# CAVADEX for the treatment of atherosclerosis heart disease

Professor Laurence Guy Howes MB BS PhD FRACP FCSANZ.
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***Cavadex (dihydroxypropyl) ß cyclodextrin for the treatment of atheromatous disease. Prof L.G. Howes. March 2023.***

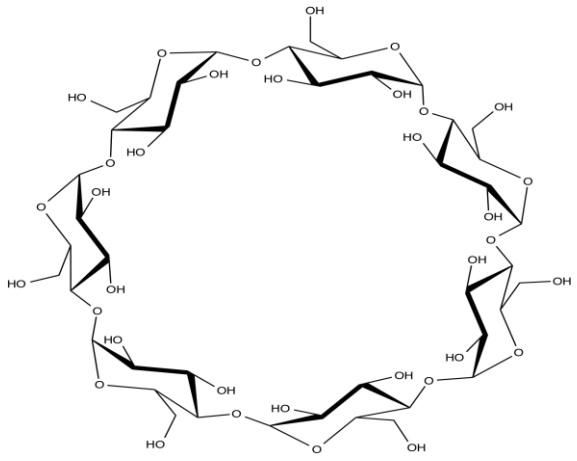
## *What is atheromatous vascular disease?*

1. Atheromatous disease occurs when cholesterol infiltrates and causes inflammation and damage in the artery wall of arteries (called plaques) which cause thrombosis, the net effect being to block the artery's blood flow, leading to tissue damage. Examples of atheromatous diseases are myocardial infarction, angina, stroke, and peripheral vascular disease.

2. Atheromatous vascular disease is the most prevalent non-infective disease in humans. The cost of detecting and managing the consequences of atheromatous disease is close to US$1 trillion per annum in the US alone.

## *What are cyclodextrins ?*

3. Cyclodextrins are a family of compounds that have a ring of glucose molecules with hydroxyl groups that are attracted to water pointing outwards and an inner ring which is attracted to fatty molecules such as cholesterol. Cholesterol in plaques is attracted to the middle of the cyclodextrin ring and is taken from the plaques and eliminated from the body. Cyclodextrins have been used in high concentrations for many decades as a carrier to improve the performance of other drugs. They are **approved** by regulatory bodies for this purpose and are very safe.



Beta cyclodextrin

4. The optimal number of glucose molecules in the cyclodextrin ring for the capture of cholesterol molecules is 7, otherwise known as a ß ring. Cyclodextrins may also have a side chain attached to the outer surface of the ring. This attachment affects the pharmacological properties of the compound and the substitution on ***Cavadex*** (*dihydroypropyl)* appears to assist with the uptake of cholesterol. ***Cavadex*** *is dihydroxypropyl ß cyclodextrin.* ***Cavadex*** is given rectally at a dose of 3g/day (as a suppository) or intravenously at a dose of 6mg/day. It is not active when given by mouth.

5. Intravenous infusions of *dihydroxy propyl ß cyclodextrin* have been administered to mice with experimental atheromatous disease and cholesterol plaques, and rapid reductions in the content of cholesterol accompanied by resolution of the plaques were observed. Laboratory studies have demonstrated the molecular pathways involved in the removal of cholesterol from arterial plaques in response to *dihydroxy propyl ß cyclodextrin* administration.

## *Have cyclodextrins been used to treat atheromatous disease in humans?*

6. So far the human data in atheromatous diseases have been from observations of individuals and groups of individuals with atheromatous disease treated with for one to several months. There have been no clinical trials of cyclodextrins. However, over 170 people with atheromatous have received ***Cavadex*** and there is observational evidence for plaque regression after only one to 2 months. These effects occur after either intravenous or rectal administration. In addition, in patients suffering from angina (chest pain), angina rapidly resolved after only a few weeks. This most likely occurs because the removal of cholesterol has immediate effects to reduce local chemical molecules that modulate inflammatory responses and vasodilation in and around plaques.

7. The rapid resolution of angina symptoms has been reported by a cardiologist in a US Mid West Clinic. Twenty patients with active angina were treated with ***Cavadex*** using rectal administration. A **marked improvement** or **resolution of angina** occurred in **18 (90%)** compared with an expected spontaneous improvement of about **10%** (Ghandi et al). Putting these figures into a 2x2 contingency table comparing the 20 patients with 20 fictitious untreated controls the probability of a 90% improvement rate being spontaneous is **P< 0.0001** by Fishers' Exact Test or the Chi Squared test.

8. These effects must be considered to be specific for ***Cavadex*** as the pharmacological characteristics of cyclodextrins varies with changes in the size of the polysaccharide ring, the nature of the chemical group attached to the external part of the ring and the degree of polymerisation of the ***Cavadex*** molecules (the number of molecules stacked on top of each other).

## *Do other treatments cause plaque regression and rapid resolution of angina ?*

9. Plaque regression has been observed in about 80% of patients following intensive, high dose statin therapy to reduce LDL cholesterol to less than 1.8 mmol/L. However, the process is slow, about a couple of mm in plaque size over one to several years. Other methods are undergoing clinical trials using the protein constructs of HDL eg Apoprotein A infused intravenously. The treatment is more invasive than ***Cavadex*** and if it is ever marketed it will be much more expensive than ***Cavadex.***

## *What products will Cavadex be in competition with?*

10. ***Cavadex*** will be a new additive therapy used in conjunction with other established therapies for the treatment and prevention of atheromatous disease. Cyclodextrins will have no immediate competitors for reducing plaque cholesterol and will be given along with statins. It is expected that ***Cavadex*** will lead to less requirement for percutaneous coronary intervention and less anti anginal drug use.

## *What is the potential market size?*

It is difficult to comprehend the size of the market for ***Cavadex.*** The first drug to the market that causes rapid plaque regression will be enormously popular. I would not be surprised if sales in the first year were constrained by logistics rather than the attraction of customers. I believe the initial sales after launch will return a Company profit greater than US$1 billion in the first year in the US alone. *Dihydropropyl ß cyclodextrin* therapy to reduce atheromatous plaques will be one of the greatest therapeutic advances of our time. It will be the greatest therapeutic advance in cardiovascular medicine since the introduction of the statins.

Cyclodextrins *will* come on the market for treating atheromatous diseases and their impact *will* be huge. The only question is who will get them into the marketplace first.

Professor Laurence Guy Howes MB BS PhD FRACP FCSANZ.
Preeminent Consultant Physician (Cardiology)
Professor of Pharmacology and Therapeutics

(see attached Curriculum Vitae)

**Reference**

Gandhi MM, Lampe FC, Wood DA
Incidence, clinical characteristics, and short-term prognosis of angina pectoris.
*Heart* 1995; **73:**193-198.

**Professor Laurence Guy Howes MB BS PhD FRACP FCSANZ.**

# Preeminent Consultant Cardiologist and Director of cardiovascular research at GCUH.

In addition I am Professor of Pharmacology and Therapeutics at Griffith University
I have over 230 peer reviewed publications principally in preventive cardiology and clinical cardiovascular pharmacology.
I have been a full professor of medicine for over 30 years.
Over this time I have been an External Drug Evaluator for the TGA and constant to the pharmaceutical industry . I served on the South East Sydney Area Human Ethics Committee for 13 consecutive years

My main areas of research at present are multi centre clinical trials of novel cardiovascular drugs and the effects of nutraceutical mediated reduction of oxidative stress on vascular function.
My principal clinical specialty is preventive cardiology.