Fimasartan potassium + Amlodipine

Dukarb® Film-Coated Tablets

Read package insert carefully before use.

Consult your doctor for more information.

Prescription medicine only. Keep out of reach of children.

Brand or Product Name

Fimasartan potassium + Amlodipine (Dukarb®) Film-Coated Tablets 60 mg /10 mg
Dosage form: Film Coated Tablets

Formulation

Fimasartan potassium + Amlodipine (Dukarb®) Film-Coated Tablets 60 mg /10 mg contains fimasartan potassium granules (in-house)… 150.00 mg (as Fimasartan potassium 60 mg) and amlodipine besylate… 13.88 mg (as amlodipine 10 mg). It also contains 0.42 mg of Sunset Yellow FCF (Food Yellow No. 5)

Product Description

Fimasartan potassium + Amlodipine (Dukarb®) Film-Coated Tablets 60 mg /10 mg are orange apple-shaped film-coated tablet.

Pharmacodynamics/Pharmacokinetics

Pharmacodynamic properties

Fimasartan :
Pharmacotherapeutic group: Angiotensin II antagonists, ATC code: C09CA10

The renin-angiotensin system (RAS), acting through the major effector peptide angiotensin II, has potent effects on blood pressure, water, and sodium homeostasis and end-organ damage in the heart, vessels, brain, and kidneys. Consequently, inhibiting RAS has been an important therapeutic strategy for the treatment of hypertension and related end-organ damage. Fimasartan selectively binds to angiotensin II receptor type 1 receptor in in vitro experiments. In humans, fimasartan increased plasma renin activity, coupled with increased angiotensin I and II concentrations, strongly supporting the notion that it is a specific angiotensin II receptor blocker.

This is also the proposed mechanism of action for fimasartan, which reduces blood pressure in patients with hypertension. The clinically and statistically significant blood pressure lowering effects, compared to placebo, as seen in therapeutic clinical trials of fimasartan also support this mechanism of action.

Amlodipine:
Pharmacotherapeutic group: Calcium antagonists, ATC code: C08CA01

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.
The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischaemic burden by the following two actions:

- Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.
- The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

Pharmacokinetic properties
Fimasartan/Amlodipine
In terms of the safety and pharmacokinetics ($AUC_{T,\ ss}$ and $Cmax,\ _{ss}$), no clinically significant differences were observed when fimasartan 120 mg was concomitantly administered with amlodipine 10 mg in healthy male adults compared to the administration of fimasartan or amlodipine alone.

Fimasartan
Absorption
Time to peak plasma concentration (T_{max}) following single oral administration of fimasartan at doses of 20 – 480 mg in healthy subjects ranged between 0.5 – 3 hours with the terminal half-life ($t_{1/2}$) being 5 – 16 hours. Similar results were obtained in patients with hypertension, i.e., T_{max} ranged 0.5 – 1.3 hours and $t_{1/2}$ were 7 – 10 hours following fimasartan administration at doses 20 – 180 mg. Several subjects showed a second peak, and the total systemic exposure as assessed by the AUC was linear (i.e., dose-independent). Accumulation index was 1.20 – 1.26 and 1.02 – 1.08 for healthy subjects and patients with hypertension, respectively. The absolute bioavailability of fimasartan in healthy subjects following 60 mg oral administration compared to 30 mg intravenous infusion was estimated to be 19%.
These results support the notion that oral fimasartan is rapidly absorbed, have linear pharmacokinetic profiles over 20 – 480 mg doses, and accumulation is minimal when dosed once daily. Therefore, the total systemic exposure can be easily predicted for each dose, which helps increase certainty about the safe and effective use of fimasartan in a clinical setting.

Distribution and Protein Binding
In vitro protein binding in human plasma ranged 95.6 – 97.2% at fimasartan concentrations of 0.01 – 100 μg/mL, which was not dose-dependent. These results were similar to those obtained in the dogs and rats using the *in vitro* and *ex vivo* methods.

Metabolism
In vitro study showed CYP3A4 would be mainly involved in fimasartan metabolism. Fimasartan has not been shown to inhibit or induce other CYP enzymes. The parent drug was ≥ 85% of the fimasartan moieties found in human plasma with a few metabolites identified, which supports the notion that the pharmacological action of fimasartan is mainly driven by the parent drug. The most abundant circulating metabolites of fimasartan in plasma in healthy male subjects were identified as desulfo-fimasartan and fimasartan-S-oxide. These metabolites accounted for approximately 14% (each 7%) of the total drug related exposure. No parent or metabolite has been assayed in human feces; however, *in vivo* metabolism of fimasartan is most likely to be minimal given the systemic exposure level of fimasartan was weakly increased by specific CYP3A4 inhibitors. These favorable pharmacokinetic properties of fimasartan enable its safe use in a clinical setting.

Elimination
Approximately 3 – 5% of fimasartan dose was recovered in urine by 24 or 144 hours postdose following oral administration in healthy male subjects and patients with hypertension. Therefore, the kidney is very less likely involved in the elimination of fimasartan.

Food Effect
A preliminary exploration was made in a phase I study conducted in the United Kingdom for food effect on the pharmacokinetics of fimasartan, and no food effect was noted. A formal food effect study was performed in South Korea, in which the point estimates for the geometric mean ratios of $AUC_{0-\infty}$ and C_{max} with and without food were 0.6371 and 0.3481, respectively, suggesting food affects the absorption of fimasartan. However, given the fact that the exposure-response relationship of fimasartan in reducing blood pressure has been well established and is relatively flat over the therapeutically recommended doses of 60 – 120 mg, and it took 2 – 4 weeks for antihypertensive effect to be exerted, the observed food effect on the pharmacokinetics of fimasartan is considered insignificant large enough to justify dosage adjustment with food.

<u>Pharmacokinetic Characteristics in Special populations</u>

Elderly
Elderly subjects (i.e., aged ≥ 65 years old) had a 1.69 times greater systemic exposure than young adults. However, since RAS activity in the elderly is generally lower than young adults, increased systemic exposure will be less likely to result in greater blood pressure reduction. This assumption has been frequently affirmed in other angiotensin receptor blockers. In fact, the blood pressure reduction in elderly subjects enrolled in therapeutic fimasartan clinical trials was numerically smaller than the one seen in those under the age of 65. In addition, no difference in the safety profiles was noted between elderly and young subjects. These results collectively support the notion that increased systemic exposure in elderly subjects has less clinical significance, and does not require any dosage adjustment in this population.

Hepatic Impairment
Fimasartan 120 mg was administered to patients with hepatic impairment (Child-Pugh Classification A or B) and C_{max} and AUC were compared with the healthy subjects. The geometric mean ratios of C_{max} and AUC were 0.77 and 1.10, respectively, in the Child-Pugh Classification A (mild) group. In the Child-Pugh Classification B (moderate) group, the geometric mean ratios of C_{max} and AUC were 6.55 and 5.20, respectively. There was no significant change in blood pressures before and after the drug administration, and no difference safety profiles was observed among three groups. Based on these results, no initial dosage adjustment is required for subjects with mild hepatic impairment. However,

fimasartan is not recommended to patients with moderate to severe hepatic impairment patients.

Renal Impairment
When fimasartan 120 mg was administered to patients with severe renal impairment (estimated GFR < 30 mL/min/1.73m^2 and not subjected to dialysis), C_{max} and AUC were increased 1.87 and 1.73 times, respectively, compared to healthy subjects. Safety profiles were not different between the two groups. No initial dosage adjustment is required for subjects with mild to moderate renal impairment (creatinine clearance 30 – 80 mL/min). For severe renal impairment (creatinine clearance < 30 mL/min), the recommended initial dose is 30 mg once daily and the dose should not exceed 60 mg.

Drug Interaction

Pharmacokinetic drug interaction potential for fimasartan was investigated using drugs that may be concomitantly used with fimasartan in diverse clinical settings. Antihypertensive drugs such as hydrochlorothiazide and amlodipine did not show a significant pharmacokinetic interaction with fimasartan. Therefore, fimasartan can be safely co-administered with hydrochlorothiazide and amlodipine without dosage adjustment to achieve further blood pressure reduction in those who do not respond well enough to these antihypertensive medications alone.

Likewise, atorvastatin, digoxin and warfarin, which are frequently used in patients with hypertension, showed no clinically significant pharmacokinetic drug interaction with fimasartan, enabling safe concomitant use without dosage adjustment.

Ketoconazole, a CYP3A4 inhibitor, increased systemic exposure of fimasartan by 2 folds, which is considered weak drug interaction. This magnitude of drug interaction does not require any dosage adjustment for concomitant use, but close monitoring of patients may be recommended. In addition, rifampicin, a strong OATP1B1 inhibitor, increased systemic exposure of fimasartan by 4.6 folds as assessed using AUC. Since OATP1B1 is known to play a significant role in transport of fimasartan into hepatic cells, and rifampicin also induces CYP3A4, co-administration of rifampicin with fimasartan is not recommended.

Based on these results, fimasartan can be safely co-administered with most drugs in patients with hypertension.

Population Pharmacokinetics

A formal population pharmacokinetic-pharmacodynamic modeling analysis was performed using data obtained from two phase I studies (healthy subjects), conducted in the United Kingdom, and an early phase II study (patients with mild to moderate hypertension), conducted in South Korea. In addition, a back-of-the-envelope type of population pharmacokinetic analysis was performed using concentrations collected in the ambulatory blood pressure monitoring (ABPM) study.

Population pharmacokinetic parameters derived from the formal population pharmacokinetic- pharmacodynamic analysis was similar to those estimated using the non- compartment analysis approach. Population pharmacokinetic parameters of fimasartan were not significantly affected by race, sex, or GFR. Instead, body weight, bilirubin and age were significant covariates. Given that the between-subject variability (BSV) on the fimasartan concentration yielding 50% of the maximal blood pressure reduction (i.e., EC50) was large (i.e., 130 – 140%), those significant covariates on pharmacokinetic parameters are less likely to affect the extent of blood pressure reduction

by fimasartan. Therefore, no dosage adjustment for fimasartan is warranted based on covariates. Similar findings were obtained in the back-of-the-envelope population pharmacokinetic analysis, i.e., height was identified as a significant covariate, but no dosage adjustment based on height is required.

These results support the notion that dosage adjustment for fimasartan based on individual's extrinsic and intrinsic factors is not required to treat patients with hypertension. Rather, dosage adjustment based on treatment response (i.e., blood pressure reduction) will be more practical in a clinical setting.

Amlodipine

Absorption, distribution, plasma protein binding

A therapeutic dose of amlodipine was well absorbed after oral administration, and the maximum level in blood was reached after 6–12 hours. Absolute bioavailability was assumed to be 64–80%, and a volume of distribution was approximately 21 l/kg. Absorption of amlodipine was not related to food intake. In vitro studies have shown that approximately 97.5% of circulation amlodipine is bound to plasma proteins.

Metabolism/elimination

Terminal fecal excretion half-life of amlodipine was about 35–50 hours, and this corresponds to a once-daily dosing regimen, the dosage of this drug. A steady state in plasma was reached after continued administration for 7–8 days. Amlodipine was metabolized mostly as inactive metabolome in the liver, and 10% of unchanged form and 60% of metabolites were excreted in urine.

Pharmacokinetic Characteristics in Special populations

Elderly

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients.

Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

A population PK study has been conducted in 74 hypertensive children aged from 12 months to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3 L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

Indication

Fimasartan potassium + Amlodipine (Dukarb®) Film-coated Tablets are indicated for the treatment of essential hypertension that is not adequately controlled with fimasartan monotherapy.

Posology and method of administration

Posology in Hypertension

The recommended dose is one tablet of Fimasartan potassium + Amlodipine (Dukarb®) once daily, and the drug should be taken with water regardless of meal intake. Whenever possible, it is recommended that Fimasartan potassium + Amlodipine (Dukarb®) Film-Coated Tablets should be taken at the same time during the day (e.g., morning).
Dosage adjustment with fimasartan alone is recommended prior to administration of fimasartan/ amlodipine combination, but immediately switching to this drug can be considered if blood pressure is not controlled as shown below.

- Fimasartan potassium + Amlodipine (Dukarb®) Film-Coated Tablets 60 mg /10 mg: this drug may be administered to patients whose blood pressure is not adequately controlled with fimasartan 60 mg monotherapy.

In the case of patients taking fimasartan and amlodipine concomitantly, switching to Fimasartan potassium + Amlodipine (Dukarb®) Film-Coated Tablets (a combination drug with the identical amount of the individual active ingredients) is allowed for convenient drug administration.

Geriatric population
No initial dosage adjustment is required for elderly population (age ≤ 70 years). In the study comparing the pharmacokinetics of healthy elderly volunteers aged 65 years or more and healthy young volunteers, the area under the curve (AUC) of fimasartan in the elderly group increased by 69%. However, no differences in the efficacy and safety were noted in a total of 21 elderly patients (≥ 65 years, 9.3%) out of 226 patients receiving fimasartan in phase III clinical trials, between the elderly and non-elderly groups. Therefore, no dosage adjustment seems to be required in elderly patients (≤ 70 years), although greater sensitivity in some elderly patients cannot be ruled out.

Renally impaired population
No dose adjustment is required for patients with mild to moderate renal impairment (creatinine clearance 30 – 80 mL/min); however, patients with severe renal impairment (creatinine clearance < 30 mL/min) patients, start with Fimasartan potassium + Amlodipine (Dukarb®) Film-Coated Tablets containing fimasartan 30mg. Fimasartan and Amlodipine are not dialyzable.

Hepatically impaired population
No dose adjustment is required for patients with mild hepatic impairment. Fimasartan potassium + Amlodipine (Dukarb®) Film-Coated Tablets are not recommended for patients with moderate to severe hepatic impairment.

Pediatric population
The efficacy and safety of Fimasartan potassium + Amlodipine (Dukarb®) Film-Coated Tablets have not been established in patients under 18 years of age.

Mode/Route of Administration

To be taken orally

Contraindications

Fimasartan potassium + Amlodipine (Dukarb®) Film-Coated Tablets are contraindicated in the following patients:
- Patients who are hypersensitive to the active ingredients of this drug and dihydropyridine derivatives
- Pregnant women or nursing mothers
- Patients on renal dialysis (no experience of use in this population)
- Patients with moderate to severe hepatic impairment
- Patients with biliary obstruction
- Patients with diabetes or moderate to severe renal impairment (glomerular filtration rate (GFR) <60mL/min/1.73 ㎡) who are taking renin inhibitors (aliskiren)
- Patients with diabetic nephropathy who are taking angiotensin converting enzyme (ACE) inhibitors
- Since this drug contains lactose, it should not be administered to patients with a hereditary disorder, such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.
- Patients with severe aortic stenosis
- Patients with shock

Warnings and Precautions

Pregnancy
Drugs directly acting on the renin-angiotensin system (RAS) may cause injury or death to the developing fetus when administered to a pregnant woman during the second and third trimesters. Therefore, fimasartan/amlodipine should be discontinued when pregnancy is detected.

Intravascular volume- or salt-depletion
Patients (e.g., patients receiving high doses of diuretics), whose RAS is activated, may experience symptomatic hypotension at the time of initial fimasartan/amlodipine administration or at an increased dosage. Therefore, close monitoring is required in these patients.

Renal impairment
Patients who are sensitive to drugs inhibiting RAS may experience changes in the renal function. ACE inhibitors or angiotensin II receptor antagonists may cause oliguria, progressive azotaemia, and rarely acute renal failure or death in patients whose renal function is dependent on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure).

Renovascular hypertension
Patients with uni-lateral or bi-lateral renal artery stenosis may have an increased risk for severe hypotension or renal failure when drugs affecting RAS are administered. An increase in the levels of serum creatinine and blood urea nitrogen (BUN) has been reported in patients with uni-lateral or bi-lateral renovascular hypertension when administered with angiotensin II receptor antagonists such as fimasartan. Although fimasartan has not been administered to patients with uni-lateral or bi-lateral renal artery stenosis, similar effects may occur.

Aortic and mitral valve stenosis (obstructive hypertrophic cardiomyopathy)

As with other vasodilators, special caution is required in patients suffering from haemodynamically relevant aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

Primary aldosteronism
Patients with primary aldosteronism will not generally respond to antihypertensive medicinal products acting via inhibition of the renin-angiotensin-aldosterone system. Therefore, the use of fimasartan/amlodipine is not recommended in this population.

Geriatric patients

Hypotension
Symptomatic hypotension may occur in volume- and salt-depleted patients (e.g., high doses of diuretics, restricted dietary salt intake, diarrhea and vomit), especially after initiation of treatment or dosage increase. Volume- and salt-depletion should be corrected before the treatment is initiated, or patients should be started with a lower dose, followed by a gradual dosage increase and close monitoring.

Transient symptomatic hypotension (e.g., shock, loss of consciousness, dyspnea) may occur after fimasartan/amlodipine treatment. If symptomatic hypotension occurs, patients should lie flat, and start intravenous fluid therapy when necessary. Treatment can be resumed after blood pressure is stabilized.

Hyperkalaemia
Drugs that exert effects on RAS may cause hyperkalaemia in patients with congestive heart failure or renal impairment. When fimasartan/amlodipine is administered to these patients, close monitoring of the serum potassium level is recommended.

Dual blockade of the renin-angiotensin system
Drugs blocking RAS, particularly when co-administered with drugs that may affect RAS, have been reported to cause changes in the renal function, including acute renal failure in patients sensitive to these drugs. Therefore, dual blockade of RAS, i.e., co-administration of an angiotensin II receptor antagonist and an ACE inhibitor is not generally recommended. If needed, however, treatment can be given on a limited basis to individuals whose safety has been confirmed.

Anesthetic and operative procedures
Hypotension may occur during anesthetic and operative procedures in patients receiving an angiotensin II receptor antagonist via the inhibition of RAS. Very rarely, severe hypotension may occur, requiring the treatment with intravenous fluid or vasopressors.

Ischemic heart disease or ischemic cerebrovascular disease
Like other blood pressure-lowering agents, excessive blood pressure reduction in patients with ischemic heart disease or ischemic cerebrovascular disease may worsen the underlying diseases. Caution needs to be exercised in these patients.

Heart failure:
In a long-term, placebo-controlled study (PRAISE-2) for amlodipine with patients with heart failure of New York Heart Association (NYHA) class III and IV without ischemic etiology, amlodipine was related to the increase in the reports of pulmonary edema even though there was no significant difference in the aggravation rate of heart failure between amlodipine and placebo.

I*mpaired hepatic function*:

As in all calcium channel blockers, the half-life of amlodipine became longer in patients with impaired hepatic function, and the recommended dose for these patients has not been established. Therefore, caution must be taken in the administration to these patients. Since gradual hypotensive effect may occur even after the administration of amlodipine has been stopped due to the long half-life of plasma concentration, caution must be taken in dose and dosing interval when administering other antihypertensive agents after stopping the administration of fimasartan/amlodipine, and the administration must be performed cautiously while observing the patient's condition.
Since the effect of amlodipine is manifested slowly, no effect can be expected for unstable angina which requires urgent treatment.

Allergy or hypersensitivity to food dyes
Caution is required for patients who have an allergy or are hypersensitive to tartrazine (Sunset Yellow FCF (Food Yellow No.5, only for Fimasartan potassium + Amlodipine (Dukarb®) Film-Coated Tablets 60 mg /10 mg).

Administration in Specific Populations
Pregnant Mothers and Nursing Mothers

Fimasartan
Pregnancy
Drugs that act directly on RAS can cause fetal and neonatal morbidity and death when administered to pregnant women. The use of drugs that act directly on RAS during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. When pregnancy is detected, fimasartan should be discontinued as soon as possible. These adverse events do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be informed so. Nonetheless, when patients become pregnant, physicians should advise the subject to discontinue the use of fimasartan as soon as possible. Infants with a history of in utero exposure to an angiotensin II receptor antagonist should be closed observed for hypotension, oliguria, and hyperkalemia.

Breast feeding
It is not known whether fimasartan and/or amlodipine is excreted in human milk, but fimasartan has been found to be excreted in the milk of lactating rats; therefore, it is not recommended to administer fimasartan/amlodipine to nursing mothers. A decision should be made whether to discontinue nursing or discontinue fimasartan/amlodipine, taking into account the importance of the drug to the mother.

Amlodipine
Pregnancy
The safety of amlodipine in human pregnancy has not been established.
In animal studies, reproductive toxicity was observed at high doses. Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries

greater risk for the mother and fetus.

Breast feeding
It is not known whether amlodipine is excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother.

Fertility
Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility.

Interactions with Other Medicines and Other Forms of Interaction
No significant pharmacokinetic drug interactions were observed after the concomitant administration of fimasartan and amlodipine. The drug–drug interactions between fimasartan/amlodipine and other drugs have not been studied.
The drug–drug interactions reported after using fimasartan or amlodipine with other substances are as shown below.

Fimasartan
The blood pressure-lowering effect of fimasartan can be increased when co-administered with other antihypertensive agents, including diuretics. When high doses of diuretics are used prior to fimasartan administration, leading to a volume-depleted state, excessive blood pressure reduction may occur with the initiation of fimasartan treatment.
Dual blockade of RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. In general, combined use of RAS inhibitors should be avoided. Aliskiren should not be co-administered with fimasartan in patients with diabetes or renal impairment (GFR < 60mL/min/1.73m^2). Co-administering ACE inhibitors with fimasartan is not recommended and use of ACE inhibitors with fimasartan in patients with diabetic nephropathy should be avoided.

Potassium supplements and potassium-sparing diuretics
Serum potassium can be increased by fimasartan and other drugs that exert effects on RAS when co-administered with potassium-sparing diuretics (e.g., spironolactone), potassium supplements, salt alternatives containing potassium, and drugs that may increase serum potassium (e.g., heparin).

Lithium
Reversible increases in serum lithium levels and toxicities have been reported when lithium was used with ACE inhibitors, whereas those reactions have been very rarely reported when angiotensin II receptor antagonists were co-administered with lithium. Although co-administration of lithium with fimasartan is not generally recommended, should it be necessary, close monitoring of lithium levels is required.

Non-steroidal anti-inflammatory drugs (NSAIDs)
When an NSAID (e.g., aspirin, COX-2 inhibitors) is co-administered, the blood pressure-lowering effect of an angiotensin II receptor antagonist may be reduced. Deterioration of damaged renal function including acute renal failure (generally reversible) has been reported when an angiotensin II receptor antagonist is co-administered with a COX inhibitor in some patients with renal impairment (e.g., dehydrated patients and renally

impaired elderly patients). Therefore, caution needs to be exercised when co-administering fimasartan with NSAIDs, especially in elderly patients. Adequate hydration is required in this case, and the renal function should be closely monitored.

Hydrochlorothiazide
No significant pharmacokinetic drug interaction between fimasartan and hydrochlorothiazide was found when co-administered.

The effects of other drugs on fimasartan

Ketoconazole
The systemic exposure of fimasartan, as measured by the AUC, was increased approximately by two times when co-administered with ketoconazole. Caution needs to be exercised when fimasartan is co-administered with ketoconazole.

Rifampicin or other OATP1B1 transporter inhibitors
Fimasartan is a substrate of OAT1 and OATP1B1. When fimasartan is co-administered with rifampicin (OATP1B1 inhibitor), the AUC of fimasartan was increased approximately by 4.6 times. Therefore, co-administration of fimasartan with rifampicin is not recommended. When co-administered with other OATP1B1 transporter inhibitors (e.g., cyclosporine), the systemic exposure of fimasartan may increase, and caution is required.

Warfarin
The pharmacokinetics and pharmacodynamics of warfarin were not significantly affected by co-administered fimasartan.

Atorvastatin
The AUC's of atorvastatin and its active metabolite were not affected by co-administered fimasartan. Maximum plasma concentrations (C_{max}) of atorvastatin and its active metabolite were increased by 1.9 and 2.5 times, respectively.

Digoxin
The pharmacokinetics and creatinine clearance of digoxin was not affected by co-administered fimasartan. However, C_{max} of digoxin was increased by 30%. Close monitoring of digoxin levels may be required when co-administered with fimasartan.

Other drug interactions
Fimasartan does not inhibit or induce the CYP450 enzymes.

Amlodipine
Amlodipine was safe when administered concomitantly with thiazide diuretics, alpha-blockers, beta-blockers, ACE inhibitors, long-acting nitrates, nitroglycerin sublingual tablets, non-steroidal anti-inflammatory agents, antibiotics, and oral hypoglycemic agents.

In vitro data indicate that amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

Grapefruit juice: When amlodipine is taken with a grapefruit or grapefruit juice, hypotensive effect can be increased due to the increase in bioavailability in some patients. It is not recommended to be administered with grapefruit or grapefruit juice consumption.

<u>The effects of other drugs on amlodipine</u>
Cimetidine
Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Aluminum/magnesium (antacid)
Co-administration of a magnesium and aluminum hydroxide antacid with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil
A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Cytochrome P3A4 inhibitors
Co-administration of cytochrome P3A4 inhibitors (erythromycin in young adults and diltiazem in the elderly) with amlodipine results in 22% and 57% increase of the plasma concentration of amlodipine respectively, but their clinical relationship has not been determined. The possibility of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, and ritonavir) inhibiting the plasma concentration of amlodipine to a greater extent than that shown when it was concomitantly administered with diltiazem, cannot be ruled out. Caution must be taken when amlodipine is co-administered with CYP3A4 inhibitors. However, no adverse event has been reported to have been caused by this drug interaction.

Cytochrome P3A4 inducers
Upon co-administration of known inducers of the CYP3A4 (e.g., rifampicin, hypericum perforatum), the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers.

<u>The effects of amlodipine on other drugs</u>
Atorvastatin
Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady-state pharmacokinetic parameters of atorvastatin.

Digoxin
Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Ethanol (alcohol)
Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

Warfarin
Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

Cyclosporine
Amlodipine did not alter the pharmacokinetics of cyclosporine significantly in the pharmacokinetic study on cyclosporine.

Tacrolimus
Co-administration of amlodipine with tacrolimus may have a risk of increased blood concentration of tacrolimus. Therefore, when this drug is administered in patients being treated with tacrolimus, the blood concentration of tacrolimus should be monitored, and the dose of tacrolimus should be adjusted appropriately in order to avoid tacrolimus toxicity.

Mechanistic Target of Rapamycin (mTOR) Inhibitors
mTOR inhibitors (e.g., sirolimus, temsirolimus, and everolimus) are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Simvastatin
Co-administration of multiple 10 mg doses of amlodipine with 80 mg of simvastatin resulted in a 77% increase in simvastatin systemic exposure when compared to simvastatin monotherapy. In patients receiving amlodipine, the maximum dose of simvastatin per day is up to 20 mg.

Adverse Effects/Undesirable Effects

Adverse Reactions Related to Fimasartan/Amlodipine
From the clinical trials, the safety of fimasartan/amlodipine was evaluated in patients with essential hypertension, who had received fimasartan/amlodipine at the dose of 30/5, 30/10, 60/5, 60/10 mg and eligible for safety analysis (i.e., the safety database). Adverse reactions (i.e., adverse events considered to be certainly related, probably related, possibly related to fimasartan/amlodipine, or unassessable) are summarized in Table 1 below, reported in the clinical trials of fimasartan/amlodipine.

Table 1. Frequency of Adverse Reactions from Clinical Trials

MedDRA Standard System Organ Class	**Frequency[1)]**	**Adverse Reaction**
Nervous system disorders	Common	Dizziness
	Uncommon	Dizziness postural, Headache
General disorders and administration site conditions	Uncommon	Face oedema, Oedema peripheral
Renal and urinary disorders	Uncommon	Dysuria
Psychiatric disorders	Uncommon	Insomnia
Vascular disorders	Uncommon	Flushing

1) Very common (≥1/10); common (≥1/100, < 1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); unknown (unable to estimate from available information)

Adverse Reactions Related to Fimasartan
From the clinical trials, the safety of fimasartan was evaluated in patients with essential hypertension, who had received fimasartan at the dose range of 30 to 120 mg for 4 to 24 weeks and eligible for safety analysis (i.e., the safety database). In addition, adverse reactions in the patients, who had received fimasartan in the postmarketing surveillance (PMS) study which was conducted for 6 years, were also evaluated. Adverse reactions (i.e., adverse events considered to be certainly related, probably related, possibly related to fimasartan, or unassessable) are summarized in Table 2 below, reported in the clinical trials and the PMS study of Fimasartan.

Table 2. Frequency of Adverse Reactions from Clinical Trials and Postmarketing Surveillance Study

MedDRA Standard System Organ Class	Frequency[1)]	Adverse Reaction
Nervous system disorders	Common	Dizziness
	Uncommon	Headache
	Rare	Syncope, Sedation, Migraine, Paraesthesia, Tremor
Gastrointestinal disorders	Uncommon	Dyspepsia, Nausea, Gastritis
	Rare	Vomiting, Upper abdominal pain, Abdominal distension, Flatulence, Gastrooesophageal reflux disease, Constipation, Abdominal pain, Dry mouth
General disorders and administration site conditions	Uncommon	Asthenia
	Rare	Sensation of foreign body, Chest discomfort, Oedema, Oedema peripheral
Investigations (abnormalities in laboratory findings)	Uncommon	Increased ALT[2)]
	Rare	Increased AST[3)],Hepatic enzyme increased, Platelet count decreased, Blood CPK[4)] increased, Blood creatinine increased, Blood pressure increased
Respiratory, thoracic and mediastinal disorders	Uncommon	Cough
	Rare	Productive cough, Dyspnoea
Musculoskeletal and connective tissue disorders	Rare	Muscle twitching, Musculoskeletal stiffness, Spinal column stenosis, Osteoporosis, Osteoarthritis, Arthralgia, Muscular weakness
Skin and subcutaneous tissue disorders	Rare	Pruritus, Urticaria, Rash
Vascular disorders	Uncommon	Hot flush, Hypotension, Orthostatic hypotension
	Rare	Flushing
Reproductive system and breast disorders	Rare	Erectile dysfunction
Cardiac disorders	Uncommon	Palpitations
	Rare	Supraventricular extrasystoles, Tachycardia
Infections and infestations	Rare	Nasopharyngitis, Pharyngitis, Bronchitis, Herpes zoster, Gastroenteritis
Metabolism and nutrition disorders	Rare	Gout, Hyperlipidaemia, Hyperkalaemia
Psychiatric disorders	Rare	Insomnia, Depression
Renal and urinary disorders	Rare	Chronic kidney disease, Pollakiuria
Eye disorders	Rare	Retinal disorder, Vitreous floaters, Visual impairment
Injury, poisoning and procedural complications	Rare	Procedural pain

1) Very common (≥1/10); common (≥1/100, < 1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); unknown (unable to estimate from available information)

2) ALT = Alanine Aminotransferase
3) AST = Aspartate Aminotransferase
4) CPK = Creatine Phosphokinase

Adverse Reactions Related to Amlodipine

Amlodipine has good tolerability. In a placebo-controlled clinical trial conducted in patients with hypertension and angina pectoris, the adverse events which occurred most commonly are as follows:

- Vascular disorders: Flushing
- General disorders: Fatigue, edema
- Cardiovascular disorders: Palpitation
- Central and peripheral nerve system disorders: Dizziness, headache, somnolence
- Gastrointestinal disorders: Abdominal pain, nausea
- No clinically significant changes in laboratory test were observed in relation to amlodipine in the clinical study.

The adverse events which were observed at relatively low frequency after marketing are as follows:

- General disorders: Asthenia, malaise, pain, weight gain, weight decrease
- Vascular disorders: Hypotension, vasculitis
- Nervous system disorders: Hypertonia, hypoesthesia, paresthesia, neuropathy peripheral, syncope, taste perversion, tremor, extrapyramidal disorders
- Reproductive disorders: Sexual dysfunction (male), gynecomastia
- Gastrointestinal disorders: Change of bowel habit, dry mouth, dyspepsia, gingival hyperplasia, pancreatitis, vomiting
- Metabolism and nutritional disorder: Hyperglycemia
- Musculoskeletal disorders: Arthralgia, back pain, muscle cramps, myalgia
- Hemopoietic disorders: Leukopenia, thrombocytopenia
- Psychiatric disorders: Insomnia, mood swings
- Respiratory disorders: Coughing, dyspnea, rhinitis
- Skin and appendages disorders: Alopecia, sweating increased, purpura, skin discoloration, urticarial, toxic epidermal necrolysis
- Sensory disorders: Tinnitus, abnormal vision
- Urinary system disorders: Micturition frequency, micturition disorder, nocturia
- Hepatobiliary system disorders: Hepatitis, jaundice, hepatic enzyme elevations, etc., were reported on very rare occasions, and most of them were related to cholestasis. Some cases were severe enough to require hospitalization and had been reported in association with use of amlodipine, but in most cases, the causal relationship to amlodipine is not clear.
- Allergic reactions including pruritus, rash, angioedema, and erythema multiform were reported on rare occasions.

As with other calcium channel blockers, the following adverse events were occurred sporadically and it is not certain whether these are due to the medication or concurrent disease states, such as myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), and chest pain.

Further, the following adverse events were observed:

- Cardiovascular disorder: Blood pressure decreased, sinoatrial blocks or atrioventricular blocks can occur occasionally, and flatulence can occur on rare occasions.

- Gastrointestinal disorders: Epigastric pain, diarrhea, loose stools, constipation, etc., can occur occasionally.
- Skin disorders: Erythromelalgia, rash maculopapular, etc. can occur on rare occasions.
- Other: Heaviness of head, hot flush, glucose tolerance decreased, weakness, etc., can occur occasionally.

Overdose and Treatment

Fimasartan
No data are available about overdosage of fimasartan in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be provided. It is not known whether fimasartan is removed from the plasma by hemodialysis.

Amlodipine
Overdosage of amlodipine might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. Also, there have been fatal cases where shock occurred or the symptom of systemic hypotension was severe and continued for a long time, which resulted in the status of shock. When activated charcoal was administered immediately or until 2 hours after amlodipine 10 mg had been administered to healthy volunteers, the absorption of amlodipine was decreased significantly. In some cases, gastrolavage can be useful. If massive overdose should occur, active cardiac and respiratory monitoring should be initiated.
Should hypotension occur, cardiovascular support including elevation of the extremities with attention to circulating volume and urine output should be provided. If it is not a special case in which the use of vasopressors is contraindicated, vasopressors can be useful in recovering the tone of blood vessels or blood pressure. The intravenous administration of calcium gluconate can be useful in reversing the effect of a calcium channel blocker. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

Carcinogenesis, mutagenesis, impairment of fertility
The following non-clinical information on fimasartan and amlodipine is known.

1) Fimasartan
No carcinogenetic effects were observed when fimasartan was administered orally for up to 2 years in mice and rats. The maximum tested doses were 100 mg/kg/d (mice) and 1,000 mg/kg/d (rats), which represent 4 and 81 times, respectively, the maximum recommended human dose on a mg/m^2 basis, assuming an oral dose of 120 mg/d in a 60 kg subject.

No mutagenicity or chromosomal aberration was observed.

Fimasartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 1,000 mg/kg/d, including fertility, early embryonic development, maternal function and neonatal development. Likewise, no teratogenic effects were observed.

2) Amlodipine

(1) Carcinogenesis: Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 amlodipine mg/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m^2 basis, similar to the maximum recommended human dose of 10 mg amlodipine/day*. For the rat, the highest dose was, on a mg/m^2 basis, about twice the maximum recommended human dose*.
(2) Mutagenicity: Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome level.
(3) Impairment of fertility: There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times the maximum recommended human dose* of 10 mg/day on a mg/m^2 basis).
* Based on a patient weight of 50 kg
(4) Reproductive toxicology: Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labor and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

3) Fimasartan/ Amlodipine
No data are available about carcinogenesis, mutagenicity, reproductive toxicology.
No toxicologically significant changes related to the study substances were observed in the study on repeated administration of the mixture of fimasartan and amlodipine for 4 weeks. Also, in the toxicokinetic study, accumulation of amlodipine besylate was observed, but it showed dose- dependent systemic exposure. The maximum tolerated dose in the fimasartan + amlodipine group was found to be 180 + 15 mg/kg/day.

In the 13-week repeated oral administration toxicity and 4-week recovery studies using the mixture of fimasartan and amlodipine, it is considered that the no-observed- adverse-effect level of fimasartan + amlodipine under the conditions is 11.25 + 0.94 mg/kg/day in male animals and 45 + 3.75 mg/kg/day in female animals.

Storage Condition

1) It is recommended that Fimasartan potassium + Amlodipine (Dukarb®) Film-Coated Tablets should be stored at room temperature (i.e., 1-30℃) in a light- protected container.
2) Fimasartan potassium + Amlodipine (Dukarb®) Film-Coated Tablets should be stored in a place a child cannot reach.
3) Repackaging of Fimasartan potassium + Amlodipine (Dukarb®) Film-Coated Tablets is not recommended because it may cause accidental mislabeling or adversely affect the product quality.

Dosage Forms or Presentation

60 mg /10mg Film-coated tablets: 3 blisters x 10 tab. / box
**Not all presentations may be available locally*

Name and Address of Manufacturer or Product Owner

Product Owner:

Boryung Corporation
Address: Boryung Bldg., 136, Changgyeonggung-ro, Jongro-gu, Seoul, Korea

Manufacturer:

Boryung Corporation
Address: 107,109 Neungan-ro, Danwon-gu, Ansan-si, Gyeonggi-do, Korea

Name and Address of Marketing Authorization Holder

Imported and Distributed by:
Zuellig Pharma Corporation
Km. 14 West Service Rd., South Super Highway corner Edison Ave., Sun Valley, Parañaque City, Philippines

Caution

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADR Reporting

For suspected adverse drug reaction, report to FDA: www.fda.gov.ph. Seek medical attention immediately at the first sign of any adverse drug reaction.

Registration Number

Fimasartan potassium + Amlodipine (Dukarb®) Film-Coated Tablets 60 mg /10 mg:

DR-XY48276

Date of First Authorization

11 August 2022

Date of Revision of Package Insert

10 January 2023