Fimasartan Potassium & Hydrochlorothiazide

Kanarb®Plus

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

Kanarb®Plus Film Coated Tablets 60mg/12.5mg

Name and Strength of Active Substance(s)

Kanarb®Plus Tablets 60mg/12.5mg contains 66.01mg of Fimasartan potassium trihydrate (as 60mg of Fimasartan potassium) and 12.50mg of Hydrochlorothiazide

Product Description

Kanarb®Plus Tablets 60mg/12.5mg are yellow, oval biconvex film-coated tablets with “BR” on front, “F6H” on back.

Excipients:
Lactose Monohydrate, Microcrystalline Cellulose, Croscarmellose Sodium, Hydroxypropyl Cellulose, Magnesium Stearate, Purified Water, Ethanol, Opadry 03B62599 and Carnauba Wax

Pharmacodynamics/Pharmacokinetics

Pharmacodynamic properties
Fimasartan :

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 to reduce 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.

Hydrochlorothiazide :

Hydrochlorothiazide is a thiazide diuretic and blocks the reabsorption of sodium ions in the distal tubule of the kidney. The major action in nephron is the Na^+ -Cl^- co-transporter. It competes with the Cl^- ion to block the reabsorption of the Na+ and Cl^- ions, which results in natriuresis and decreased body fluids and ends up decreasing the blood pressure. On the other hand, it also increases the reabsorption of Ca^{2+} regardless of the Na^+ transporter and it is known to decrease the resistance of the peripheral blood vessels. The diuretic effects appeared within 2 hours after the oral administration, and showed maximum diuretic effects within 3 to 6 hours after the oral administration and lasted up to 6 to 12 hours. The antihypertensive effect showed within 3 to 4 days.

Pharmacokinetic properties
Fimasartan/Hydrochlorothiazide :
Pharmacotherapeutic group : Angiotensin II antagonists and diuretics, ATC code: C09DA10

The pharmacokinetics analysis results of the single administration of fimasartan and the combined administration of fimasartan and hydrochlorothiazide showed that the point estimations of the geometric mean ratios of fimasartan C_{max},ss and $AUC_{\tau,ss}$ (90% CI) were 1.30 (0.84-2.01) and 1.17 (0.93-1.47), respectively. The point estimations of the geometric mean ratios of hydrochlorothiazide $C_{max,ss}$ and $AUC_{\tau,ss}$ (90% CI) were 0.94 (0.84-1.04) and 0.88 (0.795-0.97), respectively.
As such, the difference in the safety and pharmacokinetics parameters were not clinically significant between the single administration of either fimasartan or hydrochlorothiazide and the combined therapy of fimasartan 240 mg and hydrochlorothiazide 25 mg in healthy male volunteers.

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 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.

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 dog and rat 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.

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 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 to take on drug effect, 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 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 < 65 years old. 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.

<u>Drug Interaction</u>
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., EC_{50}) 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.

Hydrochlorothiazide :

Hydrochlorothiazide reaches its maximum plasma concentration 2 to 5 hours after its oral administration. Its bioavailability is about 70%, and its action is unaffected by food intake. Its plasma protein binding range is 40- 70%, and it easily passes through the placenta. It is also excreted in breast milk but does not pass the blood-brain barrier (BBB).

Within 24 hours of the oral administration of hydrochlorothiazide, 55-77% of its dose and 95% of its absorbed dose in the body is excreted as parent drug form through the urine. Its half-life is 5.6-15 hours.

Indication

Kanarb®Plus (Fimasartan Potassium Trihydrate and Hydrochlorothiazide) is indicated for the treatment of mild to moderate hypertension that was not adequately controlled with fimasartan monotherapy.

Recommended Dosage

- Adult Hypertension

The recommended dose is one tablet of Kanarb®Plus once daily with or without food. Whenever possible, it is recommended that Kanarb®Plus be taken at the same time during the day (e.g., morning).
Before starting Kanarb®Plus combination therapy, it is recommended that fimasartan monotherapy be taken. If blood pressure is not adequately controlled with fimasartan 60 mg, Kanarb®Plus combination therapy may be considered according to the following dosage and administration:

- Kanarb®Plus 60mg/12.5 mg: this drug may be administered to patients whose blood pressure is not adequately controlled with fimasartan 60 mg.

- Geriatric Use

No initial dose adjustment is required for elderly patients (age ≤ 70 years).
In the study to compare the pharmacokinetics of elderly healthy volunteers aged 65 years or more and young healthy 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.

- Renal Impairment

No dose adjustment is required for patients with mild to moderate renal impairment (creatinine clearance 30 - 80 mL/min). For patients with severe renal impairment (creatinine clearance < 30 mL/min), Kanarb®Plus should not be administered.

- Hepatic Impairment

No dose adjustment is required for patients with mild hepatic impairment. Kanarb®Plus is not recommended for patients with moderate to severe hepatic impairment.

- Pediatric Use

The safety and efficacy of Kanarb®Plus have not been established in pediatric patients aged 18 years old or younger.

If patients need to take a rest at night, it is desired that Kanarb®Plus be administered in the morning to avoid urination at night.

Mode/Route of Administration

To be taken orally

Contraindications

Kanarb®Plus Tablets is contraindicated in the following patients:

1) Patients who are hypersensitive to any component of this product
2) Patients who are or have been hypersensitive to thiazide diuretics and sulfonamide derived drugs
3) Pregnancy or lactation
4) Patients who have acute or severe renal impairment, receive peritoneal or hemodialysis, or have anuria
5) Patients with moderate to severe hepatic impairment
6) Patients with hepatobiliary obstruction
7) Patients with hyponatremia, hypokalemia, or hypercalcemia
8) Patients with Addison's disease
9) Patients with diabetes or renal impairment (glomerular filtration rate (GFR) <60mL/min) who are taking aliskiren
10) Patients with diabetic nephropathy who are taking angiotensin converting enzyme (ACE) inhibitors
11) Patients with genetic disorders such as galactose intolerance, Lapp lactose deficiency, or glucose- galactose malabsorption (since fimasartan/hydrochlorothiazide tablets contains lactose)

Warnings and Precautions

Drugs directly acting on the renin-angiotensin system may cause injury and even death to the developing fetus when used in pregnancy during the second and third trimesters. When pregnancy is detected, Kanarb®Plus should be discontinued immediately.

Effects on Driving and Operation of Machinery

Effects of Kanarb®Plus on driving and operation of machinery have not been studied. However, drowsiness and dizziness may occur sometimes with blood pressure lowering agents, therefore, patients taking Kanarb®Plus should be warned about these risks when driving or operating machinery.

Patients Requiring Close Monitoring During Kanarb®Plus Tablets Treatment

1) Hypotension and Electrolyte/Volume Imbalance: Symptomatic hypotension may occur in volume- and salt-depleted patients (e.g., high doses of diuretics, restricted dietary salt intake, diarrhea and vomit), particularly, after initiation of treatment or dose 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 dose increase as patients are closely monitored. If symptomatic hypotension occurs, patients should be lied down, and start intravenous fluid treatment, if necessary. The treatment can be resumed after blood pressure is stabilized.
2) Hyperkalemia: Drugs that exert effects on renin-angiotensin system may cause hyperkalemia in patients with congestive heart failure or renal impairment. When Kanarb®Plus is administered to these patients, close monitoring of the serum potassium level is recommended.

3) Renovascular Hypertension: An increase in the levels of serum creatinine and BUN has been reported in patients with uni-lateral or bi-lateral renal artery stenosis when angiotensin II receptor antagonists such as Kanarb®Plus were administered. Although Kanarb®Plus has not been administered to patients with uni-lateral or bi-lateral renal artery stenosis, similar effects may occur.
4) Dual Inhibition of Renin-Angiotensin System: : Drugs inhibiting the renin-angiotensin system, particularly when co-administered with drugs that may affect the rennin-angiotensin system, have been reported to cause changes in the renal function, including acute renal failure in subjects sensitive to these drugs. Therefore, dual inhibition of the renin-angiotensin system, i.e., co-administration of an angiotensin II receptor antagonist and an angiotensin converting enzyme inhibitor, is not generally recommended. If needed, however, treatment can be applied to a limited basis to individuals whose safety has been confirmed.

   There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see *Interactions with Other Medicines and Other Forms of Interaction*). If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE- Inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.
5) Transient Symptomatic Hypotension (carrying shock, loss of consciousness, dyspnea and so on) may occur after treatment with Kanarb®Plus. If these symptoms occur, discontinue the administration and supportive treatment should be applied as appropriate.
6) Hypotension may occur during anaesthetic and operative procedures in patients receiving an angiotensin II receptor antagonist via inhibition of the renin-angiotensin system. Very rarely, severe hypotension may occur, requiring the treatment with intravenous fluid or vasopressors.
7) 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.
8) Diuretic effect of Kanarb®Plus may occur rapidly. Caution needs to be exercised in occurrences of electrolyte imbalance or dehydration, and patients should start with a lower dose followed by a gradual dose increase.
9) Continuous administration of Kanarb®Plus may cause electrolyte imbalance and therefore, periodic examination is recommended.
10) *Effects on Driving and Operation of Machinery*: Effects of Kanarb®Plus on driving and operation of machinery have not been studied. However, drowsiness and dizziness may occur sometimes with blood pressure-lowering agents, therefore, patients taking Kanarb®Plus should be warned about these risks when driving or operating machinery.
11) *Acute Myopia and Secondary Angle-Closure Glaucoma*: Hydrochlorothiazide, a sulfonamide, can cause acute transient myopia and acute angle-closure glaucoma may occur. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for

developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

12) Allergy or hypersensitivity to Tartrazine: Caution is required for patients who have an allergy or are hypersensitive to Tartrazine (FD&C Yellow No.5) (only for Kanarb®Plus 60mg/12.5mg).

Administration in Specific Populations

1) Pediatric
   Safety and effectiveness in pediatric patients (age ≤ 18 years) have not been established.
2) Geriatric
   No initial dose adjustment is required for geriatric patients aged ≤70 years. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant diseases or other drug therapy.
3) Hepatic Impairment
   The pharmacokinetics of fimasartan was compared in patients with mild and moderate hepatic impairment to healthy volunteers. A 20% decrease in AUC and 10% increase in C_{max} were observed in patients with mild hepatic impairment. The AUC and C_{max} in moderate hepatic impairment were increased by 6.5-fold and 5-fold, respectively. Kanarb®Plus Tablets is not recommended to moderate to severe hepatic impairment.

Interactions with Other Medicines and Other Forms of Interaction

Drug Interactions related to Fimasartan

1) *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).
   The blood pressure-lowering effect of fimasartan can be increased when co-administered with other antihypertensive agents, including diuretics. When high doses of diuretics were used previously, leading to a volume-depleted state, excessive blood pressure reduction may occur with the initiation of Fimasartan treatment.
2) *Lithium*: Reversible increases in serum lithium levels and toxicities have been reported when lithium was used with angiotensin converting enzyme inhibitors whereas these reactions have been very rarely reported when angiotensin II receptor antagonists were co-administered with lithium. Although co-administration of lithium with Kanarb®Plus Tablets is not generally recommended, if inevitable, periodic monitoring of lithium levels is required.
3) *Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)*: When an NSAID (e.g., aspirin or COX-2 inhibitor as anti-inflammatory therapy) is co-administered with angiotensin II receptor antagonist, the blood pressure-lowering effect may be reduced. Deterioration of damaged renal function (including acute renal failure, although 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.

4) *Hydrochlorothiazide*: No significant pharmacokinetic drug interaction between fimasartan and hydrochlorothiazide was found when co-administered.
5) *Amlodipine*: No significant pharmacokinetic drug interaction between fimasartan and amlodipine was found when co-administered.
6) Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, syncope, hyperkalaemia, and changes in renal function (including acute renal failure) compared to monotherapy. In general, avoid combined use of RAS inhibitors. Do not co-administer aliskiren with fimasartan in patients with diabetes or renal impairment (GFR < 60mLl/min). Co-administer ACE inhibitors with fimasartan are not recommended and avoid use of ACE inhibitor with fimasartan in patients with diabetic nephropathy.

The Effects of Other Drugs on Fimasartan

1) *Ketoconazole*: The systemic exposure of Fimasartan, as measured by the area under the concentration-time curve (AUC), was increased approximately by two times when co-administered with ketoconazole. Caution needs to be exercised when fimasartan is co-administered with ketoconazole.
2) *Rifampicin* or *OATP1B1 transporter inhibitors*: Fimasartan is a substrate of OAT1 and OATP1B1 transporter. 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 be increased and hence, caution needs to be exercised.

The Effects of Fimasartan on Other Drugs

1) *Warfarin*: The pharmacokinetics and pharmacodynamics of warfarin were not significantly affected by co-administered fimasartan.
2) *Atorvastatin*: Although, the AUC's of atorvastatin and its active metabolite were not significantly affected by co-administered fimasartan, the maximum plasma concentrations (C_{max}) of atorvastatin and its active metabolite were increased by 1.9 and 2.5 times, respectively.
3) *Digoxin*: Although the pharmacokinetics and creatinine clearance level of digoxin were not significantly affected by co-administered fimasartan, the C_{max} of digoxin was increased by 30%. Close monitoring of digoxin level may be required when co-administered with fimasartan.
4) *Other Drug Interactions*: Fimasartan does not inhibit or induce CYP450 enzymes.

Drug Interactions related to Hydrochlorothiazide

1) Prolonged QT interval and ventricular arrhythmia have been reported when other diuretic (furosemide) is co-administered with terfenadine. Therefore co-administration with terfenadine is not recommended. Co-administration with astemizole may also cause prolonged QT interval and ventricular arrhythmia and co-administration with astemizole is not recommended.
2) It has been reported that hydrochlorothiazide reduces reactivity of vessel wall towards amines such as norepinephrine that increase blood pressure, and increases paralysis of tubocurarine and other similar chemicals. Therefore, it is recommended to discontinue the drug temporarily in patients before operation.
3) Increase of orthostatic hypotension has been reported when co-administered with barbiturates or opium alkaloid narcotics, or drinking.
4) The effect of anti-hypertensive agents (other diuretics, anesthetic, and alcohol) may be increased. Co-administration with ACE inhibitors may also increase the anti-hypertensive effects and caution needs to be exercised.
5) Release of potassium may be increased when co-administered with adrenal cortical hormones or adrenocorticotropic hormones. Therefore, caution needs to be exercised.

6) The effect of digitalis on heart may be increased and therefore, caution needs to be exercised when co-administered with digitalis.
7) Reduced excretion of lithium through kidney may cause increased cardiotoxicity and neurotoxicity of lithium. Patients should be closely monitored with controlled doses.
8) Absorption of thiazide diuretics may be inhibited when co-administered with cholestyamine or colestipol.
9) The effect of thiazide diuretic may be reduced when co-administered with NSAIDs (e.g. indomethacin).
10) Ulcer in or stenosis of small intestine may occur when co-administered with potassium chloride.
11) The effect of salicylic acid on the central nervous system may be increased when co-administered with high dose of salicylic acid.
12) Release of calcium may be increased when co-administered with purgatives
13) Excretion of quinidine, an anti-arrythmic agent, may be decreased when co-administered.
14) Severe hypokalemia and bradycardia may occur when co-administered with vincamine, erythromycin IV or sultopride. Co-administration with those drugs is not recommended.
15) Lactic acidosis by metformin may occur. Therefore, co-administration with metformin is not recommended when patients' serum creatinine levels is ≥ 1.5 mg/dL (men) or 1.2 mg/dL (women).
16) Sufficient water supply is required before treatment when co-administered with iodide-containing agents in patients with fluid depletion owing to diuretics.

Use during Pregnancy/Lactation

Pregnancy

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. The use of drugs that act directly on the renin-angiotensin system 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 ductusarteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. When pregnancy is detected, Kanarb®Plus Tablets should be discontinued as soon as possible. These adverse effects 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 so informed. Nonetheless, when patient become pregnant, physicians should advise the patient to discontinue the use of Kanarb®Plus Tablets as soon as possible. Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia.

Thiazide diuretics may cause hyperbilirubinemia and thrombocytopenia in newborn babies or infants. Also, reduction of plasma volume, hemoconcentration and reduction of uteroplacental blood volume may occur due to diuretic effects. Pregnant women at the third trimester may be administered only when the benefits overweigh the risks.

Breast Feeding

It is not known whether or not fimasartan is excreted in human milk, but fimasartan was excreted in the milk of lactating rats; therefore, it is not recommended to administer fimasartan

to nursing mothers. A decision should be made whether to discontinue nursing or discontinue fimasartan, taking into account the importance of the drug to the mother.
Hydrochlorothiazide inhibits milk production and excretion in human milk has been reported. Therefore, administration should be avoided and if inevitable, discontinue nursing.

Adverse Effects/Undesirable Effects

Adverse Reaction Related to Kanarb®Plus Tablets

Of 263 patients with essential hypertension, 175 patients were randomly assigned to Kanarb®Plus Tablets (fimasartan/hydrochlorothiazide combination therapy) and 88 patients to Kanarb® Tablets (fimasartan monotherapy) during the clinical study. Adverse events that have a causal relationship with Kanarb®Plus were mostly mild to moderate, and no severe adverse event has been reported. The most frequently reported adverse events after administration of Kanarb®Plus were nervous system disorders such as dizziness and headache. The adverse events related to Kanarb®Plus are summarized in the table below.

Adverse Reactions for Kanarb®Plus Tablets[1)] in Clinical Experience[†]

System Organ Class Classification	**Frequency**[2)]	**Symptoms**
Nervous System Disorders	Common	Headache, Dizziness, Dizziness postural
	Uncommon	Somnolence
Investigations	Common	ALT[3)] increased
	Uncommon	AST[4)] increased, Blood triglyceride increased, Blood chloride decreased, Blood potassium increased, Blood sodium decreased
Musculoskeletal and Connective Tissue Disorders	Uncommon	Musculoskeletal stiffness
General Disorders and Administration Site Conditions	Uncommon	Chest discomfort, Asthenia
Skin and Subcutaneous Tissue Disorders	Uncommon	Pruritus
Vascular disorders	Uncommon	Flushing
Reproductive System and Breast Disorders	Uncommon	Erectile dysfunction

† Adverse reactions were coded using the Medical Terminology

1) Adverse events whose relationship to Kanarb®Plus Tablets was certain, probable or possible

2) 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 when using available information)
3) ALT = Alanine Aminotransferase
4) AST = Aspartate Aminotransferase

Adverse Reaction Related to Fimasartan
Of 852 patients with essential hypertension, the safety was evaluated in 406 patients who were administered 60-120 mg of fimasartan for 4-12 weeks. Of these patients, 85 patients were administered for 6 months. The observed adverse events were mostly mild to moderate and transient. The occurrence rate was not related to the dose. The most frequently reported adverse events were headache and dizziness. The adverse events considered to be related to fimasartan, reported in the clinical studies of fimasartan, summarized in the table on the next page. The occurrence frequency is defined as follows: 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 using the available information).

Adverse Reactions for Fimasartan[1)] in Clinical Experience

System Organ Class Classification	**Frequency**	**Symptoms**
Nervous System Disorders	Common	Headache, Dizziness
	Uncommon	Syncope, Sedation, Migraine
Gastrointestinal Disorders	Uncommon	Dyspepsia, Vomiting, Nausea, Upper abdominal pain
General Disorders and Administration Site Conditions	Uncommon	Asthenia, Sensation of foreign body
Investigations	Uncommon	Hepatic enzyme (ALT, AST) increased, Platelet count decreased, Blood Creatine phosphokinase increase
Respiratory, Thoracic and Mediastinal disorders	Uncommon	Cough
Musculoskeletal and Connective Tissue Disorders	Uncommon	Muscular twitching, Musculoskeletal stiffness
Skin and Subcutaneous Tissue Disorders	Uncommon	Pruritus, Localized urticaria
Vascular disorders	Uncommon	Hot flush, Flushing
Reproductive System and Breast Disorders	Uncommon	Erection dysfunction

1) Adverse Events that were observed in patients during clinical study whose relationship to Kanarb® was certain, probable, or possible

Adverse Reactions Related to Fimasartan of Postmarketing Experience in Republic of Korea†
As a result of the postmarketing surveillance study conducted in 3,729 subjects during 6 years for re-examination in Republic of Korea, the incidence rate of adverse events regardless of causal relationship was 19.42% (724/3,729 subjects, total 1,043 cases).

Serious adverse events are listed in the table below according to the frequency, and there are no serious adverse drug reactions that cannot exclude causal relationship. Adverse reactions were coded using the WHO-ART (World Health Organization Adverse Reactions Terminology).

Frequency	**System Organ Class Classification**	**Serious Adverse Events** 1.90% (71/3,729 subjects, Total 82 cases)
< 0.1%	Central and Peripheral Nervous System Disorders	Dizziness, Epilepsy, Amyotrophic lateral sclerosis, Radiculopathy, Neuronitis, Paralysis facial, Normal pressure hydrocephalus, Spinal stenosis, Headache
	Gastro-Intestinal System Disorders	Pancreatitis acute, Ileus, Duodenal ulcer haemorrhagic, Appendicitis, Haemorrhoids, Abdominal pain
	Vascular (Extracardiac) Disorders	Haemorrhage intracranial, Transient ischaemic Attack, Atherosclerosis, Cerebral infarction aggravated†, Cerebral haemorrhage
	Neoplasm	Hepatic neoplasm, Colon carcinoma, Neoplasm NOS, Cervical carcinoma, Prostate cancer
	Urinary System Disorders	Renal failure acute, Renal failure chronic, Renal calculus, Pyelonephritis, Urinary incontinence
	Respiratory System Disorders	Rhinitis, Alveolitis fibrosing, Pharyngitis, Pneumonia, Pulmonary disorders
	Body as a Whole General Disorders	Death, Back pain aggravated, Asthenia
	Musculo-Skeletal System Disorders	Osteoarthritis, Arthrosis
	Metabolic and Nutritional Disorders	Hypoglycaemia, Hyperkalaemia

	Platelet, Bleeding and Clotting Disorders	Embolism Pulmonary, Purpura
	Heart Rate and Rhythm Disorders	Bradycardia, Fibrillation atrial
	Myocardial, Endocardial, Pericardial and Valve Disorders	Coronary artery disorder, Aortic stenosis
	Cardiovascular Disorders, General	Cardiac failure, Blood pressure increased
	Liver and Biliary System Disorders	Hepatitis acute
	Endocrine Disorders	Pituitary neoplasm benign
	Resistance Mechanism Disorders	Otitis media
	Reproductive Disorders, Female	Uterine prolapse
	Secondary Terms – Events	Recurrent cancer
≥0.1%, <5%	Vascular (Extracardiac) Disorders	Cerebral infarction
	Musculo-Skeletal System Disorders	Fracture
	Body as a Whole General Disorders	Chest pain

† Adverse reactions were coded using the Medical Terminology.

In addition, unexpected adverse events and unexpected adverse drug reactions that cannot exclude causal relationship are listed in the table below according to the frequency.

Frequency	**System Organ Class Classification**	**Unexpected Adverse Events** 13.14% (490/3,729 subjects, Total 643 cases)	**Unexpected Adverse Drug Reactions** 0.94% (35/3,729 subjects, Total 42 cases)
< 0.1%	Central and Peripheral Nervous System Disorders	Epilepsy, Polyneuropathy, Hemiparesis, Dementia, Parkinson's syndrome, Amyotrophic lateral sclerosis, Walking difficulty, Optic nerve injury, Optic neuritis, Radiculopathy, Neuronitis,	Paraesthesia, Tremor, Spinal stenosis

		Blepharospasm, Paralysis facial, Facial pain, Normal pressure hydrocephalus, Vertebro-Basilar Artery Syndrome†, Restless legs, Optic ischaemic neuropathy	
	Gastro-Intestinal System Disorders	Stomatitis Ulcerative, Peptic ulcer, Tooth ache, Tympanites, Oral haemorrhage, Haemorrhoids, Xerosis, Pancreatitis acute, Colitis, Colonic polyp, Gum pain, Ileus, Duodenal ulcer haemorrhagic, Appendicitis, Periodontitis, Salivation, Melaena	Gastroesophageal reflux, Constipation, Gastroenteriti
	Skin and Appendages Disorders	Rash, Onychomycosis, Dermatitis seborrhoeic, Skin disorder, Keratosis, Diaphoresis, Nail dystrophy, Paronychia, Dermatitis contact, Alopecia, Dermatitis	Rash
	Musculo-Skeletal System Disorders	Osteoarthritis, Muscle weakness, Tenosynovitis, Osteomyelitis, Rotary Cuff syndrome, Lateral epicondylitis†, Synovitis, Ischial neuralgia, Jaw Pain	Arthralgia, Arthrosis, Osteoporosis, Muscle weakness
	Vascular (Extracardiac) Disorders	Haemorrhage intracranial, Transient Ischaemic attack, Atherosclerosis, Cerebral infarction aggravated†,	-

		Cerebral haemorrhage, Arteriosclerosis, Peripheral vascular Disease, Vein varicose	
	Body as a Whole General Disorders	Carpal tunnel syndrome, Tuberculosis pulmonary, Pain axillary, Oedema periorbital, death, Allergy, Chills, Back pain aggravated, Nasal polyp	Oedema, Oedema peripheral
	Respiratory System Disorders	Pneumonia, Pulmonary disorders, Haemoptysis, Rhinitis aggravated, Alveolitis fibrosing, Asthma, Pulmonary granuloma, Chest X-ray abnormal	Pharyngitis, Sputum†, Bronchitis
	Metabolic and Nutritional Disorders	Hypercholesterolaemia, Diabetes mellitus, Hypertriglyceridaemia, Thirst, Diabetes mellitus Aggravated, Calcinosis, Hyponatraemia, Gout	-
	Vision Disorders	Eye pain, Retinal disorder, Glaucoma, Cataract, Diplopia,	Vision abnormal, Retinal disorder, Muscae
	Liver and Biliary System Disorders	Hepatitis acute, Alcoholic liver disease	-
	Application Site Disorders	Inflammation localized, Cellulitis	-
	Platelet, Bleeding and Clotting Disorders	Embolism pulmonary	-
	White Blood Cell and Reticulo-Endothelial System Disorders	Lymphadenopathy	-
	Secondary Terms - Events	Abrasion NOS, Nasal septum deviation, Surgical intervention, Post-operative pain, Heat intolerance, Recurrent cancer,	Post-operative pain

		Fall	
≥0.1%, <5%	Body as a Whole - General Disorders	Chest pain, Back pain, Oedema, Pain in limb, Oedema Peripheral, Face Oedema, Fatigue, Fever	-
	Musculo-skeletal System Disorders	Pain neck/shoulder, Fracture, Arthralgia, Arthrosis, Osteoporosis, Myalgia	-
	Respiratory System Disorders	Pharyngitis, Upper respiratory tract infection, Sputum†, Rhinitis, Epistaxis, Bronchitis	-
	Central and Peripheral Nervous System Disorders	Paraesthesia, Numbness, Tremor, Spinal stenosis, Hypertonia	-
	Psychiatric Disorders	Insomnia, Depression, Anxiety, Memory impairment, Anorexia	-
	Gastro-Intestinal System Disorders	Gastroesophageal reflux, Gastritis, Diarrhoea, Constipation, Intestinal functional disorder, Gastroenteritis	Gastritis
	Urinary System Disorders	Micturition frequency, Urinary incontinence, Renal calculus, Renal failure chronic, Difficulty in micturition	-
	Metabolic and	Hyperlipaemia, Dyslipidaemia,	-
	Nutritional Disorders	Hypoglycaemia	
	Vascular (Extracardiac) Disorders	Cerebral infarction	-
	Resistance Mechanism Disorders	Herpes zoster	-
	Vision Disorders	Vision abnormal	-
	Heart Rate and Rhythm Disorders	Tachycardia	-
	Cardiovascular Disorders, General	Blood pressure increased	Blood pressure increased

	Platelet, Bleeding and Clotting Disorders	Purpura	-
	Liver and Biliary System Disorders	Liver fatty	-

† Adverse reactions were coded using the Medical Terminology.

Adverse Reaction Related to Hydrochlorothiazide

1) Metabolism: Electrolyte imbalances such as hypokalemia, hyponatremia, hypomagnesemia, hypochloremic alkalosis, and hypercalcemia may occur, and hence, caution needs to be exercised. As hyperuricemia and hyperglycemia may occur as well, close monitoring is required. In occurrence of these adverse reactions, appropriate actions such as reduction of dose or discontinuation of the medication should be taken. Gout, increase of cholesterol and neutral fat may also occur.
2) Blood: Hematologic disorders such as thrombocytopenia, leukopenia, aplastic anemia, hemolytic anemia, and purpura may rarely occur. Close monitoring is required and administration should be discontinued when the reaction is observed.
3) Digestive System: Anorexia, nausea, vomiting, thirst, abdominal discomfort, constipation, gnawing pain on abdomen, pancreatitis, diarrhea, sialadenitis, dry mouth and gastralgia may rarely occur.
4) Psychiatric and Nervous System: Dizziness, headache, fatigue, drowsiness and apathy may occur.
5) Respiratory System: Respiratory distress including pneumonitis and pulmonary oedema may rarely occur. In occurrence of these adverse reactions, administration should be discontinued.
6) Vascular System: Palpitation, occasionally orthostatic hypotension and rarely arrhythmia may occur.
7) Eye: Visual disturbances such as blurred vision and xanthopsis may rarely occur. Acute myopia and acute angle-closure glaucoma may occur.
8) Liver: Jaundice, hepatitis, and acute cholecytitis may rarely occur.
9) Hypersensitivity: Necrotizing vasculitis, dyspnea, rash, urticaria, facial flush, photosensitivity and anaphylaxis may occur. In occurrence of these adverse reactions, administration should be discontinued.
10) Kidney: Elevation of BUN (blood urea nitrogen): creatinine level, acute renal failure and interstitial nephritis may occur.
11) Others: Occasionally malaise, nasal obstruction (stuffy nose), impotence, and rarely hypoparathyroidism with worsening of SLE (Systemic Lupus Erythematosus) and hypercalcemia, and muscle cramp may occur. Paresthesia may also occur.

Overdose and Treatment

No data is available on overdosage of Kanarb®Plus in humans. The most likely manifestations of overdose of fimasartan would be hypotension and tachycardia; bradycardia may occur from parasympathetic (vagal) stimulation. The most likely manifestations of overdose of hydrochlorothiazide would be depletion of electrolytes (hypokalemia, hypochloremia, and hyponatremia) and dehydration resulting from excessive diuresis. The most common signs and symptoms caused by overdosage are nausea and lethargy. If digitalis has been co-administered, hypokalemia may worsen to cardiac arrhythmias. It is not known whether or not

fimasartan can be removed by hemodialysis. As well, the degree of hydrochlorothiazide removal by hemodialysis has not been reported.
Patients should be closely monitored when overdosed. If symptoms occur, appropriate actions should be taken. Induced vomiting or gastric lavage may be one of measures, and use of active carbon may be helpful. Serum electrolytes and creatinine levels should be frequently monitored, and in case of hypotension, the patient should be lied down and salt and fluid should be supplied immediately.

Incompatibilities (for injections only)

Not Applicable

Storage Condition

1) Kanarb®Plus Tablets should be in tightly closed container. It is recommended that Kanarb®Plus Tablets should be stored at room temperature (store at or below 30°C) in a light-protected container.
2) Kanarb®Plus Tablets should be stored in a place a child cannot reach.
3) Repackaging of Kanarb®Plus Tablets is not recommended because it may cause some accidental mislabelling or adversely affect the product quality.

Dosage Forms or Presentation

60mg/12.5mg 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, Jongno-gu, Seoul, Korea

Manufacturer:

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

Date of Revision of Package Insert

20 April, 2022