Clarke’s Analysis of Drugs and Poisons

**Disposition in the Body** Orlistat is not absorbed following oral administration and plasma concentrations of intact orlistat are non-measurable. There is no evidence of accumulation and no defined systemic pharmacokinetics. Metabolism may occur within the gastrointestinal wall. There are two metabolites M1 (4-member lactone ring hydrolysed) and M3 (M1 with N-formyl leucine moiety cleaved) which account for ~42% of the total plasma concentration. Elimination is mainly by faecal excretion of the unabsorbed drug, with ~97% of the administered dose excreted in this way, 83% of which is the unchanged drug. Cumulative renal excretion of total orlistat related material was ~<2% of the dose. Complete excretion occurs within 3 to 5 days. Orlistat, M1 and M3 are all subject to biliary excretion.

**Therapeutic Concentration** With therapeutic doses, detection of intact orlistat in plasma is difficult and concentrations are extremely low, <10 μg/L. Low plasma levels of M1 (26 μg/L) and M3 (108 μg/L) are observed 2 to 4 h after a therapeutic dose. ~<5 μg/L 8 h following administration with 360 mg orlistat.

**Half-life** Ranges between 1 and 2 h for the parent drug; for the metabolites ~2 h for M1 and 13.5 h for M3.

**Volume of Distribution** Cannot be determined because it is minimally absorbed and no definite systemic pharmacokinetics are observed.

**Distribution in Blood** Minimally partitions into erythrocytes.

**Protein Binding** >99%. Mainly lipoprotein and albumin.

**Dose** 120 mg three times a day.


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**Orphenadrine**

***Anticholinergic***

C₁₉H₂₃N₂O₂ = 269.4

CAS = 83-98-7

**IUPAC Name** N,N-Dimethyl-2-[(2-methylphenyl)phenylmethoxy]ethanamine

**Synonyms** Mephenamine; orphenadrin.

![Chemical Structure of Orphenadrine](Image)

**Chemical Properties** Liquid; pKₐ 8.4. Log P (octanol/water), 3.8.

**Orphenadrine Citrate** C₁₉H₂₃N₂O₄, C₂H₅O₂⁺ = 461.5

CAS = 4832-36-4

**Proprietary Names** Banflex; Flexoject; Flexon; Myoline; Norflex; Orphenac.

**Chemical Properties** White crystalline powder. Mp 134° to 138°. Soluble 1 in 70 of water; slightly soluble in ethanol; practically insoluble in chloroform and ether.

**Orphenadrine Hydrochloride** C₁₉H₂₃N₂O⁺, HCl = 305.5

CAS = 341-69-5

**Synonym** BS-5930

**Proprietary Names** Biophen; Dispal; Lyantas; Orfenal.

**Chemical Properties** White crystalline powder. Mp 156° to 157°. Soluble 1 in 1 of water, 1 in 1 of ethanol, and 1 in 2 of chloroform; sparingly soluble in acetone and benzene; practically insoluble in ether.

**Colour Tests** Mandelin’s test—orange; Marquis test—yellow-orange; sulfaric acid—orange.

**Thin-layer Chromatography** System TA—R₀ 0.55; system TB—R₀ 0.48; system TC—R₀ 0.33; system TE—R₀ 0.68; system TL—R₀ 0.16; system TAE—R₀ 0.25; system TAF—R₀ 0.49; system TAJ—R₀ 0.14; system TAK—R₀ 0.02; system TAL—R₀ 0.47 (Dragendorff spray, positive; acidified iodoplatinate solution, positive; Marquis reagent, yellow).

**Gas Chromatography** System GA—orphenadrine RI 1935, M (nor-) RI 1900, M (methylbenzophenone) RI 1700; system GB—orphenadrine RI 2014, M (nor-) RI 2007, M (methylbenzophenone) RI 1700; system GF—RI 2185.

**High Performance Liquid Chromatography** System HA—orphenadrine k 3.0, N-monodesmethylorphenadrine k 1.7, orphenadrine N-oxide k 1.1 (tailing peak); system HX—RI 418, system HY—RI 32; system HZ—RI 6.0 min.

**Ultraviolet Spectrum** Aqueous acid—258, 264 nm (A) = 244a. No alkaline shift.

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**Mass Spectrum** Principal ions at m/z 58, 73, 44, 45, 165, 42, 40, 181 (no peaks above 200); N-monodesmethylorphenadrine 44, 59, 165, 166, 181, 179, 178, 43; orphenadrine N-oxide 58, 181, 43, 45, 60, 44, 165, 73.

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**Quantification**

**Blood** GC Column: DB-1 (30 m × 0.32 mm i.d., 0.25 μm). Carrier gas: He, 3 mL/min. Temperature programme: 170° for 1 min to 280° at 10°/min. FID. Limit of detection, 136 μg/L. [Nishikawa et al. 1997]. Column: DB-1 fused silica capillary (30 m × 0.32 mm i.d., 0.23 μm). Carrier gas: He, 22 cm/s. Temperature programme: 100° to 280° at 8°/min. NPD. Retention time: 14.7 min. Limit of detection, 100–250 ng/L. [Hattori et al. 1992]. Column: 2.5% OV-101 on Supelco Chromosorb AW DMCS 80/100 mesh (1 m × 2 mm i.d.). Temperature: 210°. FID. Limit of detection not reported [Wilkinson et al. 1983]. Column: 3.8% W-98 on 80/100 mesh AW-DMCS Chromosorb W (1.8 m × 3.5 mm i.d.). Carrier gas: N₂, 40 mL/min. Temperature: 220°. FID. Retention time: 2.1 min. Limit of detection not reported [Robinson et al. 1977].

**Plasma** GC Column: DB-17 (30 m × 0.35 mm i.d.). Carrier gas: N₂, 15 mL/min. Temperature: 220°. NPD. Limit of detection, 0.8 ng/mL. [Contin et al. 1987]. Column: 3% KTH plus 3% Carbowax 20M on 100/120 mesh Gas Chrom Q (1.5 and 1.5 m × 2.3 mm i.d.). Carrier gas: 30 mL/min. AFID. Retention time: 3.65 min. Limit of detection, 1 μg/L [Labout et al. 1977].


**GC See Blood [Hattori et al. 1992].**
Orthocaine

**Anesthetic (Local)**

*C₈H₁₈N₂O₃* = 167.2

**CAS** — 536-25-4

**IUPAC Name** Methyl 3-amino-4-hydroxybenzoate

**Synonyms** Aminobenz; methyl aminobenzoate.

**Proprietary Name** Orthoform

**Chemical Properties** White crystalline solid. Very soluble in water. Oral solutions of oseltamivir phosphate with sodium benzoate have been shown to be stable for up to 46 days [Albert, Beckson 2007].

**High Performance Liquid Chromatography** Column: *C₈* ODS-2 (150 × 4.6 mm i.d., 5 μm). Mobile phase: methanol:water (80:20) aqueous formic acid (pH 3:50:50). Flow rate 0.5 mL/min. Ultraviolet detection (λ = 220 nm). Limit of quantification, 5 μg/mL; limit of detection, 2 μg/mL [Eisenberg, Cundy 1998].

**Thin-layer Chromatography** System T1—R₂ 0.71 (location reagent: p-dimethylaminobenzaldehyde spray; yellow; potassium permanganate spray, positive reaction).

**Ultraviolet Spectrum** 0.1 N sulfuric acid—253 nm (E₁%, 1 cm 836).

**Disposition in the Body** Readily absorbed after oral administration and rapidly distributed. Up to ~60% of an oral dose is excreted in the urine in 3 days. During 24 h after dosage, under uncontrolled conditions, ~4% of a dose is excreted as unchanged drug, ~5% as N,N-dimethyllorphenadine (tofenacin), ~3% as orphenadrine N-oxide, ~8% as a conjugate of 2-methylbenzhydrol acid, and ~6% as a conjugate of 2-methylbenzhydrol. The urinary excretion appears to be dependent on urinary pH.

**Therapeutic Concentration** In plasma, usually 0.1–0.2 mg/L.

**Toxicity** The lethal dose is estimated to be >2 g. Blood concentrations >0.5 mg/L may cause toxic reactions and concentrations >5 mg/L may be lethal. In a survey of 9 fatalities attributed to orphenadrine overdose, blood concentrations ranged from 1.1–37 mg/L (mean 15); in 5 cases the bile concentration was 85–234 mg/L (mean 150), and in 7 cases the urine concentration was 3–122 mg/L (mean 53). In 1 case in which a more complete analysis was reported, the concentrations were: blood 33 mg/L, bile 202 mg/L, brain 3.3 μg/g; kidney 15 μg/g, liver 23 μg/g; lung 19.5 μg/g, spleen 26.5 μg/g [Robinson et al. 1977].

In a fatality due to an orphenadrine overdose in which death occurred within 2.5 h of ingestion, the following postmortem concentrations were reported: blood 18.1 mg/L, liver 242 mg/L, urine 7 mg/L. [Wilkinson et al. 1983].

A 38-year-old male whose death was attributed to massive ingestion of orphenadrine and clozapine with suicidal intent, had the following postmortem tissue concentrations: heart blood 183 and 44 mg/L (orphenadrine and clozapine, respectively); urine 331 and 245 mg/L; gastric contents — and 859 mg/L; the blood heart concentration of orphenadrine (183 mg/L) was the highest reported thus far in an acute intoxication [Fucci et al. 2001].

**Half-life** Plasma half-life, ~14 h.

**Protein Binding** >98%.

**Dose** 150 to 400 mg of orphenadrine hydrochloride daily.

**References**