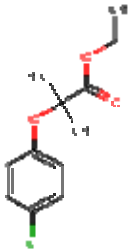
Identification

Name	**Clofibrate**
Accession Number	**DB00636** (APRD00879)

Type	small molecule
Groups	approved
Description	A fibric acid derivative used in the treatment of hyperlipoproteinemia type III and severe hypertriglyceridemia. (From Martindale, The Extra Pharmacopoeia, 30th ed, p986)
Structure	 Download: MOL | SDF | SMILES | InChI Display: 2D Structure | 3D Structure
Synonyms	• Chlorfenisate • Chlorphenisate • Clofibate • Clofibrato • Clofibratum • CPIB • EPIB • Ethyl chlorophenoxyisobutyrate • Ethyl clofibrate • Ethyl p-chlorophenoxyisobutyrate • Ethyl para-chlorophenoxyisobutyrate
Synonyms	Chlorfenisate Chlorphenisate Clofibate Clofibrato Clofibratum CPIB EPIB Ethyl chlorophenoxyisobutyrate Ethyl clofibrate Ethyl p-chlorophenoxyisobutyrate
Salts	Not Available

	Name	Company
Brand names	Amotril Amotril S Angiokapsul Anparton Antilipid Antilipide Apolan Arterioflexin Arterosol Artevil	

Brand mixtures	Not Available
Categories	• Anticholesteremic Agents • Antilipemic Agents
CAS number	637-07-0
Weight	Average: 242.699 Monoisotopic: 242.070972053
Chemical Formula	$C_{12}H_{15}ClO_3$
InChI Key	InChIKey=KNHUKKLJHYUCFP-UHFFFAOYSA-N
InChI	InChI=1S/C12H15ClO3/c1-4-15-11(14)12(2,3)16-10-7-5-9(13)6-8-10/h5-8H,4H2,1-3H3 Plain Text
IUPAC Name	ethyl 2-(4-chlorophenoxy)-2-methylpropanoate
SMILES	CCOC(=O)C(C)(C)OC1=CC=C(Cl)C=C1Plain Text
Mass Spec	show (7.78 KB)

Taxonomy

Kingdom	Organic
Classes	• Phenoxyacetates
Substructures	• Carboxylic Acids and Derivatives • Acetates • Phenols and Derivatives • Phenoxyacetates • Short-chain Hydroxy Acids • Ethers • Benzene and Derivatives • Aryl Halides • Halobenzenes • Aromatic compounds • Anisoles • Phenyl Esters

Pharmacology

Indication	For Primary Dysbetalipoproteinemia (Type III hyperlipidemia) that does not respond adequately to diet. This helps control high cholesterol and high triglyceride levels.
Pharmacodynamics	Clofibrate is an antilipidemic agent similar to gemfibrozil. It acts to lower elevated serum lipids by reducing the very low-density lipoprotein fraction (S_f 20-400) rich in triglycerides. Serum cholesterol may be decreased, particularly in those patients whose cholesterol elevation is due to the presence of IDL as a result of Type III hyperlipoproteinemia. Several investigators have observed in their studies that clofibrate may produce a decrease in cholesterol linoleate but an increase in palmitoleate and oleate, the latter being considered atherogenic in experimental animals. The significance of this finding is unknown at this time. Reduction of triglycerides in some patients treated with clofibrate or certain of its chemically and clinically similar analogs may be associated with an increase in LDL cholesterol. Increase in LDL cholesterol has been observed in patients whose cholesterol is initially normal. Animal studies suggest that clofibrate interrupts cholesterol biosynthesis prior to mevalonate formation.
Mechanism of action	Clofibrate increases the activity of extrahepatic lipoprotein lipase (LL), thereby increasing lipoprotein triglyceride lipolysis. Chylomicrons are degraded, VLDLs are converted to LDLs, and LDLs are converted to HDL. This is accompanied by a slight increase in secretion of lipids into the bile and ultimately the intestine. Clofibrate also inhibits the synthesis and increases the clearance of apolipoprotein B, a carrier molecule for VLDL. Also, as a fibrate, Clofibrate is an agonist of the PPAR-α receptor[4] in muscle, liver, and other tissues. This agonism ultimately leads to modification in gene expression resulting in increased beta-oxidation, decreased triglyceride secretion, increased HDL, increased lipoprotein lipase activity.
Absorption	Completely but slowly absorbed from the intestine. Between 95% and 99% of an oral dose of clofibrate is excreted in the urine as free and conjugated clofibric acid; thus, the absorption of clofibrate is virtually complete.
Volume of distribution	Not Available
Protein binding	Highly protein-bound (95% to 97%).
Metabolism	Hepatic and gastrointestinal: rapid de-esterification occurs in the gastrointestinal tract and/or on first-pass metabolism to produce the active form, clofibric acid (chlorophenoxy isobutyric acid [CPIB]).
Route of elimination	Not Available
Half life	Half-life in normal volunteers averages 18 to 22 hours (range 14 to 35 hours) but can vary by up to 7 hours in the same subject at different times.
Clearance	Not Available
Toxicity	Oral, mouse: LD_{50} = 1220 mg/kg; Oral, rabbit: LD_{50} = 1370 mg/kg; Oral, rat: LD_{50} = 940 mg/kg. No reported case of overdosage in humans.

Affected organisms	• Humans and other mammals
Pathways	Not Available

Pharmacoeconomics

Manufacturers	• Wyeth ayerst laboratories • Banner pharmacaps inc • Sandoz inc • Teva pharmaceuticals usa inc • Usl pharma inc • Watson laboratories inc
Packagers	• Banner Pharmacaps Inc. • Major Pharmaceuticals • Novopharm Ltd.

Dosage forms	Form	Route	Strength
	Capsule	Oral	

Prices	Not Available
Patents	Not Available

Properties

State	liquid
Melting point	< 25 oC (boiling point 148-150°C at 25 mm Hg)

Experimental Properties

Property	Value	Source
water solubility	Insoluble	PhysProp
logP	3.3	PhysProp

Predicted Properties

Property	Value	Source
water solubility	2.90e-02 g/l	ALOGPS
logP	3.99	ALOGPS
logP	3.4	ChemAxon Molconvert
logS	-3.9	ALOGPS
pKa	0	ChemAxon Molconvert
hydrogen acceptor count	2	ChemAxon Molconvert
hydrogen donor count	0	ChemAxon Molconvert
polar surface area	35.53	ChemAxon Molconvert
rotatable bond count	5	ChemAxon Molconvert
refractivity	62.14	ChemAxon Molconvert

	polarizability	24.7	ChemAxon Molconvert

References

Synthesis Reference	Not Available
General Reference	Not Available

	Resource	Link
External Links	KEGG Drug	D00279
	KEGG Compound	C06916
	PubChem Compound	2796
	PubChem Substance	46504748
	ChemSpider	2694
	ChEBI	3750
	ChEMBL	3750
	Therapeutic Targets Database	DAP000262
	PharmGKB	PA449045
	Drug Product Database	2038
	RxList	http://www.rxlist.com/cgi/generic2/clofibrate.htm
	Drugs.com	http://www.drugs.com/mtm/clofibrate.html
	Wikipedia	http://en.wikipedia.org/wiki/Clofibrate

ATC Codes	• C10AB01 • C10AB03
AHFS Codes	Not Available
PDB Entries	Not Available
FDA label	Not Available
MSDS	show (62.6 KB)

Interactions

	Drug	Interaction
Drug Interactions	Acenocoumarol	The fibrate increases the anticoagulant effect
	Acetohexamide	Clofibrate may increase the effect of sulfonylurea, acetohexamide.
	Anisindione	The fibrate increases the anticoagulant effect
	Chlorpropamide	Clofibrate may increase the effect of sulfonylurea, chlorpropamide.
	Dicumarol	The fibrate increases the anticoagulant effect
	Gliclazide	Clofibrate may increase the effect of sulfonylurea, gliclazide.
	Glipizide	Clofibrate may increase the effect of sulfonylurea,

	glipizide.
Glisoxepide	Clofibrate may increase the effect of sulfonylurea, glisoxepide.
Glyburide	Clofibrate may increase the effect of sulfonylurea, glibenclamide.
Glycodiazine	Clofibrate may increase the effect of sulfonylurea, glycodiazine.
Insulin	Clofibrate may increase the effect of insulin.
Insulin Aspart	Increases the effect of insulin
Insulin Detemir	Increases the effect of insulin
Insulin Glulisine	Increases the effect of insulin
Tolazamide	Clofibrate may increase the effect of sulfonylurea, tolazamide.
Tolbutamide	Clofibrate may increase the effect of sulfonylurea, tolbutamide.
Ursodeoxycholic acid	The fibric acid derivative decreases the effect of ursodiol
Warfarin	The fibrate increases the anticoagulant effect

Food Interactions

- Take with food, since it may reduce gastric irritation.

Targets

1. Peroxisome proliferator-activated receptor alpha

Pharmacological action: **yes**
Actions: **agonist**

Receptor that binds peroxisome proliferators such as hypolipidemic drugs and fatty acids. Once activated by a ligand, the receptor binds to a promoter element in the gene for acyl-CoA oxidase and activates its transcription. It therefore controls the peroxisomal beta-oxidation pathway of fatty acids

Organism class: **human**
UniProt ID: Q07869
Gene: PPARA
Protein Sequence: FASTA
Gene Sequence: FASTA
SNPs: SNPJam Report

References:

1. Barclay TB, Peters JM, Sewer MB, Ferrari L, Gonzalez FJ, Morgan ET: Modulation of cytochrome P-450 gene expression in endotoxemic mice is tissue specific and peroxisome proliferator-activated receptor-alpha dependent. J Pharmacol Exp Ther. 1999 Sep;290(3):1250-7. Pubmed
2. Murata M, Kaji H, Takahashi Y, Iida K, Mizuno I, Okimura Y, Abe H, Chihara K: Stimulation by eicosapentaenoic acids of leptin mRNA expression and its secretion in

mouse 3T3-L1 adipocytes in vitro. Biochem Biophys Res Commun. 2000 Apr 13;270(2):343-8. Pubmed
3. Hunt MC, Lindquist PJ, Peters JM, Gonzalez FJ, Diczfalusy U, Alexson SE: Involvement of the peroxisome proliferator-activated receptor alpha in regulating long-chain acyl-CoA thioesterases. J Lipid Res. 2000 May;41(5):814-23. Pubmed
4. Casas F, Domenjoud L, Rochard P, Hatier R, Rodier A, Daury L, Bianchi A, Kremarik-Bouillaud P, Becuwe P, Keller J, Schohn H, Wrutniak-Cabello C, Cabello G, Dauca M: A 45 kDa protein related to PPARgamma2, induced by peroxisome proliferators, is located in the mitochondrial matrix. FEBS Lett. 2000 Jul 28;478(1-2):4-8. Pubmed
5. Komuves LG, Hanley K, Lefebvre AM, Man MQ, Ng DC, Bikle DD, Williams ML, Elias PM, Auwerx J, Feingold KR: Stimulation of PPARalpha promotes epidermal keratinocyte differentiation in vivo. J Invest Dermatol. 2000 Sep;115(3):353-60. Pubmed
6. Gelosa P, Banfi C, Gianella A, Brioschi M, Pignieri A, Nobili E, Castiglioni L, Cimino M, Tremoli E, Sironi L: PPAR-alpha agonism prevents the oxidative stress and inflammatory processes involved in brain and renal damage in stroke-prone rats. J Pharmacol Exp Ther. 2010 Jul 29. Pubmed
7. Palkar PS, Anderson CR, Ferry CH, Gonzalez FJ, Peters JM: Effect of prenatal peroxisome proliferator-activated receptor alpha (PPARalpha) agonism on postnatal development. Toxicology. 2010 Jul 15. Pubmed

Enzymes

1. Cytochrome P450 2E1

Actions: **inducer**

Metabolizes several precarcinogens, drugs, and solvents to reactive metabolites. Inactivates a number of drugs and xenobiotics and also bioactivates many xenobiotic substrates to their hepatotoxic or carcinogenic forms

UniProt ID: P05181
Gene: CYP2E1
Protein Sequence: FASTA
Gene Sequence: FASTA
SNPs: SNPJam Report

References:

1. Preissner S, Kroll K, Dunkel M, Senger C, Goldsobel G, Kuzman D, Guenther S, Winnenburg R, Schroeder M, Preissner R: SuperCYP: a comprehensive database on Cytochrome P450 enzymes including a tool for analysis of CYP-drug interactions. Nucleic Acids Res. 2010 Jan;38(Database issue):D237-43. Epub 2009 Nov 24. Pubmed

2. Glutathione S-transferase A2

Actions: **inhibitor**

Conjugation of reduced glutathione to a wide number of exogenous and endogenous hydrophobic electrophiles

UniProt ID: P09210
Gene: GSTA2
Protein Sequence: FASTA
Gene Sequence: FASTA
SNPs: SNPJam Report

References:

1. Foliot A, Touchard D, Mallet L: Inhibition of liver glutathione S-transferase activity in rats by hypolipidemic drugs related or unrelated to clofibrate. Biochem Pharmacol. 1986 May 15;35(10):1685-90. Pubmed
2. Foliot A, Touchard D, Celier C: Impairment of hepatic glutathione S-transferase activity as a cause of reduced biliary sulfobromophthalein excretion in clofibrate-treated rats. Biochem Pharmacol. 1984 Sep 15;33(18):2829-34. Pubmed

3. Cytochrome P450 3A4

Actions: **substrate, inducer**

Cytochromes P450 are a group of heme-thiolate monooxygenases. In liver microsomes, this enzyme is involved in an NADPH-dependent electron transport pathway. It performs a variety of oxidation reactions (e.g. caffeine 8-oxidation, omeprazole sulphoxidation, midazolam 1'-hydroxylation and midazolam 4- hydroxylation) of structurally unrelated compounds, including steroids, fatty acids, and xenobiotics. The enzyme also hydroxylates etoposide

UniProt ID: P08684
Gene: CYP3A4
Protein Sequence: FASTA
Gene Sequence: FASTA
SNPs: SNPJam Report

References:

1. Preissner S, Kroll K, Dunkel M, Senger C, Goldsobel G, Kuzman D, Guenther S, Winnenburg R, Schroeder M, Preissner R: SuperCYP: a comprehensive database on Cytochrome P450 enzymes including a tool for analysis of CYP-drug interactions. Nucleic Acids Res. 2010 Jan;38(Database issue):D237-43. Epub 2009 Nov 24. Pubmed

4. Cytochrome P450 1A1

Actions: **inducer**

Cytochromes P450 are a group of heme-thiolate monooxygenases. In liver microsomes, this enzyme is involved in an NADPH-dependent electron transport pathway. It oxidizes a variety of structurally unrelated compounds, including steroids, fatty acids, and xenobiotics

UniProt ID: P04798
Gene: CYP1A1
Protein Sequence: FASTA
Gene Sequence: FASTA
SNPs: SNPJam Report

References:

1. Preissner S, Kroll K, Dunkel M, Senger C, Goldsobel G, Kuzman D, Guenther S, Winnenburg R, Schroeder M, Preissner R: SuperCYP: a comprehensive database on Cytochrome P450 enzymes including a tool for analysis of CYP-drug interactions. Nucleic Acids Res. 2010 Jan;38(Database issue):D237-43. Epub 2009 Nov 24. Pubmed

5. Cytochrome P450 2A6

Actions: **inhibitor**

Exhibits a high coumarin 7-hydroxylase activity. Can act in the hydroxylation of the anti-cancer drugs cyclophosphamide and ifosphamide. Competent in the metabolic activation of aflatoxin B1. Constitutes the major nicotine C-oxidase

UniProt ID: P11509
Gene: CYP2A6
Protein Sequence: FASTA
Gene Sequence: FASTA
SNPs: SNPJam Report

References:

1. Preissner S, Kroll K, Dunkel M, Senger C, Goldsobel G, Kuzman D, Guenther S, Winnenburg R, Schroeder M, Preissner R: SuperCYP: a comprehensive database on Cytochrome P450 enzymes including a tool for analysis of CYP-drug interactions. Nucleic Acids Res. 2010 Jan;38(Database issue):D237-43. Epub 2009 Nov 24. Pubmed

6. Cytochrome P450 2B6

Actions: **inducer**

Cytochromes P450 are a group of heme-thiolate monooxygenases. In liver microsomes, this enzyme is involved in an NADPH-dependent electron transport pathway. It oxidizes a variety of structurally unrelated compounds, including steroids, fatty acids, and xenobiotics

UniProt ID: P20813
Gene: CYP2B6
Protein Sequence: FASTA
Gene Sequence: FASTA
SNPs: SNPJam Report

References:

1. Preissner S, Kroll K, Dunkel M, Senger C, Goldsobel G, Kuzman D, Guenther S, Winnenburg R, Schroeder M, Preissner R: SuperCYP: a comprehensive database on Cytochrome P450 enzymes including a tool for analysis of CYP-drug interactions. Nucleic Acids Res. 2010 Jan;38(Database issue):D237-43. Epub 2009 Nov 24. Pubmed

7. Cytochrome P450 4A11

Actions: **substrate, inducer**

Catalyzes the omega- and (omega-1)-hydroxylation of various fatty acids such as laurate, myristate and palmitate. Has little activity towards prostaglandins A1 and E1

UniProt ID: Q02928
Gene: CYP4A11
Protein Sequence: FASTA
Gene Sequence: FASTA
SNPs: SNPJam Report

References:

1. Preissner S, Kroll K, Dunkel M, Senger C, Goldsobel G, Kuzman D, Guenther S, Winnenburg R, Schroeder M, Preissner R: SuperCYP: a comprehensive database on Cytochrome P450 enzymes including a tool for analysis of CYP-drug interactions. Nucleic Acids Res. 2010 Jan;38(Database issue):D237-43. Epub 2009 Nov 24. Pubmed