seriousness of symptoms after taking. Vomiting and/or gastrolavage may be considered. Activated charcoal may be useful for treatment. Serum electrolyte value and creatinine value should be monitored frequently. If low blood pressure appears, lay down the patient and supply salts and body fluid substitutes rapidly.

Amlodipine
When administering excessive amount, it was stated in documents so far that reflective frequent pulse could appear along with expansion of peripheral blood vessel. In addition, it was reported to cause a deadly result such as low blood pressure symptom over whole body for a long time to the extent of a shock. Immediately after administering amlodipine 10 mg to health applicants or up to 2 hours after administering activated charcoal, absorption of amlodipine showed a meaningful decrease. In some cases, gastrolavage may be useful. In case of clinically serious low blood pressure due to excessive administration of amlodipine, active supplementary treatment regarding cardio-blood vessel system such as monitoring heart and breathing frequency and securing body circulating fluid like blood and urine quantity enough by maintaining limbs higher than the body. Unless blood vessel contraction agents are prohibited specially, blood vessel contraction agents may be useful for recovering blood vessel tension and blood pressure. In reversing the effect of calcium channel inhibitor, intravenous injection of calcium gluconate may be useful. Since amlodipine has a very high protein bound rate, blood dialysis isn't helpful.

CAUTION ON STORAGE AND HANDLING
Keep out of reach and sight of children
Since placing in a different container may cause an accident and is not desirable to maintain quality, caution should be exercised.

STORAGE CONDITION
Store at temperatures not exceeding 30°C.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at +632-8-**UNILAB**-1 (+632-8-**864522**-1) for Metro Manila or toll-free +1-800-10-UNILAB-1 for provinces, or e-mail productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY
Synergia® 40 mg/ 5 mg Tablet, in Alu/Alu blister pack x 10's (Box of 30's)
Synergia® 40 mg/ 10 mg Tablet, in Alu/Alu blister pack x 10's (Box of 30's)
Synergia® 80 mg/ 5 mg Tablet, in Alu/Alu blister pack x 10's (Box of 30's)

Manufactured by Dasan Pharmaceutical Co., Ltd.
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Imported and Distributed by **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City, Metro Manila, Philippines

Trusted Quality Healthcare

Date of First Authorization:
Synergia® 40 mg/ 5 mg Tablet: July 30, 2021
(DRP-10144)
Synergia® 40 mg/ 10 mg Tablet: July 29, 2021
(DRP-10131)
Synergia® 80 mg/ 5 mg Tablet: July 29, 2021
(DRP-10132)

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UNILAB

Telmisartan +Amlodipine

Synergia®

40 mg/5 mg, 40 mg/10 mg, 80 mg/5 mg Tablet

Angiotensin II Receptor Blocker/ Calcium Channel Blocker

Rx

FORMULATION
Each tablet contains:
40 mg + 5 mg
Telmisartan powder (23.9%) ..... 167.36 mg (equivalent as Telmisartan 40 mg)
Amlodipine besylate (EP) ..... 6.935 mg (equivalent as Amlodipine 5mg)

40 mg + 10 mg
Telmisartan powder (23.9%) ..... 167.36 mg (equivalent as Telmisartan 40 mg)
Amlodipine besylate (EP) ..... 13.87 mg (equivalent as Amlodipine 10 mg)

80 mg + 5 mg
Telmisartan powder (23.9%) ..... 334.72 mg (equivalent as Telmisartan 80 mg)
Amlodipine besylate (EP) ..... 6.935 mg (equivalent as Amlodipine 5 mg)

Additives (tar color): Blue No. 1 Aluminum Lake

DESCRIPTION
Synergia® 40 mg + 5 mg, 40 mg + 10 mg, 80 mg + 5 mg are pale gray and white oval, biconvex shaped two layer tablets.

PHARMACOLOGY
CLINICAL PHARMACOLOGY
Mechanism of Action
Telmisartan Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis. There is also an AT2 receptor found in many tissues, but AT2 is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3000 fold) for the AT1 receptor than for the AT2 receptor. Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because telmisartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Telmisartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of telmisartan on blood pressure.
Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggests that amlodipine binds to both dihydropyridine and non dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Bioequivalence study report Synergia® Tablets 80/5 mg 10/147 Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

PHARMACOKINETICS
Synergia® Tablets
The pharmacokinetics of amlodipine and telmisartan when combined are similar to the pharmacokinetics of amlodipine and telmisartan when administered separately. After administering Synergia® 80/10mg tablet with a high-fat meal, the total area under the plasma concentration-time curve (AUC) and C_{max} for telmisartan decreased by about 24% and 60%, respectively. For amlodipine, AUC and C_{max} were not altered. Telmisartan, following oral administration, peak concentrations (C_{max}) of telmisartan are reached in 0.5 to 1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration-time curve (AUC) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose. The absolute bioavailability of telmisartan is dose-dependent At 40 and 160 mg the bioavailability is 42% and 58%, respectively. The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range 20 to 160 mg, with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half life of approximately 24 hours. Trough plasma concentrations of telmisartan with once daily dosing are about 10% to 25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing. Bioequivalence Study Report Synergia®Tablets 80/5mg 13/147 Amlodipine peak plasma concentrations of amlodipine are reached 6 to 12 hours after administration of amlodipine alone. Absolute bioavailability has been estimated to be between 64% and 90%. The bioavailability of amlodipine is not altered by the presence of food. Elimination of amlodipine from the plasma is biphasic with a terminal elimination half-life of about 30 to 50 hours. Steady state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

INDICATION
Synergia®is used as a treatment for essential hypertension.
Replacement Therapy: Patients receiving Telmisartan and Amlodipine from separate tablets may instead receive Synergia® containing the same component doses.
Add-on Therapy: Patients whose blood pressure are not controlled properly on Telmisartan or Amlodipine monotherapy.

DOSAGE AND ADMINISTRATION
Adults: One tablet once a day, to be taken with water regardless of meal. If possible, it is recommended to take at the same time each day (example: every morning).
Replacement Therapy: For patient who has been taking Telmisartan and Amlodipine as monotherapy, switching to Synergia® may be considered for ease of administration or to enhance compliance.
Add-on Therapy: Synergia® may be administered in patients whose blood pressure are not controlled properly with Telmisartan or Amlodipine alone.
Renal Impairment: No dosage adjustment is required for patients with renal impairment including those on hemodialysis, but for patients with severe kidney impairment, it is recommended to begin from low dosage and increase gradually. In addition, the value of serum potassium and creatinine is recommended to monitor regularly.
Hepatic Impairment: For patients with mild or moderate hepatic impairment, telmisartan dosage shall not exceed 40 mg per day. Use of Synergia®should be administered with caution.
Geriatric Use: In case of elderly not less than 75 years old, dosage should be increased gradually from low because Amlodipine's clearance rate is reduced.

WARNINGS
In the event of administering a drug acting directly on the Renin-Angiotensin System like this drug to a pregnant woman, it may cause pathogenesis and death to a growing fetus or a new born baby. In particular, administering such a drug to a woman into 3 month pregnancy stage 2 and 3 month of pregnancy stage 3 is related to the damages to a fetus or to a new born baby including low blood pressure, new born baby's cranial development decline, anuria, reversible or irreversible renal failure and death. Oligohydramnios has been reported in relation to fetus' renal function decline, and oligohydramnios is related to fetus's limb contraction, craniofacial abnormalities, lung development decline.
Prematurity, retarded growth inside womb and patent ductus have been reported, but whether they were caused by exposure to this drug is not clear. When pregnancy diagnosed, administering this drug shall be suspended as fast as possible.

DO NOT administer to the following patients
- Patients who are sensitive to this drug's main ingredients or dihydropyridine derivatives
- Pregnant women (pregnancy stage 2 and 3) or women suspected of pregnancy
- Lactating women
- Biliary obstructive patients
- Severe hepatopathic patients
- Severe aortic stenosis patients
- Shock patients
- Patient who have genetic problems such as intolerance to the additives of this drug
- For diabetes or medium~severe nephropathic patients (glomerular filtration rate <60 mL/min/1.73m^2) use together with aliskiren

ADMINISTER WITH CAUTION to the following patients:
- Primary aldosteronism patients
  In case of primary aldosteronism patients, since hypotensive agents obstructing the Renin-Angiotensin System are not effective in general, this drug is not recommended.
- Patients who have artery valve or mitral stenosis or obstructive hypertrophic myocardiopathy
  Just like other blood vessel relaxants, in case of artery valve or mitral stenosis patients or obstructive hypertrophic myocardiopathy patients, special caution is needed.
- Hepatopathic patients
  Amlodipine is metabolized largely in liver and telmisartan is discharged mostly in bile. Therefore, in case of patients with cholestasis, biliary obstructive diseases or hepatopathy, liver cleansing rate is expected to decrease. Thus, it should be administered to patients with light or medium hepatosis with caution, not exceeding telmisartan 40 mg once a day.
- Patients with gastrointestinal disorders such as active stomach or duodenal ulcer
  When administering telmisartan, gastrointestinal adverse reaction occurred more frequently than administering placebo. In clinical tests, gastrointestinal tract hemorrhage was rarely observed, mostly in patients with early gastrointestinal tract disorders. Therefore, when administering this drug to gastrointestinal patients, caution is needed.
- Patient with renovascular high blood pressure
  When treating patients with renal artery stenosis on both sides or with renal artery stenosis on only one functioning kidney with a drug affecting the renin-angiotensin-aldosterone system, the risk for severe low blood pressure or renal failure increases. In case of administering this drug to patients with renal artery stenosis on both sides or a single side, serum creatinine or uric acid nitrogen in blood is expected to rise like angiotensin converting enzyme (ACE) inhibitor.
- Severe low blood pressure patients
- Renal failure patients who need dialysis
- Geriatric patients
- Renin-angiotensin-aldosterone system (RAAS)'s double obstruction: It is not recommended to use together with other drugs that affect the renin-angiotensin-aldosterone system (RAAS) such as an angiotensin receptor blocker (ARB), an ACE inhibitor or aliskiren.

PRECAUTIONS
- **Pregnancy**
  During pregnancy, angiotensin II receptor antagonist administration shall not begin. If its not necessary to continue to administer angiotensin II receptor antagonist, for a patient with pregnancy plan, it shall be replaced with another high blood pressure medicine with an established safety profile for use on pregnant women. In case that pregnancy is confirmed, treatment of angiotensin II receptor antagonist shall be suspended as fast as possible, and if appropriate, another treatment shall be adopted.

• **Low blood pressure**
After beginning to administer this drug on patients with an activated renin-angiotensin system like patients short of body fluid or salts (ex: patients treated with high capacity diuretics), symptomatic low blood pressure may occur. This state shall be corrected before administering this drug or treatment shall begin by reducing the capacity of this drug under thorough medical supervision. In case that low blood pressure occurs, the patient shall be laid down straight and physiological saline shall be injected gradually with an intravenous injection. Temporary low blood pressure reaction is not a taboo in future treatment, and in general, once blood pressure is stabilized, treatment may continue without difficulty.
• **Hyperkalemia**
In case of telmisartan, during treating with another drug affecting the renin-angiotensin-aldosterone system, in particular, nephropathic patients and/or cardiac failure patients, hyperkalaemia may occur. For patients with a risk, monitoring serum potassium value properly is recommended. Based on use experience of another drug affecting the Renin-Angiotensin System, combined use with potassium undercurrent diuretics, potassium supplement, salt substitute containing potassium and other medicine (heparin etc.) which may increase potassium value may increase serum potassium value, so combined administration of this drug with these other drugs shall be considered carefully.
• **Nephropathic patient**
In case of telmisartan, change of renal function may occur to sensitive patients as a result of obstruction of the renin-angiotensin-aldosterone system. Treating an angiotensin-converting enzyme (ACE) inhibitor and an angiotensin receptor antagonist to patients whose renal function may rely on activation of the renin-angiotensin-aldosterone system (ex. patients with serious congestive cardiac failure) was related to urine decrease and/or progressive azotemia and (rarely) acute renal failure and/or death. Similar results may occur to patients treated with telmisartan. When administering this drug to nephropathic patients, it is recommended to monitor the value of serum potassium and creatinine regularly. There is no experience of using this drug to patients with recent kidney transplantation.
• **Increase of myocardial infarction risk or angina**
In case of amlodipine, when beginning a calcium channel blocker therapy especially to patients with serious obstructive coronary artery diseases or increasing capacity, there are rare records of increase of frequency of occurrence of angina or acute myocardial infarction, period and seriousness. Cause for this effect has not been found.
In case of amlodipine, since gradual decrease of blood pressure appears after ceasing to administer due to long decrease period of serum concentration, in case of administering other hypotensive agents after ceasing to administer, a caution should be taken regarding capacity and administering interval and it should be administered carefully monitoring the status of patients.
• **Administration to patients with cardiac failure**
In a long-term placebo contract test of amlodipine to patients with NYHAIII, IV grade cardiac failure without ischemic cause of disease (PRAISE-2), amlodipine was related to despite no meaningful difference in aggravation rate of cardiac failure compared to placebo, it was related to increase of reports of lung edema.
Since this drug contains sorbitol, it is not appropriate for patients with genetic intolerance to fructose.
• **Diabetes**
In case of diabetes patients with an additional risk of cardiovascular disorders (ex: patients with both diabetes and coronary artery disease), administration of hypotensive agents such as an angiotensin II receptor antagonist or an angiotensin converting enzyme inhibitor may increase a death risk due to deadly myocardial infarction and unexpected cardiovascular disorders. Since coronary artery diseases may not be diagnosed on diabetes patients due to no appearance of symptoms, an appropriate diagnostic evaluation for discovering and treating coronary artery diseases (ex: exercise load test) shall be undertaken preferentially when administering this drug to diabetes patients.
• **Effect on operation and machine manipulation**
No study has been undertaken on the effect of this drug on operation and machine manipulation, but since drowsiness and dizziness may occur occasionally when taking a hypotensive agent, a patient under administration of this drug shall be careful when driving a car or manipulating machines accompanying a risk.
• **Others**
Like other hypotensive agents, an excessive decrease of blood pressure of patients with ischemic cardiovascular disorders may lead to myocardial infarction or cerebral apoplexy.

PREGNANCY and LACTATION
Pregnant women:
Use of angiotensin II receptor antagonists such as telmisartan is not recommended for 3 months in the 1st stage of pregnancy, and is prohibited for 3 months in the 2nd and 3rd stages. There is no relevant data regarding administration of this drug to pregnant women.
Deformity didn't appear in non-clinical documents, but fetal toxicity appeared. For 3 months of pregnancy stage 2 and 3, exposure to angiotensin II receptor antagonist causes fetal toxicity to body (decrease in kidney function, amniotic fluid decrease, delay of skull ossification) and toxicity to new born babies (renal failure, low blood pressure, hyperkalaemia).
During pregnancy, treatment of angiotensin II receptor antagonist shall not begin. If continuous treatment of angiotensin II receptor antagonist is not essential, it shall be replaced with other high blood pressure treatment with established safety profile for patients with a plan for pregnancy and pregnant women. When pregnancy is diagnosed, treatment of angiotensin II receptor antagonist shall be suspended as fast as possible, if appropriate, other treatments shall be used. If exposed to angiotensin II receptor antagonist after 3 months of pregnancy stage 2, it is recommended to check liver function and ultrasound scan of skull. In case of babies of pregnant women who were administered with angiotensin II receptor antagonist, the possibility of low blood pressure, frequent urination and hyperkalaemia etc. should be monitored.
Lactating women:
Whether this drug is transferred through humans lactating has not been known but in an animal test, it was confirmed that telmisartan was contained in milk. Therefore, it is recommended not to administer this drug during lactating.
Reproductive ability:
The effect of this drug and individual main ingredients on human's reproductive ability has not been studied. No separate reproduction toxicity test was implemented concerning the joint use of telmisartan and amlodipine. In a non-clinical test, telmisartan's effect on male/female reproductive ability has not been observed, and it was the same with the amlodipine.

DRUG INTERACTIONS
No interactions between Amlodipine and Telmisartan as fixed-dose combination have been observed.
Interactions Common to Telmisartan and Amlodipine Combination: No drug interaction studies between Synergia® and other drugs has been carried out.
Drug Interaction linked to Telmisartan:
• **Digoxin:** When digoxin was administered together with telmisartan, the maximum median value (49%) and minimum median value (20%) of digoxin's plasma concentration was observed to increase. Therefore, in order to avoid an excessive or under digitalis action which may occur when beginning to administer telmisartan, adjusting administered amount or ceasing to administer, it is recommended to monitor digoxin concentration.
• **Lithium:** While administering lithium together with an angiotensin conversion inhibitor, reversible increase and toxicity of serum lithium concentration were reported. Such cases were also reported for angiotensin receptor antagonists containing telmisartan. Therefore, it is recommended to monitor the value of serum lithium while administering lithium together with telmisartan.
• **Ramipril and Ramiprilat:** In a clinical test, administering telmisartan together with Ramipril increased $AUC_{0\text{-}24}$ and C_{max} of Ramipril and Ramiprilat by up to 2.5 times. No clinical connection has been known regarding this observation.
• **Warfarin:** Administering telmisartan for 10 days decreased the minimum average plasma concentration of warfarin a little; such decrease didn't bring a change in terms of International Normalized Ratio (INR).
• **Nonsteroidal anti-inflammatory analgesics** (ex. aspirin, COX-2 inhibitor and nonsteroidal anti-inflammatory analgesics as an anti-inflammatory therapy) may weaken the blood pressure decrease effect of an angiotensin II receptor antagonist. In some patients with damaged renal function (ex. dehydrated patients, geriatric patients with damaged renal function), aggravation of renal function damage including an acute renal failure (reversible in general) when administering an angiotensin II receptor antagonist and a COX inhibitor together was reported. Therefore, they should be administered together with caution and in particular, more caution should be paid in case of geriatric patients. Enough water shall be provided to patients administered with nonsteroidal anti-inflammatory analgesics and this drug together, and renal function should be monitored regularly after beginning combined treatment.
• **Other drugs:** When administering telmisartan together with acetaminophen, amlodipine, glibenclamide, simvastatin, hydrochlorothiazide and ibuprofen, there was no clinically meaningful interaction. Since telmisartan is not metabolized by cytochrome P450 system, it has no effect on cytochrome except for obstructing CYP2C19 outside P450 system. Telmisartan is not expected to interact with drugs obstructing cytochrome P450 enzyme. Except for the possibility of obstructing metabolism of drugs metabolized by CYP2C19. Telmisartan is not expected to interact with drugs metabolized by cytochrome P450.
For interaction information of additional drugs, refer to the matters related to permission of telmisartan.
• **Double obstruction of the renin-angiotensin-aldosterone system (RAAS)** by combined administration of angiotensin receptor blocker (ARB), ACE inhibitor or aliskiren is related to increase the risk of low blood pressure, faint, hyperkalaemia and change of renal function (including acute renal failure) compared to the single use of these drugs. In case of patients for whom this drug is administered together with other drugs affecting RAAS, blood pressure, renal function and electrolyte shall be monitored thoroughly. This drug shall not be administered together with drugs containing aliskiren to patients with diabetes or middle ~ severe nephropathic (G.F.R. <60 mL/min/1.73m^2).
• **Drug Interaction linked to Amlodipine:**
• In clinical tests, amlodipine was safely administered together with thiazide diuretics, beta-blocker, angiotensin-conversion enzyme inhibitor, continuous nitrogen salts, nitroglycerin sublingual tablet, digoxin, warfarin, nonsteroidal anti-inflammatory, antibiotics and oral diabetes medicine, etc.
• Grapefruit juice: Since amlodipine may cause a blood pressure decrease effect on some patients due to increase of bioavailability when used together with grapefruit or grapefruit juice, combined administration is not recommended.
• Cimetidine, sildenafil: No meaningful pharmacokinetic interaction appeared regarding amlodipine.
• Atorvastatin, digoxin, warfarin: No meaningful pharmacokinetic or pharmacodynamic effects were caused by amlodipine.
• Simvastatin: As a result of administering various dosages of amlodipine and simvastatin 80 mg, exposure to simvastatin increased by up to 77% compared to administering simvastatin alone. Therefore, for patients taking amlodipine, simvastatin dosage is limited to maximum 20 mg per day.
• Tacrolimus: Amlodipine may increase whole body's exposure to tacrolimus. Therefore, blood concentration of tacrolimus should be monitored frequently and if necessary, adjustment of dosage is recommended.
• Cyclosporine: In multiple studies which administered this drug together with cyclosporine to patients with kidney transplantation, it was reported that when used together with this drug, minimum blood concentration of cyclosporine has no change or increased by up to 40%.
• CYP3A4 inducing agent: When administered together with CYP3A4 inducing agent (ex. rifampicin, St. John's wort (hypericum perforatum), amlodipine's plasma concentration showed a change. Therefore, in particular, during and after administering with a strong CYP3A4 inducer, monitoring of blood pressure and dosage control should be considered.
• For information on additional interaction with drugs, please refer to the matters licensed for amlodipine.

ADVERSE DRUG REACTIONS
Telmisartan and Amlodipine Combination
Clinical Test
Administration of Telmisartan and Amlodipine combination were verified safe on not less than 1,200 high blood pressure patients. Among these patients, 320 patients were exposed to these drugs for 6 months or more and 120 patients were exposed for 1 year or more. Adverse reactions appeared mostly in temporary light symptoms, and there were rare cases serious to the extent to stop treatment.
As adverse reactions that appeared at 2% or more in a clinical test designed with contract factors to placebo, adverse reactions that appeared more frequently in the amlodipine/telmisartan administer group (n=789) than in the placebo group (n=46) are as follows.

Table 1. Adverse reactions that appeared at 2% or more, higher than placebo's incidence rate

	Group administered with amlodipine/telmisartan (n=789)	Placebo group (n=46)
Peripheral edema	4.8%	0.0%
Dizziness	3.0%	2.2%
Orthostatic low blood pressure*	6.3%	4.3%
Back pain	2.2%	0%

*Orthostatic low blood pressure: blood pressure at relaxation phase > 10 mmHg decrease, and/or blood pressure at systolic phase > 20 mmHg decrease.
In addition, dizziness (2.0% vs 2.2%, in contrast to placebo) and headache (1.4% vs 4.3%, in contrast to placebo) are other extraordinary reactions that appeared at 1% or more among patients administered with this drug.
In this clinical test, 2.2% of all patients administered with this drug and 4.3% of patients administered with placebo stopped the clinical test due to extraordinary reactions. The most common reason for stopping treatment of this drug was peripheral oedema, dizziness and low blood pressure (respectively 0.5% or less).
Survey results after coming into domestic market
As a result of surveying 610 persons for 6 years after coming into the market for the purpose of reexamination in Korea, the incidence rate of extraordinary cases was reported at 3.28% (20/610 persons, 20 cases in total), regardless of causality. Among these, the incidence rate of serious extraordinary cases was reported at 0.49% (3/610 persons, 3 cases in total) with hepatocellular carcinoma, cerebral infarction and congestive cardiac failure at 0.16% each (1/610 persons, 1 case). The incidence rate of serious adverse reaction with causality with this drug was reported at 0.16% (1/610 persons, 1 case in total), which was congestive cardiac failure 0.16% (1/610 persons, 1 case).

The incidence rate of unexpected adverse cases was reported at 1.31% (8/610 persons, 8 cases in total) regardless of causality, with hepatocellular carcinoma, musculoskeletal pain, cerebral infarction, neck pain, nasopharyngitis, epigastric displeasure, epigastralgia, positional vertigo at 0.16% each (1/610 persons, 1 case). The incidence rate of unexpected adverse reaction with causality with this drug was reported at 0.33% (2/610 persons, 2 cases in total) with epigastric displeasure and positional vertigo at 0.16% each (1/610 persons, 1 case).

Additional Information on Individual Components
Telmisartan
Adverse reactions that appeared at 1% or more of patients administered with telmisartan in a clinical test designed in contract to placebo and appeared more frequently than in patients administered with placebo are as follows:

Table 2. Adverse reactions that appeared at 1% or more, higher than placebo's incidence rate.

	Group administered with telmisartan (n=1,455)	Placebo group (n=380)
Upper respiratory Infection	7%	6%
Back pain	3%	1%
Paranasal sinusitis	3%	2%
Diarrhea	3%	2%
Sore throat	1%	0%

In addition, adverse reactions that occurred in frequency similar to the placebo group among other adverse reactions that appeared at 1% or more of patients administered with telmisartan were influenza positive, indigestion, muscle pain, urinary tract infection, stomachache, headache, dizziness, pain, fatigue, cough, high blood pressure, chest pain, nausea and peripheral oedema.
Besides, other adverse reactions reported (manifestation exceeding 0.3%) are as follows:
• Autonomic nervous system: impotence, hidrosis, flush
• Whole body: allergy, fever, leg pain, feebleness
• Cardiac vessel: palpitation, dependent edema, angina, fast pulse, leg edema, abnormal ECG
• Central nerve system: insomnia, drowsiness, migraine, dizziness, involuntary muscle contraction, decreased sensation
• Gastrointestinal tract: fart, constipation, gastritis, vomiting, mouth dryness, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, nonspecific gastrointestinal disorder
• Metabolic: gout, hypercholesterolemia, diabetes
• Musculoskeletal system: arthritis, joint pain, leg numbness
• Psychological system: anxiety, depression, hypersensitivity
• Tolerance mechanism: infection,mycete infection, abscess, ear infection
• Respiratory infection: asthma, bronchitis, rhinitis, breathing difficulty, nose hemorrhage
• Skin: skin infection, rash, eczema, itchiness
• Urinary system: frequent urination, bladder infection
• Blood vessel system: cerebrovascular disease
• Special sensation: abnormal vision, conjunctivitis, ear noise, ear pain
During the initial clinical test, 1 case of angioedema was reported.
In a clinical test in contrast to placebo, the following laboratory abnormalities were reported.
• Hemoglobin: 0.8% of patients administered with telmisartan and 0.3% of patients administered with placebo were reported to have decreased by 2 g/dL or more. There was no patient who stopped administration due to anemia.
• Creatinine: 0.4% of patients administered with telmisartan and 0.3% of patients administered with placebo were reported to have increased by 0.5 mg/dL or more. Out of the telmisartan administered group, 1 subject stopped administration due to an increase in creatinine and blood urea nitrogen (BUN).
• Liver enzyme: Some patients among those administered with telmisartan reported increase in liver enzyme value. Significant increase occurred in the placebo group with higher frequency. There was no patient who stopped treatment due to problem with liver function among patients administered with telmisartan.
For additional information on safety, refer to the permission of telmisartan single agent.

Amlodipine
Most frequently reported adverse reactions are headache and edema. Incidence rate of adverse reactions reported dependent on quantity is as follows:

Table 3. Incidence rate of adverse reactions reported dependent on quantity

Adverse reaction	Amlodipine 2.5 mg (n=275)	Amlodipine 5.0 mg (n=296)	Amlodipine 10.0 mg (n=268)	Placebo (n=520)
Edema	1.8%	3.0%	10.8%	0.6%
Dizziness	1.1%	3.4%	3.4%	1.5%
Flush	0.7%	1.4%	2.6%	0.0%
Palpitation	0.7%	1.4%	4.5%	0.6%

In addition, other adverse reactions that appeared at 1% or more among patients administered with amlodipine in the clinical test in contrast to placebo are as follows.

Table 4. Adverse reactions that appeared at 1% or in the clinical test in contrast to placebo

Adverse Reaction	Group administered with Amlodipine (n =1,730)	Placebo group (n=1,250)
Headache	7.3%	7.8%
Fatigue	4.5%	2.8%
Nausea	2.9%	1.9%
Stomach ache	1.6%	0.3%
Drowsiness	1.4%	0.6%

Besides, other adverse reactions reported (manifestation rate at 0.1% ~ 1%) are as follows.
• Cardio-blood vessel system: arrhythmia (including ventricular frequent pulse and atrial fibrillation), bradycardia, chest pain, peripheral ischemia, faint, positional low blood pressure, blood vessel disorder
• Central and peripheral nerve system: peripheral nerves disorder, abnormal sensation, tremble, dizziness
• Gastrointestinal tract: low appetite, constipation, indigestion, problem with swallowing, diarrhea, fart, pancreatitis, vomit, gingival hyperplasia
• Whole body: allergy reaction, asthenia, back pain, hot flush, feebleness, pain, spasticity, weight increase, weight loss
• Musculoskeletal system: arthritis, arthropathy, muscle spasm, muscle pain
• Psychological system: hypogonadism (men and women), insomnia, hypersensitivity, depression, abnormal dream, anxiety, depersonalization
• Respiratory system: breathing difficulty, nose hemorrhage
• Skin and supplementary organs: blood vessel edema, polymorphism erythema, itchiness, rash, erythema rash, maculopapular rash
• Special senses: problem with vision, conjunctivitis, double vision, eyeball pain, ear noise
• Urinary system: frequent urination, urination disorder, enuresis
• Autonomic nervous system: mouth dryness, hidrosis
• Metabolism and nutrition: hyperglycemia, thirst
• Blood: leukopenia, purpura, thrombocytopenia

In the clinical test, no laboratory abnormalities clinically significant related to amlodipine administration were observed.

Other adverse reactions reported in the frequency of 0.1% or less in the patients administered with amlodipine are as follows; cardiac failure, irregular impulse, ectopic contraction, skin decolorization, itchiness, skin dryness, hair loss, dermatitis, muscle weakening, single contraction, harmonic motion inability, excessive muscle tension, migraine, cold-moist skin, ataraxy, anxiety, memory loss, gastritis, appetite increase, loose feces, rhinitis, urination disorder, polyuria, abnormal olfactory sense, palate deviation, abnormal eyeball movement, eye dryness

For additional information on safety, refer to the permission of amlodipine single agent.

Experiences of use after launch into the market

Adverse reactions reported in experiences of use after Telmisartan or Amlodipine came into the market.
- Telmisartan: Most frequent adverse reactions voluntarily reported were headache, dizziness, asthenia, cough, nausea, fatigue, weakness, edema, facial edema, leg edema, blood vessel edema (accompanying deadly results), itchiness, oversensitive reaction, perspiration increase, erythema, chest pain, atrial fibrillation, congestive cardiac failure, myocardial infarction, blood pressure increase, high blood pressure, high blood pressure aggravation, low blood pressure (including orthostatic low blood pressure), hyperkalaemia, hypoglycemia (in diabetes patients), faint, indigestion, diarrhea, pain, urinary tract infection, impotency, back pain, Stomachache, muscle spasm (including leg spasm), muscle pain, bradycardia, acidophilia, thrombocytopenia, uric acid increase, liver dysfunction and liver disease*, nephropathic anemia including acute renal failure, CPK increase, anaphylaxis reaction and tendon pain (including tendinitis and tendosynovitis). Among patients administered with angiotensin II receptor blocker containing telmisartan, rhabdomyolysis was rarely reported.

• Liver dysfunction and liver disease of telmisartan: Adverse reactions after release to the market occurred to most Japanese patients who were expected to manifest such adverse reaction.

- Amlodipine: Female mastosis was rarely reported and causality with the medicine is unclear. Jaundice and increase in liver enzyme value (occurring with cholestasis or hepatitis in most cases) were reported in relation to the use of amlodipine and some cases were severe enough to be hospitalized. Extrapyramidal disease, leukopenia, derangement, desquamative skin infection, Stevens-Johnson syndrome, light-sensitive reaction and toxic epidermal necrolysis were reported (frequency unknown).

SPECIAL POPULATION
Pediatric Use
There is no data for pediatric use but is recommended that Synergia® should not be administered to pediatric patient without consultation with physician.
Geriatric Use
It is not required to adjust dosage when administering this drug to geriatric patients, caution should be exercised because there exists a possibility of more sensitive reaction in some geriatric patients. In case of geriatric patients not less than 75 years old, dosage should be increased gradually from low because amlodipine's clearance rate is reduced.

OVERDOSAGE AND TREATMENT
Telmisartan
Useful information on excessive administration on humans is limited.
As most significant symptoms of excessive administration of telmisartan, low blood pressure, frequent pulse (due to irritation of parasympathetic nerve), bradycardia, dizziness and acute renal failure etc. were reported. When blood pressure signs appear low, supplementary treatment should be implemented. Telmisartan is not removed by blood dialysis. Patients should be watched carefully, and allopathic and supplementary treatment should be implemented according to lapse time and