

# Combination Tops Monotherapy for Hypertension

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CHICAGO — Combining the calcium channel blocker amlodipine with the angiotensin receptor blocker olmesartan provides greater reductions in blood pressure than does either agent used as monotherapy, Dr. Steven G. Chrysant said at the annual meeting of the American Society of Hypertension.

Daiichi Sankyo Inc. filed a new drug ap-

plication in November 2006 for a fixed-dose combination of the two antihypertensives.

Known as Azor, this investigational agent is currently under regulatory and trade name review in the United States.

Lead investigator Dr. Chrysant reported data from a phase III double-blind, placebo-controlled factorial study in which 1,940 patients with mild to severe hypertension were randomized to either monotherapy or co-administration of am-

lodipine 5-10 mg/day and olmesartan 10-20 mg/day for 8 weeks.

Hypertension was defined as seated diastolic BP between 95 mm Hg and 120 mm Hg.

At admission, the average age of patients was 54 years, and their mean blood pressure was 164/102 mm Hg; 13.5% of patients had diabetes, and 34% were hypertensive treatment-naïve, said Dr. Chrysant, who reported that he has received grant and research support from

the study sponsor, Daiichi Sankyo Pharma Development.

After 8 weeks, all of the combinations of amlodipine and olmesartan resulted in significantly greater blood pressure reductions than either medication alone or placebo, said Dr. Chrysant, a cardiologist at the Oklahoma Cardiovascular and Hypertension Center, University of Oklahoma, Oklahoma City. Blood pressure reductions were dose related.

Amlodipine 10 mg/day plus olmesartan 40 mg/day produced the best results, re-



Only the high-dose combination dropped the pressure below 140 over 90 mm Hg.

DR. CHRYSANT

ducing systolic BP an average of 30.1 mm Hg and diastolic BP an average of 19.0 mm Hg.

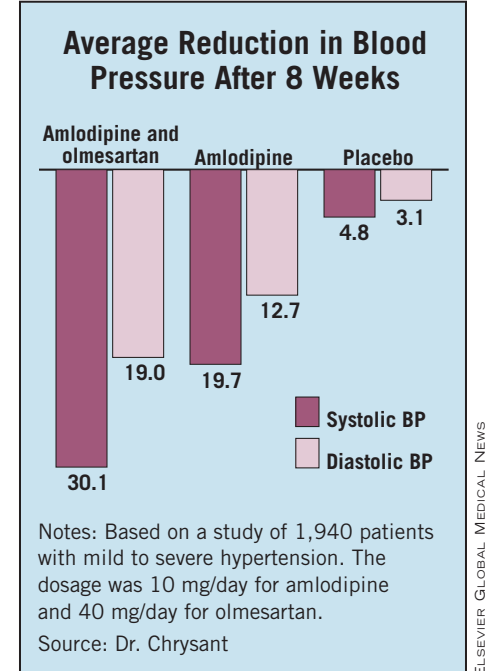
In contrast, the average reductions were 19.7/12.7 mm Hg for amlodipine 10 mg alone and 4.8/3.1 mm Hg for placebo.

“Only the high-dose combination dropped the pressure below 140 over 90 [mm Hg],” Dr. Chrysant said at a press briefing.

Adverse events were comparable between groups, occurring in 511 of 970 (53%) combination therapy patients and in 91 of 162 placebo-treated patients (56%). There was one stroke in the olmesartan monotherapy group that was possibly drug related, he said.

Reports of headache, fatigue, and dizziness were highest in the placebo group. The highest incidence of edema (25%) was reported in the amlodipine monotherapy group.

But adding on 40 mg of olmesartan halved this incidence rate, Dr. Chrysant said. He suggests this could be an added benefit of the combination regimen, because many hypertensive patients stop taking their medication because of swollen feet.



## Typhoid Vi Polysaccharide Vaccine Typhim Vi®

**Brief Summary: Please see package insert for full prescribing information.**

### INDICATIONS AND USAGE

Typhim Vi vaccine is indicated for active immunization against typhoid fever for persons two years of age or older. Immunization with Typhim Vi vaccine should occur at least two weeks prior to expected exposure to *S typhi*.

Typhim Vi vaccine is not indicated for routine immunization of individuals in the United States (US).<sup>1</sup> Selective immunization against typhoid fever is recommended under the following circumstances: 1) travelers to areas where a recognized risk of exposure to typhoid exists, particularly ones who will have prolonged exposure to potentially contaminated food and water, 2) persons with intimate exposure (ie, continued household contact) to a documented typhoid carrier, and 3) workers in microbiology laboratories who frequently work with *S typhi*.<sup>1</sup>

Typhoid vaccination is not required for international travel, but is recommended for travelers to such areas as Africa, Asia, and Central and South America where there is a recognized risk of exposure to *S typhi*. Current CDC advisories should be consulted with regard to specific locales. Vaccination is particularly recommended for travelers who will have prolonged exposure to potentially contaminated food and water. However, even travelers who have been vaccinated should use caution in selecting food and water.<sup>2</sup>

An optimal reimmunization schedule has not been established. Reimmunization every two years under conditions of repeated or continued exposure to the *S typhi* organism is recommended at this time.

Typhim Vi vaccine has efficacy against typhoid fever caused by *S typhi* infection but will not afford protection against species of *Salmonella enterica* serovar *typhi* other than *S typhi* or other bacteria that cause enteric disease.

For recommended primary immunization and reimmunization see **DOSE AND ADMINISTRATION** section. Typhim Vi vaccine should not be used to treat a patient with typhoid fever or a chronic typhoid carrier.

### CONTRAINDICATIONS

TYPHIM VI VACCINE IS CONTRAINDICATED IN PATIENTS WITH A HISTORY OF HYPERSENSITIVITY TO ANY COMPONENT OF THIS VACCINE.

### WARNINGS

Allergic reactions have been reported rarely in the post-marketing experience (see **ADVERSE REACTIONS** section). The safety and immunogenicity of Typhim Vi vaccine in children under two years of age has not been established. As with other polysaccharide vaccines, the antibody response may be inadequate. The decision whether to vaccinate children under 2 years of age depends upon the risk incurred by the child on the basis of the epidemiological context.

Typhim Vi vaccine provides protection against the risk of infection related to *Salmonella typhi*, but gives no protection against *Salmonella paratyphi A* or *B*.

If the vaccine is used in persons deficient in producing antibodies, whether due to genetic defect, immunodeficiency disease, or immunosuppressive therapy, the expected immune response may not be obtained.

As with any intramuscular injection, Typhim Vi vaccine should be given with caution to individuals with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection (see **DRUG INTERACTIONS** section).

As with any vaccine, vaccination with Typhim Vi vaccine may not protect 100% of individuals.

### PRECAUTIONS

**GENERAL**  
Care is to be taken by the health-care provider for the safe and effective use of Typhim Vi vaccine.

**EPINEPHRINE INJECTION (1:1000) MUST BE IMMEDIATELY AVAILABLE FOLLOWING IMMUNIZATION SHOULD AN ANAPHYLACTIC OR OTHER ALLERGIC REACTIONS OCCUR DUE TO ANY COMPONENT OF THE VACCINE.**

Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible hypersensitivity to the vaccine or similar vaccines.

Acute infection or febrile illness may be reason for delaying use of Typhim Vi vaccine except when in the opinion of the physician, withholding the vaccine entails a greater risk.

A separate, sterile syringe and needle or a sterile disposable unit must be used for each patient to prevent the transmission of infectious agents from person to person. Needles should not be recapped and should be properly disposed.

Special care should be taken to ensure that Typhim Vi vaccine is not injected into a blood vessel.

Safety and immunogenicity data from controlled trials are not available for Typhim Vi vaccine following previous immunization with whole-cell typhoid or live, oral typhoid vaccine (See **ADVERSE REACTIONS** section).

### DRUG INTERACTIONS

There are no known interactions of Typhim Vi vaccine with drugs or foods.

No studies have been conducted in the US to evaluate interactions or immunological interference between the concurrent use of Typhim Vi vaccine and drugs (including antibiotics and antimalarial drugs), immune globulins or other vaccines (including common travelers vaccines such as tetanus, polio, hepatitis A, yellow fever and meningococcus). (See **ADVERSE REACTIONS** section.)

As with other intramuscular injections, Typhim Vi vaccine should be given with caution to individuals on anticoagulant therapy.

**CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY**  
Typhim Vi vaccine has not been evaluated for its carcinogenic potential, mutagenic potential or impairment of fertility.

**PREGNANCY CATEGORY C**  
Animal reproduction studies have not been conducted with Typhim Vi vaccine. It is not known whether Typhim Vi vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Typhim Vi vaccine should be given to a pregnant woman only if clearly needed.<sup>3</sup>

When possible, delaying vaccination until the second or third trimester to minimize the possibility of teratogenicity is a reasonable precaution.<sup>3</sup>

**NURSING MOTHERS**  
It is not known if Typhim Vi vaccine is excreted in human milk.

There is no data to warrant the use of this product in nursing mothers for passive antibody transfer to an infant.

**PEDIATRIC USE**  
Safety and effectiveness of Typhim Vi vaccine have been established in children 2 years of age and older.<sup>4,5</sup> (See **DOSE AND ADMINISTRATION** section.) FOR CHILDREN BELOW THE AGE OF 2 YEARS, SAFETY AND EFFECTIVENESS HAVE NOT BEEN ESTABLISHED.

**ADVERSE REACTIONS**  
Adverse event information is derived from clinical trials and worldwide post-marketing experience.

**DATA FROM CLINICAL TRIALS**  
Safety of Typhim Vi vaccine, the US licensed liquid formulation, has been assessed in clinical trials in more than 4,000 subjects both in countries of high and low endemicity. In addition, the safety of the lyophilized formulation has been assessed in more than 6,000 individuals. The adverse reactions were predominately minor and transient local reactions. Local reactions such as injection site pain, erythema and induration almost always resolved within 48 hours of vaccination. Elevated oral temperature, above 38°C (100.4°F), was observed in approximately 1% of vaccinees in all studies. No serious or life-threatening systemic events were reported in these clinical trials.<sup>4,5</sup>

Adverse reactions from two trials evaluating Typhim Vi vaccine lots in the US (18- to 40-year-old adults) are summarized in TABLE 1. No severe or unusual side effects were observed. Most subjects reported pain and/or tenderness (pain upon direct pressure). Local adverse experiences were generally limited to the first 48 hours.<sup>4,5</sup>

**TABLE 1.5 PERCENTAGE OF 18- TO 40-YEAR-OLD US ADULTS PRESENTING WITH LOCAL OR SYSTEMIC REACTIONS WITHIN 48 HOURS AFTER THE FIRST IMMUNIZATION WITH TYPHIM VI VACCINE**

REACTIONS	Trial 1 Placebo N=54	Trial 1 Typhim Vi vaccine N=54 (1 Lot)	Trial 2 Typhim Vi vaccine N=98 (2 Lots combined)
<b>Local</b>			
Tenderness	7 (13.0%)	53 (98.0%)	95 (96.9%)
Pain	4 (7.4%)	22 (40.7%)	26 (26.5%)
Induration	0	8 (14.8%)	5 (5.1%)
Erythema	0	2 (3.7%)	5 (5.1%)
<b>Systemic</b>			
Malaise	8 (14.8%)	13 (24.0%)	4 (4.1%)
Headache	7 (13.0%)	11 (20.4%)	16 (16.3%)
Myalgia	0	4 (7.4%)	3 (3.1%)
Nausea	2 (3.7%)	1 (1.9%)	8 (8.2%)
Diarrhea	2 (3.7%)	0	3 (3.1%)
Feverish (subjective)	0	6 (11.1%)	3 (3.1%)
Fever ≥100°F	0	1 (1.9%)	0
Vomiting	0	1 (1.9%)	0

No studies were conducted in US children. Adverse reactions from a trial in Indonesia in children one to twelve years of age are summarized in TABLE 2.<sup>4,5</sup> No severe or unusual side effects were observed.

**TABLE 2.4 PERCENTAGE OF INDONESIAN CHILDREN ONE TO TWELVE YEARS OF AGE PRESENTING WITH LOCAL OR SYSTEMIC REACTIONS WITHIN 48 HOURS AFTER THE FIRST IMMUNIZATION WITH TYPHIM VI VACCINE**

REACTIONS	N=175
<b>Local</b>	
Soreness	23 (13.0%)
Pain	25 (14.3%)
Erythema	12 (6.9%)
Induration	5 (2.9%)
Impaired Limb Use	0
<b>Systemic</b>	
Feverishness*	5 (2.9%)
Headache	0
Decreased Activity	3 (1.7%)

\* Subjective feeling of fever.

In the US Reimmunization Study, subjects who had received Typhim Vi vaccine 27 or 34 months earlier, and subjects who had never previously received a typhoid vaccination, were randomized to placebo or Typhim Vi vaccine, in a double-blind study. Safety data from the US Reimmunization Study are presented in TABLE 3.<sup>4,6</sup> In this study 5/30 (17%) primary immunization subjects and 10/45 (22%) reimmunization subjects had a local reaction. No severe or unusual side effects were observed. Most subjects reported pain and/or tenderness (pain upon direct pressure). Local adverse experiences were generally limited to the first 48 hours.<sup>4,6</sup>

**TABLE 3.4 REIMMUNIZATION STUDY, SUBJECTS PRESENTING WITH LOCAL AND SYSTEMIC REACTIONS WITHIN 48 HOURS AFTER IMMUNIZATION WITH TYPHIM VI VACCINE**

REACTIONS	PLACEBO (N=32)	FIRST IMMUNIZATION (N=30)	REIMMUNIZATION (N=45*)
<b>Local</b>			
Tenderness	2 (6%)	28 (93%)	44 (98%)
Pain	1 (3%)	13 (43%)	25 (56%)
Induration	0	5 (17%)	8 (18%)
Erythema	0	1 (3%)	5 (11%)
<b>Systemic</b>			
Malaise	1 (3%)	11 (37%)	11 (24%)
Headache	5 (16%)	8 (27%)	5 (11%)
Myalgia	0	2 (7%)	1 (2%)
Nausea	0	1 (3%)	1 (2%)
Diarrhea	0	0	1 (2%)
Feverish (subjective)	0	3 (10%)	2 (4%)
Fever ≥100°F	1 (3%)	0	1 (2%)
Vomiting	0	0	0

\* At 27 or 34 months following a previous dose given in different studies.

### DATA FROM WORLDWIDE POST-MARKETING EXPERIENCE

The following adverse events have been reported during post-approval use of Typhim Vi vaccine. These events have been very rarely reported; however, because they were reported voluntarily from a population of uncertain size, it is not always possible to reliably calculate their frequencies or to establish a causal relationship to Typhim Vi vaccine exposure.

- Gastro intestinal disorders  
Nausea, vomiting, diarrhea
- General disorders and administration site condition  
Local Reactions: injection site pain, injection site inflammation, injection site induration, injection site erythema, and lymphadenopathy.  
Fever, asthenia, malaise, flu-like episode, abdominal pain.
- Immune system disorders  
Allergic-type reactions such as pruritus, rash, urticaria, difficulty breathing, hypotension.  
Serum sickness.
- Musculoskeletal and connective tissue disorders  
Myalgia, arthralgia, cervical pain.
- Nervous system disorders  
Headache, loss of consciousness, tremor.

### Additional Adverse Events:

Post-marketing reports of glomerulonephritis, neutropenia, bilateral retinitis, and polyarthritis have been reported in patients who had also received other vaccines; however a causal relationship has not been established.

### DOSE AND ADMINISTRATION

Before administration, parenteral drug products should be checked visually for any deviation from normal appearance including container integrity. The syringe or vial and its packaging should also be inspected prior to use for evidence of leakage, premature activation of the plunger, or a faulty tip seal. If evidence of such defects are observed, the syringe should not be used.

For intramuscular use only. Do NOT inject intravenously.

Typhim Vi vaccine is indicated for persons two years of age and older.

The immunizing dose for adults and children is a single injection of 0.5 mL. The dose for adults is given intramuscularly in the deltoid, and the dose for children is given IM either in the deltoid or the vastus lateralis. The vaccine should not be injected into the gluteal area or areas where there may be a nerve trunk.

A reimmunizing dose is 0.5 mL. Reimmunization consisting of a single dose for US travelers every two years under conditions of repeated or continued exposure to the *S typhi* organism is recommended at this time.<sup>1</sup>

The syringe is intended for single use only, must not be reused, and must be disposed of properly and promptly following its use.

The skin at the site of injection first should be cleansed and disinfected. Tear off upper seal of vial cap. Cleanse top of rubber stopper of the vial with a suitable antiseptic and wipe away all excess antiseptic before withdrawing vaccine.

**STORAGE**  
Store between 2°–8°C (35°–46°F). DO NOT FREEZE.

- REFERENCES**
1. Recommendations of the Immunization Practices Advisory Committee (ACIP). Typhoid Immunization. MMWR 43: No. RR-14, 1994
  2. CDC. Health Information for International Travel 1992. U. S. Department of Health and Human Services, Public Health Service
  3. ACIP: Update on Adult Immunization. MMWR 40: No. RR-12, 1991
  4. Unpublished data available from Sanofi Pasteur, Inc., compiled 1991
  5. Unpublished data available from Sanofi Pasteur, Inc.
  6. Keitel WA, et al. Clinical and serological responses following primary and booster immunization with *Salmonella typhi* Vi capsular polysaccharide vaccines. Vaccine 12: 195-199, 1994

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Product Information as of December 2005

Manufactured by: Sanofi Pasteur SA, Lyon France  
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