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Report on Investigational Drugs

Fimasartan, a Novel Angiotensin II Receptor Antagonist

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Fimasartan (Kanarb®), an angiotensin II receptor antagonist with selectivity for the AT1 receptor subtype, is a pyrimidinone-related heterocyclic compound that was developed by Boryung Pharm. Co., Ltd. Among numerous synthetic derivatives, fimasartan was chosen as a new drug candidate through *in vitro* and *in vivo* screening studies. Pharmadynamic-pharmacokinetic properties and safety profiles were determined in a series of nonclinical and clinical studies. Fimasartan is a new angiotensin receptor blocker, and the first new molecular entity acting on cardiovascular system approved by Korean Food and Drug Administration for the treatment of essential hypertension in September 2010. Further development process for combination therapy and overseas registration is currently ongoing.

Hypertension is a chronic disease associated with significant cardiovascular morbidity and mortality. Despite the effectiveness of various medications, hypertension still remains inadequately controlled, with only 43.6% of patients who are diagnosed to be hypertension and 69.7% of patients who receive treatment successfully achieving the goals for systolic and diastolic blood pressure (KNHNES, 2011).

The renin-angiotensin system (RAS) is an important regulator of blood pressure and fluid-electrolyte homeostasis, the alterations of endothelial function, vascular reactivity, fibrosis, tissue remodeling, oxidative stress and inflammation which may predispose to the development of cardiovascular disease. Among classes currently available to reduce blood pressure, agents that modulate the RAS are most commonly chosen as the first drug or in combination therapy because of the efficacy and lower side effect profile (Volpe and Savoia, 2012) (Fig. 1). The concept of treating hypertension and congestive heart failure by a specific blockade of RAS was first established with the use of saralasin, a peptidic antagonist of angiotensin II receptors. However, saralasin had to be administered intravenously because it is a peptide, and had some partial agonistic and angiotensin II-like effects at higher doses (Burnier, 2001). The involvement of RAS in various pathological cardiovascular conditions including hypertension has also been shown by the introduction of angiotensin converting enzyme (ACE) inhibitors (Antonaccio and Wright, 1987) and ACE inhibitors are recognized as an effective therapeutics for the treatment of these conditions. However, ACE inhibitors increase the blood bradykinin levels and contribute to the side effects such as angioedema or dry cough (Wood et al., 1987). Orally active, nonpeptide Angiotensin Receptor Blockers (ARBs) represent today the best-tolerated and rational option to inhibit RAS activity since they selectively block the coupling of angiotensin II (Ang II) to type 1 angiotensin II receptor (AT1R) (Volpe and Savoia, 2012). Until recently, eight ARBs were approved: losartan (Cozzar®, Merck), valsartan (Diovan®, Norvatis), telmisartan (Micardis®, Boerhinger Ingelheim), eprosartan (Teveten®, Abbott), irbesartan (Avapro®, Bristol-Myers Squibb/Sanofi), candesartan (Atacand®, AstraZeneca), olmesartan (Benicar®, Daiichi Sankyo), and azilsartan (Edarbi®, Takeda). Among them, all except for azilsartan were registered in Korea.

Fimasartan is a new addition to the ARB class of

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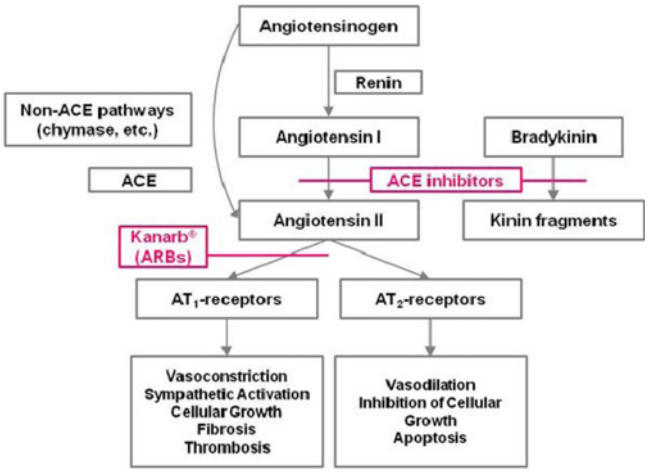
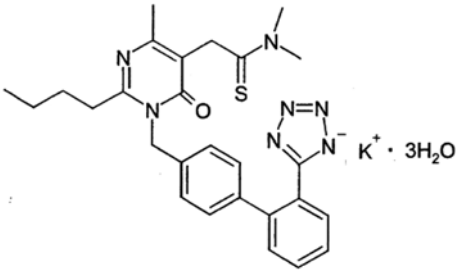


Fig. 1. Mechanism of action of fimasartan (Kanarb®).

antihypertensive drugs. It was successfully approved by the Korean Food and Drug Administration (KFDA) for hypertension management in September 2010 as 60 mg and 120 mg film coated tablets with the brand name of Kanarb®, which means Khan or ruler of ARBs.

Fig. 2 shows the chemical structure of fimasartan. Its chemical name is 2-butyl-5-dimethylaminothiocarbonylmethyl-6-methyl-3-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl] pyrimidin-4(3*H*)-one potassium trihydrate with molecular weight of 593.79, which is the replacement of imidazole ring of losartan, the first drug developed in ARB class, with pyrimidinone moiety tethered with biphenyl tetrazole at its 3-position (Kim et al., 2012). Hundreds of pyrimidin-4(3*H*)-one derivatives were designed, synthesized, and evaluated for their biological activity through *in vitro* and *in vivo* screeing tests. Among them, fimasartan was finally chosen as a candidate for the development of a new antihypertensive drug.

The potassium salt and trihydrate are used in the product formulation of fimasartan. This salt is freely soluble in methanol and ethanol, slightly soluble in acetone and acetonitrile, very slightly soluble in water,



Molecular formula: **$C_{27}H_{30}N_7OS{\cdot}K{\cdot}3H_2O$ ($C_{27}H_{36}N_7O_4S{\cdot}K$)**
Molecular weight: **593.79**

Fig. 2. Chemical structure of fimasartan.

and practically insoluble in isopropyl alcohol and ether.

Fimasartan is a selective AT1 receptor antagonist. The concentration that inhibits the binding of [^{125}I]Ang II to the AT1 receptor from rat adrenal cortex by 50% (IC_{50}) was 0.13 nM, compared with 80.0 nM for losartan (Kim et al., 2012). Fimasartan showed superior inhibitory activity in the contraction of isolated rabbit thoracic aorta compared to other ARBs such as losartan and candesartan. In various animal models including renal hypertensive rats, spontaneously hypertensive rats and Beagle dogs, fimasartan effectively reduced blood pressure in a dose-dependent manner following single or repeated oral and intravenous administration. These pharmacological evidences convinced the possibility of a new antihypertensive drug development. Fimasartan did not affect general behavior, respiratory rate or tidal volume in experimental animals, and showed no adverse findings in the human ether-a-go-go-related gene (hERG) test or monkey telemetry study. A number of general toxicity, carcinogenic toxicity, genetic toxicity, and developmental toxicity studies given either orally or intravenously in various species including mice, rats, monkeys and dogs were conducted and these preclinical results demonstrated the safety and tolerability of fimasartan for long-term clinical use and offered sufficient safety margins to support the expected human therapeutic dose.

In 'first-time-in-human' phase I clinical studies, the safety and tolerability and the pharmacokinetic profiles of fimasartan in humans were demonstrated, and pharmacodynamic changes specific to ARBs were investigated. These results confirmed the mechanism of action of fimasartan in humans which has been previously shown in animal studies.

Fimasartan was rapidly absorbed following oral administration with the time to peak plasma concentration (T_{max}) ranging 0.5-3 h and the terminal half-life ($t_{1/2}$) being 5-16 h at doses of 20 to 480 mg in healthy subjects. Similar results were obtained in patients with hypertension, i.e., T_{max} ranged 0.5-1.3 h and $t_{1/2}$ was 7-10 h following fimasartan administration at doses 20-180 mg in the subsequent phase II study. Fimasartan showed linear first-order pharmacokinetic profiles over the dose range. The urinary excretion of fimasartan was low, with the overall urinary excretion of unchanged drug over the first 24 h after dosing being less than 3% of the administered dose. In addition, the major circulating moiety in human plasma was unchanged fimasartan. These results suggest that fimasartan undergoes non-renal elimination with minimal metabolism, which is consistent with the preclinical findings that most of orally absorbed fimasartan is excreted unchanged in

bile (Chi et al., 2011). Accumulation Indeces of fimasartan following repeated administration, based on AUCT, was 1.24-1.30 for healthy subjects and 1.02-1.08 for hypertensive patients.

To meet the regulatory requirements for approval of an antihypertensive treatment, two phase II explorative clinical studies were conducted to evaluate the efficacy and tolerability of fimasartan, to determine its dose-response relationship and minimum effective dose, and to characterize its blood pressure reduction profile over the dosing intervals in male or non-childbearing female Korean patients aged 18 to 65 years with essential hypertension. Within the dose range of 20 to 240 mg, once-daily oral administration of fimasartan was well tolerated and efficacious in reducing BP in Korean hypertensive patient populations. There were no significant differences between fimasartan and placebo in terms of the proportions of patients experiencing treatment-emergent adverse events (TEAEs) and TEAEs considered drug-related were less common in the fimasartan group (Lee et al., 2012a).

Based on these results, 60 mg and 120 mg were selected as the therapeutic doses in subsequent clinical studies, and a non-inferiority, phase III confirmatory clinical study was conducted using losartan as a comparator. Five hundred six patients were randomly allocated to receive either fimasartan 60/120 (n = 256) or losartan 50/100 (n = 250) with optional titration. Antihypertensive efficacy and tolerability were evaluated for 12 weeks and patients whose blood pressure had reached goal levels participated in a 24-week extension study for additional assessment of tolerability and efficacy. The primary efficacy endpoint, the changes in mean sitting diastolic blood pressure (siDBP) from baseline after 12 weeks of treatment were −11.26 mm Hg and −8.56 mm Hg in the fimasartan and losartan group, respectively. The between-group difference was 2.70 mm Hg, favoring the fimasartan group (p = 0.0002), and the lower limit of the 2-sided 95% confidence interval (CI) (1.27 mm Hg) was higher than the prespecified non-inferiority margin (−2.5 mm Hg). The difference between fimasartan and losartan was also statistically significant at weeks 4 and 8 ($p < 0.0001$), and maintained throughout the additional 12-week extension study. The safety profile was similar as seen in healthy subjects in phase I clinical study, and there was no statistically significant differences between the two drugs in the incidence of adverse events (AEs) and proportions related to the treatments. Frequently observed AEs that had a suggestive causal relationship with the treatments were dizziness (2.75%) and headache (2.35%) in the fimasartan group, whereas headache (4.4%), dizziness (2.8%), and nausea (1.2%) in the losartan group. Three and five serious AEs occurred in each group, but these events were not related to the study drugs (Lee et al., 2012b). In conclusion, fimasartan is an effective and well-tolerated antihypertensive agent that can be administered once daily, and may become a preferred option for the treatment of patients with hypertension.

The antihypertensive effect of fimasartan was also verified to be maintained for 24 h in a separate clinical study using 24-h ambulatory blood pressure monitoring (ABPM), providing the basis for dosing interval of once a day. Moreover, additional pharmaceutical and clinical information was collected sufficiently from other clinical studies including bioavailability study of formulations used during development stages, pharmacokinetic studies in the elderly, food effect, and several drug-drug interactions (DDIs) with drugs commonly used in hypertensive patients or known to possibly affect metabolism of fimasartan. These evidences gave the scientific basis of labeling for concomitant medications.

Efforts on fimasartan to collect additional safety and efficacy data are continuously being conducted through post market surveillances (PMS) and studies on combination therapy and other cardiovascular indications. Furthermore, fimasartan is on the course of the overseas development process and being reviewed by worldwide licensing partners.

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REFERENCES

Antonaccio, M. J. and Wright, J. J., Enzyme inhibitors of the renin-angiotensin system. *Prog. Drug Res.,* 31, 161-191 (1987).

Burnier, M., Angiotensin II type 1 receptor blockers. *Circulation,* 103, 904-912 (2001).

Chi, Y. H., Lee, H., Paik, S. H., Lee, J. H., Yoo, B. W., Kim, J. H., Than, H. K., and Kim, S. L., Safety, tolerability, pharmacokinetics, and pharmacodynamics of fimasartan following single and repeated oral administration in the fasted and fed states in healthy subjects. *Am. J. Cardiovasc. Drugs.* 11, 335-346 (2011).

Kim, T. W., Yoo, B. W., Lee, J. K., Kim, J. H., Lee, K. T., Chi, Y. H., and Lee, J. Y., Synthesis and antihypertensive activity of pyrimidin-4(3H)-one derivatives as losartan analogue for new angiotensin II receptor type 1 (AT1) antagonists. *Bioorg. Med. Chem. Lett.,* 22, 1649-1654 (2012).

KNHNES. The First-year Report of the Fifth Korea National Health and Nutrition Examination Surveys (2011).

Lee, H., Yang, H. M., Lee, H. Y., Kim, J. J., Choi, D. J., Seung, K. B., Jeon, E. S., Ha, J. W., Rim, S. J., Park, J. B., Shin, J. H., and Oh, B. H., Efficacy and tolerability of once-daily oral fimasartan 20 to 240 mg/d in korean patients with hypertension: Findings from two phase II, randomized, double-blind, placebo-controlled studies. *Clin. Ther*., 34, 1273-1289 (2012a).

Lee, S. E., Kim, Y. J., Lee, H. Y., Yang, H. M., Park, C. G., Kim, J. J., Kim, S. K., Rhee, M. Y., and Oh, B. H., Efficacy and tolerability of fimasartan, a new angiotensin receptor blocker, compared with losartan (50/100 mg): a 12-week, phase III, multicenter, prospective, randomized, double-blind, parallel-group, dose escalation clinical trial with an optional 12-week extension phase in adult Korean patients with mild-to-moderate hypertension. *Clin. Ther.,* 34, 552-568 (2012b).

Volpe, M. and Savoia, C., New treatment options in the management of hypertension: appraising the potential role of azilsartan medoxomil. *Integr. Blood Press. Control*, 5, 19-25 (2012).

Wood, S. M., Mann, R. D., and Rawlins, M. D., Angio-oedema and urticaria associated with angiotensin converting enzyme inhibitors. *Br. Med. J*., 294, 91-92 (1987).

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Main Research Areas
Development of new antihypertensive drugs
Development of new anticancer drugs
Development of new drugs for immune-related disease