CHAPTER II

REVIEW OF GEMFIBROZIL

Gemfibrozil is a lipid-regulating agent, which is classified as a fibric acid derivative. It was launched to the market in 1985 under the proprietary name Lopid(R) by Parke-Davis/Warner-Lambert

1. Physicochemical Properties

Name	Gemfibrozil
Chemical Name	5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid
Description	White waxy crystalline solid
Empirical Formula	$C_{15}H_{22}O_3$
Structural Formula	

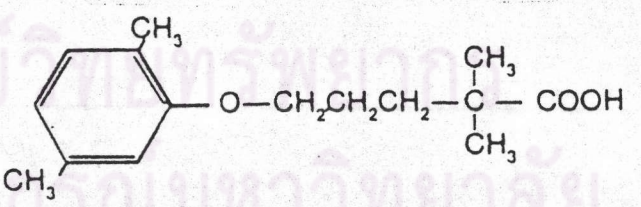

Figure 1 Chemical structure of gemfibrozil

Molecular Weight	250.35
Melting Range	Between 58° and 61°C
Solubility	Very slightly soluble in water Practically insoluble in alcohol, chloroform

2. Pharmacological Effect (Todd and Ward, 1988)

The fundamental mechanism of action of gemfibrozil is not well established. Lipoprotein lipase activity is increased and hepatic triglyceride production is decreased, but more significantly there is a marked increase in the clearance of triglycerides from plasma. Increased HDL is associated with increased synthesis of the major HDL carrier apolipoproteins AI and AII. It is difficult to interprete which of the effects of gemfibrozil are primary or secondary drug effects.

3. Therapeutic Indication (Todd and Ward, 1988)

Gemfibrozil therapy should be used selectively in patients who have not responded to dietary control or other non-pharmacological measures. It may be used in Fredrickson Types IIA, IIB, III, IV and hyperlipidemia associated with diabetes.

4. Pharmacokinetics

Absorption :

Gemfibrozil is rapidly and completely absorbed, with peak plasma levels occuring one to two hours after oral administration. The dose of gemfibrozil 600 mg twice daily produced mean peak plasma concentration between 15 and 25 mg/L (Anon, 1982; Okerholm, 1976).

Plasma drug concentration is directly proportional to dose and tends to rise during repeated administration, although steady-state is achieved within 7 to 14 days with twice daily dose (Smith, 1976).

Distribution :

The tissue distribution of gemfibrozil and transfer of the drug into breast milk or across the placenta have not been reported in humans. In vitro, gemfibrozil is highly bound to human serum albumin (97 to 98.6%) at therapeutic concentrations (Anon, 1982; Hamberger et al., 1986).

Metabolism and Excretion :

Gemfibrozil is metabolised to a number of compounds in man. The principal metabolite is the benzoic acid derivative. All the metabolites and unchanged drug form glucuronide conjugates (Randinitis et al., 1984).

The mean terminal phase elimination half-life of gemfibrozil after oral administration of 600 mg doses to healthy subjects is 1.5 to 2.0 hours (Smith, 1976).

5. Adverse Effects (Frick et al., 1987)

There have been no reports of serious adverse reactions which are definitely attributable to the drug. Gastrointestinal symptoms and rash are the only effects occuring more frequently than with placebo, although the Helsinki Heart Study results are suggestive that these adverse effects diminish with time. Additional adverse effects that have been reported where a causal relationship to treatment with lopid is probable are gallstone formation, cholestatic jaundice and cholelithiasis. No clear pattern of drug-related toxicity is indicated by clinical laboratory tests.

6. Dosage and Administration (Kovanen, Koskinen and Manninen, 1986)

The recommended dosage of gemfibrozil is 600 mg twice daily given 30 minutes before morning and evening meals. Some patients may respond to 900 mg per day and a few may require 1500 mg per day.

7. Drug Interactions (Anon, 1982; Hamberger et al., 1986)

Gemfibrozil is highly protein bound. As such, it might be expected to interact with other protein bound drugs. However, the only significant drug interaction seen

so far is an enhancement of the effect of anticoagulants. The dosage of anticoagulant should be reduced to maintain prothrombin time at the appropriate level to prevent bleeding complications.

8. Contraindication (Frick et al., 1987; Nash, 1980)

Contraindication include hepatic or renal dysfunction, gallbladder disease and known hypersensitivity to gemfibrozil. Safety and efficacy have not been established in children, and gemfibrozil should only be used in pregnant or lactating women if the benefit clearly outweighs any potential risk.