

# Medical Up-date

## NEWSLETTER

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### Asomex<sup>®</sup> by Emcure

Asomex<sup>®</sup> S(-)amlodipine is the world's first chirally pure anti-hypertensive. Emcure – putting stereochemistry into medicine.

#### Chirality and enantiomers

Chiral drugs have two structurally similar forms that can behave very differently in biological systems due to their different shapes in three dimensional space. The two mirror images of a chiral molecule are termed *enantiomers* and the two enantiomers of a given chiral drug should be considered as two different drugs.

Like hands, enantiomers come in pairs. Both molecules of an enantiomer pair have the same chemical composition and can be drawn the same way in two dimensions (drug structure on package insert) but in chiral environments, such as on the receptors or enzymes in the body, they can behave differently. A *racemate* or racemic mixture is a mixture of equal amounts of both enantiomers of a chiral drug.

*Chirality* is defined as the geometric property of a rigid object (like a molecule or drug) which is incapable of being superimposed on its mirror image. Molecules that can be superimposed on their mirror images are *achiral* (not chiral). Chirality is a property of matter found throughout biological systems in amino acids, carbohydrates and lipids. The designations D and L (note the upper case) are used for sugars and amino acids but are specific to these molecules and are not generally applicable to other compounds. The terms *d* or *dextro* and *l* or *levo* are considered obsolete and should be avoided. Instead, the R/S system for absolute configuration and the +/- system for optical rotation should be used. The two enantiomers of a chiral drug are best identified on the basis of their absolute configuration or their optical rotation. The absolute configuration at a chiral centre is designated as *R* or *S* to unambiguously describe the three dimensional structure of the molecule. *R* is from the Latin *rectus* meaning to the right (clockwise) and *S* is from *sinister* for the left (counter-clockwise). A chiral drug may have more than one chiral centre and therefore it is necessary to assign an absolute configuration to each centre. Optical rotation is often used for a given enantiomer pair, one enantiomer can be designated (+) and the other as (-) based on the direction they rotate polarized light.

Racemates can be designated as (R,S) or (+)

#### Chiral drugs in biological systems

Enantiomers of a chiral drug have identical physical and chemical properties in an achiral environment. However, in a chiral environment, one enantiomer may display different chemical and pharmacological behaviour from the other enantiomer. Because living systems are themselves chiral, each of the enantiomers of a chiral drug can behave very differently *in vivo*. In other words, the R-enantiomer of a drug will not necessarily behave the same way as the S-enantiomer of the same drug when taken by a patient. For a given chiral drug, two enantiomers should be considered as two separate drugs with different properties unless proven otherwise.

#### Importance of chirality in drugs

In the marketplace, about 50% of drugs are chiral and of these about half are mixtures of enantiomers rather than single enantiomers. It is critical to distinguish the single enantiomer drug from the racemic form because they may differ in their dosages, efficacies, side effect profiles or even indicated use.

The two enantiomers of a chiral drug may also differ significantly in their bioavailability, rate of metabolism, metabolites, excretion, potency, receptor selectivity and toxicity. The use of single-enantiomer drugs can potentially lead to simpler and more selective pharmacologic profiles, improved therapeutic indices, and decreased side effects.

#### Asomex<sup>®</sup> S(-)amlodipine

Amlodipine is a widely prescribed calcium channel blocking antihypertensive (CCB) agent. However, amlodipine is a racemate with an equal proportion of two enantiomers S and R, thus patients receiving amlodipine are in fact taking two different drugs S-Amlodipine and R-Amlodipine which do not have the same level of antagonistic effect on the calcium channel receptor. The S-enantiomer of amlodipine is active and the R-enantiomer is inactive in terms of calcium channel blocking activity.

S(-)Amlodipine has 1000 fold stronger calcium channel blocking activity than R-Amlodipine. S(-)Amlodipine is therefore responsible for all of the CCB-mediated pharmacodynamic action of amlodipine including its anti-anginal activity.

Asomex<sup>®</sup> S(-)amlodipine 2.5 and 5 mg (10s) by Emcure

## Asomex® S(-) amlodipine

Asomex® is the world's first chirally pure antihypertensive. S-Amlodipine is the only vasoactive enantiomer of amlodipine. The R-Amlodipine accumulates in the elderly and may contribute to the side-effects seen with the racemate, such as pedal edema. Randomised controlled trials of S-Amlodipine for the treatment of hypertension administered at half the dose of racemate has been shown to be as effective as racemate but with reduced incidence of peripheral edema. S-Amlodipine is also safe and effective in elderly hypertension, isolated systolic hypertension and in treatment of angina. Thus, in S-Amlodipine, drug action is stereo-specific and it is this enantiomer which best fits the receptor and has the highest therapeutic activity.

**Asomex® S(-)Amlodipine** is indicated for the treatment of:

- Angina
- Essential hypertension
- Hypertension in the elderly
- Isolated systolic hypertension

**Side effects:** On the basis of clinical data, only minor side effects have been reported with the use of S-Amlodipine. Caution should be exercised when administering S-Amlodipine to hepatic and renally impaired patients.

**Dosage and administration:** The usual recommended dosage is 2.5 mg for the treatment of hypertension. If required, the dose may be increased to 5 mg once daily. Supplied as Asomex® 2.5 and 5 mg in blister strips of 10 tablets by Emcure.

### The common cold

The cold and flu season has arrived. Many patients currently suffering from a cold will turn to a pharmacist for treatment. What should pharmacists be recommending? There is no cure for the common cold, but symptom relief should be offered. Analgesics such as paracetamol, aspirin and ibuprofen relieve fever, chills, sore throats, headaches and sinus pain. After analgesics, topical decongestants help to relieve the nasal congestion associated with colds. Cough syrups can also be recommended for relieving the cough commonly associated with respiratory conditions. Carlisle produces a wide range of cough preparations to treat the symptom complex with which the patient presents. Is there some truth in the pearls of wisdom passed down through the ages "feed a cold, starve a fever?" A few small scale studies suggest that this represents sound medical advice. The rationale may be that eating and drinking helps the body generate heat during a cold, while reducing food intake helps to relieve the inner heat produced during a fever.

## HDL in diabetics differs but improves with Niacin

Researchers are learning more about the protective effects of HDL. Besides removing cholesterol from plaque and bringing it to the liver, leading to a regression of atherosclerosis, research suggests that HDL's direct effects on nitric-oxide (NO) production are also important. Previous studies have shown that HDL cholesterol has endothelial protective effects, such as stimulating NO production and endothelial-dependent vasomotion. In addition, some studies also suggest that HDL has antioxidant effects, while others have shown that it promotes endothelial-progenitor-cell (EPC) mediated endothelial repair. Most of these studies, however, were performed using HDL isolated from healthy subjects or reconstituted HDL.

In a recent study, done at the Hannover Medical School, Germany, the researchers isolated HDL cholesterol from 10 healthy subjects and 33 individuals with diabetes and low HDL-cholesterol levels. They then measured the effects of HDL on endothelium-dependent vasodilation and EPC-mediated endothelial repair.

Compared with healthy subjects, the endothelial protective properties of HDL from diabetic patients were markedly impaired. The HDL from healthy subjects stimulated endothelial NO production and reduced endothelial oxidant stress. HDL also improved endothelium-dependent vaso-dilation and improved early EPC-mediated endothelial repair. These benefits were not observed in diabetic patients.

Diabetic patients with low HDL-cholesterol levels and those meeting the criteria for metabolic syndrome are regularly treated with HDL-raising therapies. Thus, a group of researchers wanted to evaluate whether niacin altered the quality of their HDL. They randomized the diabetic patients to niacin extended-release 1500 mg/day or placebo for three months.

Treatment with niacin increased HDL-cholesterol levels, but more importantly, also improved the endothelial protective effects compared with the HDL from healthy subjects. In those diabetics treated with niacin, endothelial-cell NO production and EPC-mediated endothelial repair was stimulated. Niacin also reduced the amount of myeloperoxidase-induced antioxidant damage to HDL.

The quality of the HDL was better after niacin. It not only raised HDL, which has been known for some time, but the quality of the HDL, the vasoprotective effects were improved and this may be more important than simply raising HDL-cholesterol levels.

*Heartwire, Jan 4, 2010.*

## Bleeding in genetically susceptible individual

A 90-year-old woman was hospitalized for gastrointestinal bleeding. Although she had been receiving only warfarin 5 mg/day, her international normalized ratio (INR) was 66. Warfarin was discontinued and her INR fell to 3.7 after transfusion of fresh-frozen plasma. However, it rose again spontaneously to 7.5. Eleven days after the last dose of warfarin had been administered, it was still detectable in the patient's plasma, indicating that impaired warfarin clearance may have caused an enhanced anticoagulation effect.

Genetic analysis of the cytochrome P450 (CYP) isoenzyme 2C9, which mediates the major deactivating pathway of S-warfarin, revealed that the patient was a compound heterozygote carrying two variant alleles: CYP2C9\*2 and CYP2C9\*3. The patient's enhanced sensitivity to warfarin 5 mg/day can be ascribed to decreased clearance of S-warfarin secondary to genetic alteration of the gene encoding CYP2C9, resulting in a life-threatening bleeding complication.

Warfarin is administered as a racemate containing equal amounts of R and S enantiomers. Most of its anticoagulant activity is attributed to the S-enantiomer which is four-fold as active as the R-enantiomer. The major deactivating pathway of warfarin is mediated predominantly by CYP2C9. About 20% of Caucasian patients carry a single CYP2C9 allelic variant (CYP2C9\*2 or CYP2C9\*3), and approximately 1% carry two mutated alleles. Carriers of these defective alleles metabolize S-warfarin more slowly than do individuals who lack an allelic variant for CYP2C9. Thus, they may exhibit excessive anticoagulation and enhanced bleeding diathesis if treated with the usual warfarin dosage. Reducing the warfarin dosage in such individuals may significantly enhance the safety of long-term therapy. In contrast, CYP2C9\*2 is present in 4% of African-Americans, and this allele is extremely rare among Japanese individuals. *Pharmacotherapy*. 2002;22(1).



"Let the healing begin."

## CT imaging and cancer risk

The use of computed tomographic (CT) scans has increased dramatically over the last few decades. Irrespective of the recognised benefits from the radiologic definitions achieved with this technology, there is growing concern about radiation exposure associated with CT imaging, particularly with the lifetime attributable risk for radiation-related secondary cancer development. The potentially harmful consequences of ionizing radiation are divided into *deterministic* and *stochastic* effects. *Deterministic* effects of ionizing radiation result from cell and tissue death. Such changes occur only at doses above a certain threshold and are proportional to the dose given. Radiation doses from medical diagnostic procedures are usually far below this threshold, but adverse effects, such as skin burns have been reported after interventional procedures that use fluoroscopy. *Stochastic* radiation effect refers to irradiated cells that are modified rather than killed. Modified cells may develop into cancer after a latency period of years. In principle, stochastic effects have no threshold. Exposed individuals do not incur ill effects but they have a higher statistical chance for toxicity including cancer. These doses delivered in diagnostic procedures are large enough to cause stochastic radiation effects and the probability increases with the magnitude of the dose.

Although exact risk estimates related to low doses of radiation exposure are difficult to ascertain, the ionizing radiation exposure from a single abdominal or chest CT scan may be associated with elevated risk for DNA damage and cancer formation. The seventh National Academy of Science report on Biological Effects of Ionizing Radiation estimated that a single dose of 10 Sv produces a lifetime risk of developing a solid cancer or leukemia of 1 in 1000.

Therefore, it may be time for a paradigm shift in the way clinicians approach the use of CT imaging and balance the risk-benefit profile for the patient.

*Arch Intern Med* 2009;22:2071.

### Skin patches and steroid spray

Some patients complain of skin redness or itching after applying Duragesic® and other skin patches. Prescribing a corticosteroid nasal spray or inhaler to use **on the site** before applying the patch will prevent rashes.

The sprays are used because of concerns that the emollients in steroid creams and ointments will affect patch adhesion. The metered dose inhaler also allows for easy delivery.

Advise patients that they can also minimize irritation by alternating sites and not applying the patch to skin that is already irritated.

## How to manage - coughs and colds

When a patient is miserable with a fever, cough, congestion or a runny nose, there are many choices for managing their symptoms. The preparation of choice depends upon the patient's age, duration and frequency of cough, type and onset of cough and the characteristics of the sputum. The patient's accompanying symptoms, smoking habits and any medications (Rx, OTC, herbal) must also be evaluated.

*Carlisle Laboratories* offers a full range of cough and cold medications for the entire family. Following are some selection guidelines:

**Tuscosed Linctus**, a cough suppressant for treating a non-productive, dry, irritating cough. It may be sedating, thus it is suitable for night-time dosing. **Histatussin DM Liquid**, a cough suppressant for a persistent, non-productive cough which is accompanied by nasal congestion. Suitable for a cough associated with a post-nasal drip. *Sucrose-free.*

**Histal DM Liquid** is a non-drowsy, day-time cough suppressant. *Sucrose free.* **Histatussin Liquid** is indicated for the relief of cold symptoms, runny nose and chestiness. *Sucrose free.* **Histal Ex Liquid** stimulates expectoration in colds and bronchitis. *Sucrose free.*

**Histal DC Liquid** is for congestion associated with colds, allergies and sinusitis.

**Histal DC tablet** is the tablet formulation for congestion associated with colds, allergies and sinusitis.

## New Drugs/Devices

**Novartis Consumer Health** is a world leader in self-medication products for the treatment and prevention of self-limiting conditions.

**Excedrin**® a triple combination of acetaminophen, aspirin and caffeine is an analgesic known for its potency and strong positioning for relief as the 'headache medicine.' Until 2005, it was manufactured by Bristol-Myers Squibb, but in July 2005 it was purchased by Novartis, along with other products from BMS's over the counter business. Following is their selection of products based on headache type and severity.

**Excedrin**® caplets 24s

**Excedrin**® Extra Strength 45 x 2s

**Excedrin**® Migraine caplets 50s

**Excedrin**® Sinus Headache caps 24s

**Excedrin**® tension caps 24s

**Procto-Glyvenol**® 400 mg Suppository is indicated for relief of the unpleasant symptoms of internal and external hemorrhoids (pain, itching). The suppositories should be inserted rectally morning and evening or simply once daily at night and **Procto-Glyvenol**® cream applied in the morning.

*Supplied as Procto-Glyvenol*® 400 mg suppository 5s and *Procto-Glyvenol*® cream 15 g by Novartis

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