

Vaxamine™

A Natural, Botanical Anti-Inflammatory 5-LOX & COX-2 Selective Inhibitor

Question: How does Vaxamine compare to the prescription COX-2 inhibitors (Vioxx and Celebrex) and the OTC NSAID pain relievers such as aspirin and ibuprofen?

Answer: In-vivo human oral dosing studies conducted with the active ingredient in **Vaxamine™** demonstrated excellent potency and selectivity for COX-2. Oral dosing of **Vaxamine™** (1 gram) produced a 56% reduction in COX-2 versus a 62% reduction for a 400 mg. (two tablets) dose of the OTC pain reliever Ibuprofen. However, the selectivity of **Vaxamine™**, which is calculated as the COX-1 IC-50/COX-2 IC-50, was 0.25 versus 1.41 for Ibuprofen. Therefore, **Vaxamine™** is of equivalent potency to Ibuprofen, but much more selective for the COX-2 form of the enzyme than COX-1. Based on numerous clinical studies done with COX-2 selective inhibitors, a COX-2 selective inhibitor is expected to be gentler on the stomach than a non-selective COX inhibitor such as Aspirin or Ibuprofen.

The prescription COX-2 inhibitor Celebrex produced a 45% reduction in COX-2 activity in our human oral dosing study, versus 56% for **Vaxamine™**, making **Vaxamine™** more potent than Celebrex. The selectivity of Celebrex (COX-1/COX-2) was 0.45 versus 1.41 for **Vaxamine™**, making **Vaxamine™** not only more potent than Celebrex, but also more selective for COX-2 inhibition.

Vioxx, the second COX-2 inhibitor to be approved by the FDA, and also a blockbuster drug, which achieved over \$3 billion in sales, is highly selective for COX-2. Published human oral dosing studies with Vioxx demonstrated that Vioxx produced an almost complete inhibition of COX-2, with no inhibition of COX-1. The COX-2 selectivity for Vioxx is therefore almost 1:100, in other words, Vioxx virtually shuts down COX-2, blocking all down stream production of prostaglandins. It is known that some prostaglandins such as prostacyclin (PGI-2) are important for cardiovascular health, whereas pro-inflammatory prostaglandins, such as PGE-2, are responsible for inflammation.

The natural anti-inflammatory patent pending ingredient in **Vaxamine™**, derived from botanical alpha acids, is therefore believed to be an effective pain reliever with equivalent potency (efficacy) to synthetic drugs, but with a stomach friendly side-effect profile, especially when used on a chronic basis. Individuals, who suffer from chronic pain such as osteoarthritis, are driven to consume pain relievers on a daily basis due to the chronic nature of the inflammation. Chronic use of dual inhibitors of both COX-1 and COX-2 will produce gastric erosion. Conversely, too much selectivity and potency for COX-2 may result in other side effects, such as potentially harmful cardiovascular events associated with the complete inhibition of prostaglandin production.

By producing about a 56% reduction in COX-2, Vaxamine™ does not completely shut down the production of all prostaglandins, but does inhibit the production of pro-inflammatory PGE-2 enough to provide pain relief equivalent to OTCs and prescription pain relievers, but with better selectivity for COX-2. By inhibiting COX-1 by about 10-15%, Vaxamine™ provides for some anti-platelet aggregation, while also preserving prostacyclin production, which is beneficial for cardiovascular health.

Vaxamine™ "The Gastro and Cardio friendly all-natural anti-inflammatory"

- Preserves prostacyclin production
- Anti-platelet aggregation via slight COX-1 inhibition
- Stomach friendly due to good COX-2 selectivity

Vaxamine™ is FDA "GRAS" Generally Recognized As Safe

Vaxamine™ Human Oral Dosing/In-Vivo Studies

Two human oral dosing clinical studies have been conducted with the COX-2 inhibitor in **Vaxamine™**. These studies were designed to assess the COX-2 and COX-1 inhibition of **Vaxamine™** in vivo. The two most important things that need to be determined when screening for new COX-2 inhibitor anti-inflammatory compounds are the potency and selectivity. The potency is determined by the magnitude of COX-2 inhibition from baseline, and the selectivity is determined from the ratio between COX-2 and COX-1. If the COX-2 inhibition is divided by the COX-1 inhibition, a number is obtained, and the lower the number, the more selective the compound is for COX-2 inhibition relative to COX-1 inhibition.

Cyclooxygenase Inhibiting Activity Of **Vaxamine™**: Oral Dosing Study In Humans : Summary of Results

Study Objective

This study was designed to assess the potential of **Vaxamine™**, to inhibit cyclooxygenase-1 and 2, (COX-1, COX-2) compared to a control product with known COX inhibiting and pain-relieving properties (400mg ibuprofen). The criterion for success was comparable COX inhibition and selectivity equal to or greater than the ibuprofen control.

Method

Twenty four healthy subjects were enrolled in the study following screening for inclusion and exclusion criteria. Twelve subjects were assigned to receive COX-2 inhibiting ingredient in **Vaxamine™** (1,000 mg.). Twelve subjects were assigned to the ibuprofen control group; dosing in the control group was a single two tablet dose (400 mg.). Blood samples were taken immediately before the dosing of test products, as well as at various time points after the dose. The subjects in the control group gave blood samples 6 hours before as well as immediately before dosing, and 0.5, 1, 2, and 3 hours after dosing.

Results

Plasma from each of the blood samples were evaluated for potency and selectivity in a validated ex vivo assay. It should be noted that the only way to measure COX-2 is by the protocol of Giuliano, F. et al, in Br J Pharmacol 126, 1824-30; 1999, in which the test compounds are administered orally, blood is drawn, and COX-1 and COX-2 are measured Ex-Vivo.

Cox-2 inhibitory potency and selectivity

The effectiveness of a Cox-2 inhibitor can be expressed in terms of its **potency**, and in terms of its **selectivity**.

Cox-2 potency refers to the ability of a product to

reduce the amount of Cox-2 enzyme in the blood by a given percent. For example, a product which inhibits Cox-2 enzyme by a maximum of 50% within a given sampling period is more potent than one that inhibits it by 30%.

Cox-2 selectivity refers to the degree to which a product

is able to inhibit Cox-2 without inhibiting Cox-1. Selectivity is calculated by dividing the *integrated Cox-1 potency* by the *integrated Cox-2 potency* (see below). The smaller the number below one, the greater the Cox-2 selectivity.

Integrated potency is potency over time: for example, if

a product inhibits Cox-2 by 50% over 4 hours, the integrated potency equals 200 (50 X 4). If the same product inhibits Cox-1 by 25% over 4 hours, its integrated Cox-1 potency will be 100, and its Cox-2 selectivity will be 100 divided by 200, or 0.5.

Product effects over the sampling time are expressed as a percentage of baseline Cox-1 and -2 activity in **Figure 1**. The maximum Cox inhibition within the 9-hour (active products) or 3 hour (ibuprofen control) sampling time represents each product's Cox-2 inhibitory potency. The Cox-2 inhibitory potency of Vaxamine™ (56%) was in the range of the Cox-2 inhibitory potency of a single 2-tablet dose of ibuprofen (62.2%). As expected from published reports¹ and in previous unpublished studies, plasma from subjects in the ibuprofen group (bottom right panel) inhibited Cox-1 and Cox-2 by 80% and 60%, respectively. The potency and selectivity results are shown in table 1.

Table 1.

Table 1. Integrated Cox potency and selectivity values. Means +/- standard error.

Product	Integrated Potency		Ratio	Cox-2 Selectivity Statistics	
	Cox-1	Cox-2		Within Products	Between Products
Vaxamine™	90.09 ±51	354.2 ±23	0.25	**	a
Ibuprofen	233.5 ±12	166.3 ±5	1.40	*	b

Integrated Potency: Increasing number indicates increasing inhibition of Cox-1 or Cox-2. Cox-2 selectivity Ratio: the smaller the number below 1, the greater the selectivity. Selectivity comparisons within products: * = P < 0.05, ** = P < 0.01, n.s. = not significant. Selectivity comparisons between products: ratios not sharing a letter are significantly different.

Vaxamine™ showed statistically significant Cox-2 selectivity. (Ibuprofen, by contrast and as expected, was selective towards Cox-1.) The Cox-2 selectivity of Vaxamine™ was significantly different (p<0.01) from that of ibuprofen.

Vaxamine™/Celecoxib Comparison Study

A comparison study was conducted to compare the effects of Vaxamine™ and Celecoxib (Celebrex®). Six subjects were dosed with Vaxamine (1,000 mg. “Now only 150mg”) and six subjects with Celecoxib and COX inhibition activity was measured in plasma according to the previous protocol. Additionally, six subjects were given a 400-mg. dose of Ibuprofen for comparison. Results of the study are summarized below.

Maximum Cox-2 reduction from baseline over 3 hours, by product, and Cox-2 specificity, by product. Comparative data from separate Celebrex and Ibuprofen pilot study included.				
	Vaxamine	Ibuprofen	Ibuprofen from 2	Celebrex
% Reduction from baseline COX-2	56%	62%	69%	45%