Kanarb®

Fimasartan Potassium trihydrate/ Fimasartan (60 mg, 120 mg)

What is in this leaflet

1. What Kanarb® is used for

Kanarb® (Fimasartan potassium trihydrate) is indicated for the treatment of essential hypertension.

2. How Kanarb® works

Kanarb® is an angiotensin II receptor antagonist, which selectively binds to the AT_1 receptor with a high affinity, giving very potent anti-hypertensive effect.

3. Before you use Kanarb®

- *When you must not use it*

Kanarb® is contraindicated in the following patients:

a) Patients who are hypersensitive to any component in this product
b) Pregnant or nursing mothers
c) Hemodialysis patients (no experience in this population)
d) Patients with moderate to severe hepatic impairment
e) Patients with hepatobiliary obstruction
f) Patients with diabetes or renal impairment (GFR <60 mL/min) who are taking aliskiren
g) Patients with diabetic nephropathy who are taking angiotensin converting enzyme (ACE) inhibitors
h) Patients with genetic disorders such as galactose intolerance, Lapp lactose deficiency, or glucose-galactose malabsorption (since Kanarb® contains lactose)
i) Drugs directly acting on the rennin-angiotensin system may cause injury or death to the developing fetus when administered to a pregnant woman during the second and third trimesters. Therefore, Kanarb® should be discontinued when pregnancy is detected in female patients.

- *Taking other medicines*

a) ***Potassium supplements and potassium-sparing diuretics*:** Serum potassium can be increased by Kanarb® and other drugs that exert effects on the renin-angiotensin system when co-administered with potassium-sparing diuretics (e.g., spirinolactone), potassium supplements, salt alternatives containing potassium, and drugs that may increase serum potassium (e.g., heparin).

b) The blood pressure-lowering effect of Kanarb® 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 Kanarb® treatment.

c) ***Lithium*:** Reversible increases in serum lithium levels and toxicities have been reported when lithium was used with angiotensin converting enzyme inhibitors whereas those reactions have been very rarely reported in case that angiotensin II receptor antagonists were co-administered with lithium. Although co-administration of lithium with Kanarb® is not generally recommended, should it be necessary, close monitoring of lithium levels is required.

d) ***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, 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 Kanarb® with NSAIDs, especially in elderly patients. Adequate hydration is required in this case, and the renal function should be closely monitored.

e) ***Hydrochlorothiazide*:** No significant pharmacokinetic drug interaction between Kanarb® and hydrochlorothiazide was found when co-administered.

f) ***Amlodipine*:** No significant pharmacokinetic drug interaction between Kanarb® and amlodipine was found when co-administered.

g) Dual blockade of the 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, avoid combined use of RAS inhibitors. Do not co-administer aliskiren with Kanarb® in patients with diabetes or renal impairment (GFR <60 mL/min). Co-adminiater ACE inhibitors with Kanarb® is not recommended and avoid use of ACE inhibitor with Kanarb® in patients with diabetic nephropathy.

The effects of other drugs on Kanarb®

a) ***Ketoconazole*:** The systemic exposure of Kanarb®, 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 Kanarb® is co-administered with ketoconazole.

b) ***Rifampicin or other OATP1B1 transporter inhibitors*:** Kanarb® is a substrate of OAT1 and OATP1B1. When Kanarb® is co-administered with rifampicin (OATP1B1 inhibitor), the AUC of Kanarb® was increased approximately by 4.6- fold. Therefore, co-administration of Kanarb® with rifampicin is not

recommended. When co-administered with other OATP1B1 transporter inhibitors (e.g., cyclosporine), the systemic exposure of Kanarb® may increase, and caution is required.

The effects of Kanarb® on other drugs

a) ***Warfarin*:** The pharmacokinetics and pharmacodynamics of warfarin were not significantly affected by co-administered Kanarb®.

b) ***Atorvastatin*:** The AUC's of atorvastatin and its active metabolite were not affected by co-administered Kanarb®. Maximum plasma concentrations (Cmax) of atorvastatin and its active metabolite were increased by 1.9-fold and 2.5-fold, respectively.

c) ***Digoxin*:** The pharmacokinetics and creatinine clearance of digoxin was not affected by co-administered Kanarb®. Cmax of digoxin was increase by 30%. Close monitoring of digoxin level may be required when co-administered with Kanarb®.

d) ***Other drug interactions*:** Kanarb® does not inhibit or induce the CYP450 enzymes.

4. How to use Kanarb®

- *How much to use*

Adult Hypertension

The recommended initial dose of Kanarb® is 60 mg once daily with or without food. If blood pressure is not adequately controlled at 60 mg, the dosage of Kanarb® may be increased to 120 mg once daily. Whenever possible, it is recommended that Kanarb® be taken at the same time during the day (e.g., morning).

The blood pressure lowering effect of Kanarb® is substantially present within 2 weeks, and maximal reduction is generally attained after 8 to 12 weeks of treatment.

Geriatric Use

No initial dosage adjustment is required for elderly patients (age ≤ 70 years).

Renal Impairment

No initial dosage adjustment is required for patients 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.

Hepatic Impairment

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

Pediatric Use

The efficacy and safety of Kanarb® has not been established in patients18 years or younger.

Intravascular Volume-Depleted Patients (e.g., Patients receiving high doses of diuretics)

For patients whose intravascular volume is depleted, at risk for symptomatic hypotension, the initial dose of 30 mg once daily is recommended**.**

- *If you use too much (overdose)*

No data are available about overdosage of Kanarb® 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 Kanarb® is removed from the plasma by hemodialysis.

5. While you are using it

- *Things to be careful of*

ADMINISTRATION IN SPECIFIC POPULATIONS

a) Pregnant mothers

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® 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® 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.

b) Nursing mothers

It is not known whether Kanarb® is excreted in human milk, but Kanarb® was excreted in the milk of lactating rats; therefore, it is not recommended to administer Kanarb® to nursing mothers. A decision should be made whether to discontinue nursing or discontinue Kanarb®, taking into account the importance of the drug to the mother.

c) Pediatric Use

Safety and effectiveness in pediatric patients (age ≤ 18 years) have not been established.

d) Geriatric Use

Kanarb® has not been administered to elderly patients more than 70 years old. In a study to compare the

pharmacokinetics of elderly healthy volunteers aged 65 years or more and young, healthy volunteers, the AUC of Kanarb® 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 Kanarb® in Phase 3 clinical trials, between the elderly and non-elderly populations. Therefore, no dosage adjustment with Kanarb® is necessary in elderly patients (≤ 70 years), although greater sensitivity of some older individuals cannot be ruled out.

e) Hepatic Impairment Use

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 Cmax were observed in patients with mild hepatic impairment. The AUC and Cmax in moderate hepatic impairment were increased by 6.5-fold and 5-fold, respectively. Kanarb® is not recommended to moderate to severe hepatic impairment.

Patients Requiring Close Monitoring During Kanarb® Treatment

a) ***Intravascular volume- or salt-depletion*:** These patients (e.g., patients receiving high doses of diuretics), whose rennin angiotensin system is activated, may experience symptomatic hypotension at the time of initial Kanarb® administration or its dosage increase. Therefore, close monitoring is required in these patients.

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

c) ***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 the rennin angiotensin system are administered.

d) Special caution is required for patients with *aortic* or *mitral valve stenosis*, *obstructive* or *hypertrophic cardiac myopathy* like other vasodilators.

e) Patients with primary aldosteronism generally do not respond to the drugs that inhibit the renin- angiotensin system, therefore Kanarb® is not recommended in this population.

f) ***Allergy or hypersensitivity to tartrazin***: Caution is required for patients who have an allergy or are hypersensitive to tartrazine (Food Yellow No.5)(only for Kanarb® 60 mg)

g) ***Allergy or hypersensitivity to Sunset Yellow FCF:*** Caution is required for patients who have an allergy or are hypersensitive to Sunset Yellow FCF (Food Yellow No.6)(only for Kanarb30mg and 120mg)

6. Side effects

a) ***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), especially after initiation of therapy with Kanarb® or its dosage increase. Volume- and salt-depletion should be corrected before Kanarb® treatment is initiated or patients should be started with a lower dose, followed by a gradual dosage increase and close monitoring. If symptomatic hypotension occurs, patients should lay down flat, and start intravenous fluid therapy when necessary. Kanarb® treatment can be resumed after blood pressure is stabilized.

b) ***Hyperkalemia*:**
Drugs that exert effects on the renin-angiotensin system may cause hyperpotassemia to patients with congestive heart failure or renal impairment. When Kanarb® is administered to these patients, close monitoring of the serum potassium level is recommended.

c) ***Renovascular hypertension*:**
The 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 Kanarb®. Although Kanarb® has not been administered to patients with uni-lateral or bi-lateral renovascular hypertension, similar effects may occur**.**

d) ***Dual Blockade of the renin-angiotensin system*:**
Drugs Blockade 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 patients sensitive to these drugs. Therefore, dual blockade of the renin-angiotensin system, i.e., co-administration of an angiotensin II receptor antagonist and angiotensin converting enzyme inhibitor is not generally recommended. Closely monitor blood pressure, renal function in patients on Kanarb® and other agents that affect the renin- angiotensin system.

e) ***Transient symptomatic hypotension***(e.g., shock, loss of consciousness, dyspnea) may occur after Kanarb® treatment. If these symptoms occur, *discontinue the*

drug and supportive treatment should be applied as appropriate.

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

g) 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 populations.

h) ***Effects on driving and the operation of machinery:*** The effects of Kanarb® on driving and the operation of machinery have not been studied. However, drowsiness and dizziness may occur sometimes with blood pressure-lowering agents, therefore patients taking Kanarb® should be warned about these risks when driving or operating machinery is anticipated.

You may report any side effects or adverse drug reactions directly to the National Centre for Adverse Drug Reaction Monitoring by visiting the website npra.gov.my [*Consumers → Reporting Side Effects to Medicines (ConSERF) or Vaccines (AEFI)*].

7. Storage and Disposal of Kanarb®

- *Storage*

- Kanarb® should be stored in a place a child cannot reach.
- Repackaging of Kanarb® is not recommended because it may cause some accidental mislabeling or adversely affect the product quality.

8. Product Description

- *What it looks like*

- **60 mg**: A yellow hexagonal biconvex film-coated tablet, debossed with 'FMS6' on front and 'B | R' on the back side.

120 mg: An orange hexagonal biconvex film-coated tablet, debossed with'FMS12' on front and 'B | R' on the back side.

Ingredients

- Active ingredient(s):

Fimasartan potassium trihydrate

- Inactive ingredients:

Lactose Monohydrate, Microcrystalline Cellulose, Croscarmellose Sodium, Hydroxypropyl Cellulose, Magnesium Stearate, Opadry® 03B62599, Carnauba Wax, Purified Water

MAL number:

Kanarb Film-Coated Tablets 60mg – MAL18026063ARZ

Kanarb Film-Coated Tablets 120mg – MAL18026065ARZ

9. Manufacturer and Product Registration Holder

Manufacturer

Boryung Corporation
107, 109, Neungan-ro, Danwon-gu, Ansan-si, Gyeonggi-do, Republic of Korea

Product Registration Holder:

Zuellig Pharma Sdn Bhd
No 15, Persiaran Pasak Bumi, Seksyen U8, Perindustrian Bukit Jelutong, 40150, Shah Alam, Selangor.

10. Date of revision:

20 April 2022

Serial Number

NPRA (R1/2) 02122022/322