


Weight Management STEPS
May 14, 2008

Recommendation	The ACP has issued guidelines that list sibutramine, orlistat, phentermine, and diethylpropion as options for pharmacotherapy of weight loss with choice among the agents being based on individual patient characteristics. Due to the lack of clinical endpoints available with this group of agents as well as the relatively high cost, none of these agents are recommended for the formulary.		
Brand Name (Generic Name)	Tenuate (Diethylpropion) Adipex P, Ionamin (Phentermine)	Meridia (Sibutramine)	Xenical, Alli (Orlistat)
Safety	-	=	+
Drug Interactions	Use with MAO inhibitors is associated with hypertensive episodes. Use with SSRIs increases risk of serotonin syndrome. Decreases effect of anti-hypertensives.	Major substrate of CYP 3A4. Inhibitors of CYP 3A4 (e.g., doxycycline, erythromycin, verapamil) may increase levels. Use with serotonergic agents increases the risk of serotonin syndrome. May increase the levels of TCA's. Drugs that increase BP may increase risk of CV complications	May decrease amiodarone absorption. Co-administration with cyclosporine may decrease levels of cyclosporine. Vitamin K absorption may be decreased – monitor patients on warfarin. Decreased absorption of fat soluble vitamins.
Pregnancy/Lactation	Diethylpropion – Category B/Excreted in breast milk Phentermine – Category C /Excretion in breast milk unknown	Category C/ Excretion in breast milk unknown	Category B/Excretion in breast milk unknown
Look-alike Sound-alike ~ (confused with)	Phentermine ~ Phentolamine, phenytoin Ionamin ~ Imodium		Xenical ~ Xeloda
Pediatric	Not recommended for children < 16years	Safety and Efficacy in children < 16yrs has not been studied	Safety and Efficacy have been evaluated in obese adolescent patients aged 12 to 16 years
Elderly	No specific recommendations	Dose selection for elderly patients should be cautious reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy	
Renal/Hepatic Impairment	Primarily excreted unchanged by the kidneys – may accumulate in renal failure. No dosing adjustment recommendations exist	Should not be used in patients with severe renal or hepatic impairment	Poorly absorbed from GI tract – dosage adjustments probably unnecessary
Contraindications	<ul style="list-style-type: none"> • Advanced arteriosclerosis • Symptomatic CV disease • Moderate-to-severe HTN • Hyperthyroidism • Known hypersensitivity to sympathomimetic amines • Glaucoma • Highly nervous or agitated states • History of drug abuse • During or within 14days of MAOI's • Administration with CNS stimulants 	<ul style="list-style-type: none"> • Patients receiving MAOIs within two weeks of sibutramine • Hypersensitivity to sibutramine • Anorexia Nervosa • Patients taking other centrally acting appetite-suppressant drugs 	<ul style="list-style-type: none"> • Chronic malabsorption syndrome or cholestasis • Hypersensitivity to orlistat

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Precautions	<ul style="list-style-type: none"> • Tolerance may develop to the anorectic effects within a few weeks. Do not exceed the recommended dose. • Do not use in combination with other anorectic agents, SSRIs, OTC preparations and herbal products. • Primary Pulmonary Hypertension • Valvular heart disease (anorectic agents in combinations) • Psychological disturbances • CV disease (mild) • Dispense the least amount feasible to minimize possibility of overdosage • Increased convulsions in those with seizure disorder • Altered insulin requirements in DM • Abuse potential • Caution while driving or performing tasks requiring alertness after abrupt cessation of prolonged high-dose use 	<ul style="list-style-type: none"> • Substantial BP and pulse increase in some patients. Monitoring is required • Caution with other agents that increase BP (i.e. pseudoephedrine & ephedrine) • CHF, CAD, arrhythmias, or stroke • Exclude organic causes of obesity (i.e., hypothyroidism) • Possible fertility impairment • Adequate contraception for women of childbearing potential • Possibility of Abuse • Caution in those with seizure history • Gallstone formation with Weight loss • Interference with cognitive and motor performance • Abnormal liver function tests that diminish with continued use 	<ul style="list-style-type: none"> • Exclude organic causes of obesity • GI events increase when taken with a diet high in fat (greater than 30% total daily calories from fat) • Multivitamin supplement that contains fat-soluble vitamins is advised • Increased levels of urinary oxalate are possible. Caution in those with a history of calcium oxalate nephrolithiasis • Altered insulin requirements and oral hypoglycemic doses in DM • Potential for misuse in inappropriate patient populations (i.e. anorexia nervosa, bulimia)
Tolerability	-	=	-
	<ul style="list-style-type: none"> • Most common: palpitations, tachycardia, elevation of BP, dizziness, HA, insomnia, restlessness, GI effects 	<ul style="list-style-type: none"> • Most common: Insomnia, nausea (6%), dry mouth, and constipation • CV: HTN (2%), palpitations (2%), tachycardia (3%), chest pain (2%) • CNS: Stimulation (2%), dizziness (7%), emotional lability (1%), migraine (2%), nervousness (5%), anxiety (5%) • GI: Nausea (6%), taste perversion (2%), appetite increased (9%), dyspepsia (5%) 	<ul style="list-style-type: none"> • CNS: HA (31%) • GI: Oily spotting (27%), abdominal pain/discomfort (26%), flatus with discharge (24%), fatty/oily stool (20%), fecal urgency (22%), oily evacuation (12%), increased defecation (11%) <p>Less Frequent: Fatigue, anxiety, menstrual irregularities, fecal incontinence, N/D, rectal/pain discomfort, arthritis</p> <p>Most GI SE's were mild and transient, and they decreased during the second year. The first occurrence was within 3 months of starting. Overall, 50% of all episodes of GI SE's lasted for < 1 week, and a majority lasted < 4 weeks. However, GI SE's may occur over a period >6 months</p>

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Efficacy	--	--	-
FDA-approved indications	For short-term (a few weeks) management of obesity as part of a weight reduction regimen. Recommended for obese patients with an initial BMI > 30kg/m ² or 27kg/m ² in the presence of other risk factors	Management of obesity, including weight loss and maintenance of weight loss, in conjunction with a reduced calorie diet. Recommended for obese patients with an initial BMI >30kg/m ² or > 27kg/m ² in the presence of other risk factors	Obesity Management (Rx): <ul style="list-style-type: none"> • Weight loss or weight maintenance when used in conjunction with a reduced calorie diet • Reduce weight regain after prior weight loss • For obese patients with BMI > 30kg/m² or >27kg/m² in the presence of other risk factors Obesity Management (OTC): <ul style="list-style-type: none"> • For weight loss in overweight adults, 18 years or older, use with a low-calorie, low-fat diet
Mechanism of Action	Stimulate the release of norepinephrine or inhibit its reuptake Reduce food intake by causing early satiety. May also have thermogenic effects	Block norepinephrine and serotonin reuptake Reduce food intake by causing early satiety. May also have thermogenic effects	Irreversible inhibitor of pancreatic and gastric lipases. Inhibition of these enzymes prevents the hydrolysis of dietary fat into absorbable free fatty acids. Undigested triglycerides are eliminated in the feces
Maximal duration of proven efficacy and safety	Short –term use (interpreted as 12 weeks).	2 years	4 years
Pooled Results of Meta-Analyses			
<ol style="list-style-type: none"> 1. Long term Pharmacotherapy for Obesity and Overweight. BMJ 2007; 335(7631):1194-9. Evaluated 30 randomized double-blind placebo controlled trials of approved anti-obesity drugs that were one year or longer in duration. 10 sibutramine trials (n = 2623) and 16 Orlistat trials (n = 10,631) were identified. 2. Meta-Analysis: Pharmacologic Treatment of Obesity. Ann Intern Med 2005; 142:532 – 546. Identified up-to-date meta-analyses of sibutramine, phentermine, and diethylpropion and assessed 50 medication studies that reported on orlistat. 			
Gross weight loss	Diethylpropion = -8.5kg Phentermine = -9.1kg	-9.95kg	-9.95kg
Net weight loss (Gross wt loss – placebo)	Diethylpropion = -3.0 (-1.6 to -11.5kg) Phentermine = -3.6	-4.45 (-5.29 to -3.62)	-2.75 (-3.31 to -2.20kg)
Waist circumference (cm)		-3.99 (-4.70 to -3.28)	-2.06 (-2.86 to -1.26)
BMI		-1.54 (-1.79 to -1.30)	-1.05 (-1.40 to -0.71)
Total Cholesterol(mg/dL)		No difference	-12.3 (-14.3 to -10.8)
Triglycerides (mg/dL)		-16 (-26.7 to -6.2) (p<0.05)	No difference
LDL (mg/dL)		No difference	-10.1 (-11.6 to -8.5)
HDL (mg/dL)		+1.5 (0.38 to 3.1)	-1.2 (-4.6 to -0.4)
SBP (mmHg)		1.69 (0.11 to 3.28)	-1.52 (-2.19 to -2.7)
DBP (mm Hg)		2.42 (1.51 to 3.32)	-1.38 (-2.03 to -0.74)
Heart rate		4.53 (3.49 to 5.57)	Not reported
Fasting glucose in DM		No difference – Inconsistently reported	-18.5 (-26.8 to -10.3)
Hemoglobin A1c (%)		No difference – Inconsistently reported	-0.38 (-0.59 to -0.18) – risk difference

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<i>Clinical Studies</i>	XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study. Diabetes Care 27:155-161, 2004. A 4 year, double-blind, prospective, randomized study (n = 3,305). Patients either received orlistat 120mg or placebo, three times daily. Participants had a BMI > 30kg/m ² and normal (79%) or impaired (21%) glucose tolerance (IGT). Primary endpoints were time to onset of type 2 diabetes and change in body weight. Cumulative incidence of diabetes was 9.0% with placebo and 6.2% with orlistat (risk reduction = 37%, p = 0.0032). This difference was only detectable in the IGT subgroup. Mean weight loss after 4 years was greater in the orlistat group (5.8 vs. 3.0 kg with placebo; p<0.001). This weight loss was similar between the normal glucose tolerance group and the IGT group.		
Price	+	=	-
Usual Dose starting dose	Tenuate 25mg tid 1 hour before meals Tenuate Dospan 75mg PO daily in mid morning Adipex-P -37.5mg PO daily before breakfast or 1 to 2 hours after breakfast Ionamin – 15mg daily before breakfast or 10 to 14 hours before bedtime	Sibutramine 10mg PO daily	Rx: 120mg PO TID either with or within 1 hour of each meal containing fat OTC: 60mg PO tid
Hospital Acquisition Cost for 1 day of therapy	Tenuate = \$\$\$ (geq) Tenuate Dospan = \$\$\$\$ (geq) Adipex-P = \$(geq) Ionamin = \$\$ (geq)	\$ x17	Rx = \$ x43 OTC = unavailable
Drugstore.com (30 day supply)	Adipex-P = \$\$ (geq) Ionamin = \$ (geq) Tenuate = \$ (geq) Tenuate Dospan = \$\$ (geq)	\$\$\$\$	Rx = \$ x13 OTC starter pack = \$\$\$ (90 caps) OTC refills = \$\$\$ (120 caps)
Simplicity	=	=	-
	<p>Schedule IV</p> <p>Administration: May be given continuously or intermittently. Must be taken in the morning or at least 10 – 14 hours before bedtime to prevent insomnia. Should be taken before meals or 1 to 2 hours after a meal.</p> <p>Tolerance may develop within a few weeks.</p> <p>Evaluate patients for a history of drug abuse and follow such patients closely. Observe for signs of misuse and abuse.</p>	<p>Schedule IV</p> <p>Administration: May be taken with or without food.</p> <p>There should be an initial HR and BP evaluation and then regular monitoring throughout therapy.</p> <p>Evaluate patients for a history of drug abuse and follow such patients closely. Observe for signs of misuse and abuse.</p> 	<p>Not a controlled substance – no abuse potential Administration: Should be taken with meals or up to 1 hour after a meal Must pay attention to fat intake:</p> <ul style="list-style-type: none"> • GI sx increase if with any 1 meal high in fat. • Omit dose if meal is skipped or contains no fat. • Distribute daily intake of fat over 3 main meals <p>Take a daily MVI with fat-soluble vitamins at least 2 hours prior to orlistat or at bedtime OTC Starter kit contains: 90 caps, “Read me first” guide, carrying case, “companion guide”, “Healthy eating guide”, Calorie & Fat counter, Daily Journal, Quick Facts pocket cards</p> 