most frequent adverse events that occurred in $>$ 2% of patients treated with EXFORGE HCT were dizziness (8.2%), edema (6.5%), headache (5.2%), dyspepsia (2.2%), fatigue (2.2%), muscle spasms (2.2%), back pain (2.1%), nausea

(2.1%) and nasopharyngitis (2.1%).

Please see accompanying full Prescribing Information.

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