21 December 2012

Press Release

Nippon Boehringer Ingelheim Co., Ltd.
Astellas Pharma Inc.

Approval for Manufacturing and Marketing of "Micamlo® Combination Tablets BP," an Antihypertensive Drug

- The first combination drug of a high-dose ARB and a long acting CCB with a powerful antihypertensive effect lasting for 24 hours in Japan -

Tokyo, Japan, December 21, 2012 – Nippon Boehringer Ingelheim Co., Ltd. (Headquarters: Shinagawa-ku, Tokyo; President: Yoshiaki Aono; hereinafter "NBI") and Astellas Pharma Inc. (Tokyo:4503, Headquarters: Chuo-ku, Tokyo; President & CEO: Yoshihiko Hatanaka; hereinafter "Astellas") today announced that they have obtained approval for manufacturing and marketing of "Micamlo® Combination Tablets BP," a combination drug of telmisartan 80 mg, a long-acting angiotensin II type 1 (AT_1) receptor blocker (ARB), and amlodipine 5 mg, a long-acting calcium channel blocker (CCB).

"Micamlo® Combination Tablets BP" is the first combination drug of high dose ARB and CCB in Japan. While "Micamlo® Combination Tablets AP" is a combination drug of telmisartan 40 mg and amlodipine 5 mg, the amount of telmisartan in "Micamlo® Combination Tablets BP" has been increased to 80 mg. This is, therefore, expected to maintain a more potent antihypertensive effect for 24 hours compared with that of the conventional ARB/CCB combination drug.

"Micamlo® Combination Tablets BP" can be, in principle, administered when blood pressure is not adequately controlled by any one of treatments with "telmisartan 80 mg in combination with amlodipine 5 mg," "telmisartan 80 mg," "telmisartan 40 mg in combination with amlodipine 5 mg," or "Micamlo® Combination Tablets AP."

In a Phase III clinical study of "Micamlo® Combination Tablets BP" conducted in Japan,

173 patients analysed with essential hypertension not having achieved a blood pressure control target (diastolic blood pressure ≥ 90 mmHg) with telmisartan 80 mg/day were randomized into either the “Micamlo® Combination Tablets BP”/day or telmisartan 80 mg/day group and received the treatment for 8 weeks. The results showed that systolic blood pressure decreased from baseline by 3.5 mmHg in the telmisartan 80 mg/day group and 18.4 mmHg in the “Micamlo® Combination Tablets BP”/day group. The difference in the decrease in blood pressure between the two groups was 14.9 mmHg; therefore, a potent antihypertensive effect of “Micamlo® Combination Tablets BP” was demonstrated. In addition, diastolic blood pressure decreased by 3.1 mmHg in the telmisartan 80 mg/day group and 12.3 mmHg in the “Micamlo® Combination Tablets BP”/day group. The difference in the decrease in blood pressure between the two groups was 9.1 mmHg, showing a potent antihypertensive effect of “Micamlo® Combination Tablets BP[1].”

In a Japanese long-term study, 255 patients analysed and received “Micamlo® Combination Tablets AP” for 6 weeks. Treatment with “Micamlo® Combination Tablets AP” was continued in patients whose diastolic blood pressure lowered to < 90 mmHg and was switched to “Micamlo® Combination Tablets BP” and continued for 8 weeks in patients who did not achieve a blood pressure control target (diastolic blood pressure ≥ 90 mmHg). Thereafter, dosage changes and co-administration with other drugs were permitted, and the treatment was continued further for 40 weeks. The results revealed that systolic blood pressure decreased by 6.9 mmHg at Week 8 and 8.6 mmHg at Week 48 in the “Micamlo® Combination Tablets BP” group; thus, it demonstrated a potent antihypertensive effect. Diastolic blood pressure also decreased by 5.2 mmHg at Week 8 and 7.3 mmHg at Week 48, showing a potent antihypertensive effect[2].

In an overseas Phase III clinical study, 562 patients analysed with stage I to II essential hypertension (diastolic blood pressure of ≥ 95 to ≤ 119 mmHg), in whom ambulatory blood pressure monitoring (ABPM) could be performed, were randomized into any one of 4 x 4 groups, telmisartan 0, 20, 40 or 80 mg/day in combination with amlodipine 0, 2.5, 5 or 10 mg/day, and received the treatment for 8 weeks. The results demonstrated that more potent antihypertensive effects lasted for 24 hours in the telmisartan 80 mg/day in combination with amlodipine 5 mg/day group[3] than in telmisartan 80 mg/day group.

In all Japanese clinical studies, 869 patients received telmisartan/amlodipine 40 mg/5 mg or 80 mg/5 mg, and adverse drug reactions including abnormal laboratory values occurred in 3.0% (26/869) of them. Main adverse drug reactions included dizziness (0.5%, 4/869) and dizziness postural (0.3%, 3/869)[4].

With the existing telmisartan drugs, “Micardis® Tablets 20 mg/40 mg/80 mg,” “Micombi® Combination Tablets AP/BP,” a combination drugs of telmisartan and hydrochlorothiazide (HCTZ) diuretic of the thiazide class, and “Micamlo® Combination Tablets AP,” a combination drug of telmisartan and long-acting CCB amlodipine, “Micamlo® Combination Tablets BP”, obtained approval for manufacturing and marketing today, constitutes the Micardis® family.

As in the previous cases for the telmisartan drugs, “Micamlo® Combination Tablets BP” will be manufactured by NBI, distributed by Astellas, and co-promoted by the two companies. They remain committed to continuously maximising the value of Micardis® family products and further contributing to hypertension treatment.

The following is a summary of the approval:

Date of approval: 21/December/2012

Product name: Micamlo® Combination Tablets BP

Generic name: Telmisartan/ amlodipine besylate

Specification/content: "Micamlo® Combination Tablets BP:"

Each tablet contains telmisartan 80 mg/ amlodipine besylate 6.93 mg (5 mg of amlodipine).

Indication: Hypertension

Dosage and administration: Usually for adults, this fixed dose combination (telmisartan/amlodipine 40 mg/5 mg or 80 mg/5 mg) is orally administered once a day. This fixed dose combination is not indicated for initial therapy of hypertension.

（underlined portion was added by this approval）

About telmisartan

Telmisartan, discovered and developed by Boehringer Ingelheim, is a drug marketed in some 100 countries around the world including Japan, the USA and European countries. Telmisartan demonstrates an excellent antihypertensive effect with its strong AT1 receptor blocker effect[5] and selective PPARγ activation effect[6]. Moreover, it is expected to play an active role in the treatment of hypertension of the metabolic syndrome as a metabolic sartan that brings about positive effects on metabolism including insulin resistance improvement[7]. The landmark ONTARGET trial as clinical study of ARB published in 2008 confirmed the effect of telmisartan to prevent cardiovascular events as strong as that of ACE inhibitor ramipril[8]. In Japan, all the telmisartan drugs, "Micardis® Tablets 20 mg/40 mg/80 mg," Micombi® Combination Tablets AP/BP," and "Micamlo® Combination Tablets AP/BP" will be manufactured by NBI, marketed by Astellas, and co-promoted by the two companies. The indication of all of these drugs is "hypertension" in Japan.

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References

1. 承認時評価資料

2. 檜垣寅男、荻原俊男：新薬と臨床 2010; 59: 1344-1358

3. White WB, et al.: Blood Press Monito 2010; 15: 205-212

4. ミカムロ®配合錠 AP/BP 添付文書

5. Kakuta, H. et al.： Int J Clin Pharmacol Res 2005; 25（1）: 41-46

6. Benson SC, et al.： Hypertension 2004; 43： 993-1002

7. 森下 竜一: Pharma Medica 2010; 28(4)

8. The ONTARGET Investigators: N Engl J Med 2008; 358: 1547-1559

Company Outlines

◇ **Nippon Boehringer Ingelheim Co., Ltd.**(www.boehringer-ingelheim.co.jp)

Established:	June 1961
Headquarters:	ThinkPark Tower, 2-1-1 Osaki, Shinagawa-ku, Tokyo
Representative:	Yoshioka Aono, President
Sales:	199,807 million yen (January – December 2011 NHI Sales)
Number of employees:	1,754 (as of 31 December 2011)
Business activities:	• Research & development, import, manufacturing, and marketing of pharmaceuticals • Import/export and marketing of pharmaceutical active ingredients and intermediates

◇ **Boehringer Ingelheim GmbH** (www.boehringer-ingelheim.com)

Established:	1885
Location:	Ingelheim, Federal Republic of Germany
Representative:	Dr. Andreas Barner, Chairman of the Board
Sales (consolidated)	13,171 million euros (January – December2009)
Number of employees (consolidated):	Approximately 44,000
Business activities:	Research & development, manufacturing and marketing of prescription medicines, consumer health care products, veterinary medicine, biopharmaceuticals, and chemicals
Affiliated companies:	145

◇ **Astellas Pharma Inc.** (www.astellas.com/jp)

Incorporated:	April 2005
Headquarters:	2-3-11 Nihonbashi-Honcho, Chuo-ku, Tokyo
Representative:	Yoshihiko Hatanaka, President & CEO
Sales (consolidated):	969.3 billion yen (for year ending March 2012)
Number of employees (consoidated):	17,085 (as of 31 March 2012)
Business activities:	Manufacturing, marketing and import/export of pharmaceuticals