

May 31, 2013

Press Release

Nippon Boehringer Ingelheim Co., Ltd.

Astellas Pharma Inc.

**Launch of Japan's First High-Dose ARB and CCB Combination:
"Micamlo[®] Combination Tablets BP"**

— powerful antihypertensive effect lasting 24 hours due to unique "delta-lock¹" structure —

Tokyo Japan, May 31, 2013 - Nippon Boehringer Ingelheim Co., Ltd. (headquartered in Shinagawa-ku, Tokyo; president, Yoshiaki Aono; hereinafter referred to as "Nippon Boehringer Ingelheim") and Astellas Pharma Inc. (Tokyo:4503, headquartered in Chuo-ku, Tokyo; president, Yoshihiko Hatanaka; hereinafter referred to as "Astellas") announced today's launch of "Micamlo[®] Combination Tablets BP," a combination drug of telmisartan 80 mg, a long-acting angiotensin II type 1 (AT₁) receptor blocker (ARB), and amlodipine 5 mg, a long-acting calcium channel blocker (CCB), following its drug price listing today.

Micamlo[®] Combination Tablets BP is Japan's first combination of high-dose ARB and long-acting CCB. While the previously launched 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 is increased to 80 mg. This is, therefore, expected to maintain a more potent antihypertensive effect for 24 hours compared to existing ARB/CCB combination tablets.

The medicine expert of the domestic clinical studies of Micamlo[®] Combination Tablets BP, Dr. Jitsuo Higaki of the Department of Cardiology, Pulmonology, Hypertension and Nephrology at Ehime University Graduate School of Medicine, made a following comment: Unlike other ARBs, Micardis[®] contained in "Micamlo[®] Combination Tablets BP contains Micardis[®] has a special feature of providing powerful antihypertensive effect due to the delta-lock¹ structure which binds with the stronger affinity to three points of AT₁ receptor. It is also long-acting, with an effect that is sustained for 24 hours. Moreover, since the selective PPAR γ -activating action of Micardis has a salutary effect upon metabolism, this drug is sometimes referred to as Metabo-sartan, and it is regarded as the first choice for hypertensive patients with metabolic syndrome or risk factors for it. Micamlo[®] Combination Tablets BP combines the highest available dosage of Micardis with amlodipine, the most prescribed hypertension drug in the world, which, like Micardis[®], is backed by evidence that it prevents cardiovascular events. While we generally get the impression that it is

more difficult to obtain antihypertensive effect by increasing the dosage of ARB, compared to increasing the dosage of CCB, it is noteworthy that powerful antihypertensive effect represented by reduction of 6.9 mmHg in systolic blood pressure was obtained by switching to Micamlo[®] Combination Tablets BP in a Japanese phase-III long-term administration study involving hypertensive patients who had not met their blood pressure targets when taking Micamlo[®] Combination Tablets AP[®].

There are also survey results indicating that approximately 60 percent of hypertensive patients have still not met their target blood pressure, and since many of the patients we see in clinical practice have hypertension that is inadequately controlled with the existing medications. Therefore, the advent of Micamlo[®] Combination Tablets BP, with its powerful and long-acting antihypertensive effect, can be expected to contribute to the treatment of a great many patients.”

With the existing telmisartan drugs, “Micardis[®] Tablets 20 mg/40 mg/80 mg,” “Micombi[®] Combination Tablets AP/BP” (combining telmisartan with hydrochlorothiazide diuretic of the thiazide class), and “Micamlo[®] Combination Tablets AP” (combining telmisartan with long-acting CCB amlodipine), Micamlo[®] Combination Tablets BP to be launched 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 two companies. They remain committed to continuously maximising the value of the Micardis[®] family products and further contributing to hypertension treatment.

The following is a summary of the approval:

Date of launch: 31/May/2013

Date of listing the price: 31/May/2013

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 corresponds to Micamlo[®] Combination Tablets BP)

Drug price: Micamlo[®] Combination Tablets BP 200.80 yen

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 effect³ and selective PPAR γ activation effect⁴. Moreover, it is expected to play an active role in the treatment of hypertension of the metabolic syndrome as a metabo-sartan that brings about positive effects on metabolism including insulin resistance improvement⁵. In addition, it was reported as a result of the 2008 ARB clinical trial ONTARGETTM, one of the largest-scale clinical trials ever, that Telmisartan has an inhibitory effect on cardiovascular events which is equivalent to ACE-inhibitor, Ramipril (domestically unapproved). 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.

References

- 1.(1)Ohno K, et al. : Biochem Biophys Res Commun 2011; 404(1): 434-437
(2)小室 一成ほか: 血圧 2011; 18(2): 154-159
・他の ARB は AT1 受容体と 2 点で結合しているが、テルミサルタンは 3 点で結合する。このテルミサルタンの 3 点での結合様式を、“デルタロック構造”と言う。
2. Obara T, et al.: J Hypertens 2005; 23(9): 1653-1660
3. Kakuta H, et al.: Int J Clin Pharmacol Res 2005; 25(1): 41-46
4. Benson SC, et al.: Hypertension 2004; 43(5): 993-1002
5. 森下 竜一: Pharma Medica 2010; 28(4): 119-125
6. The ONTARGET Investigators: N Engl J Med 2008; 358(15): 1547-1559

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