

## Second-Generation Antihistamines

Antihistamines have been used for allergic reactions, sleep, and urticaria (e.g., hives, itching) for over 70 years. The Canadian Society of Allergy Clinical Immunology recommends second-generation over first-generation antihistamines for allergic rhino-conjunctivitis and urticaria.<sup>1</sup> They advocate for the use of first-generation antihistamines as a last resort and suggest that they should be available only behind the counter in pharmacies.<sup>1</sup> Second-generation antihistamines are as effective as first-generation antihistamines, usually with less sedation and fewer adverse effects.<sup>1-3</sup>

Comparison of first- and second-generation antihistamine characteristics <sup>1-3</sup>	
First-Generation Antihistamines	Second-Generation Antihistamines
<ul style="list-style-type: none"> <li>• <b>Non-selective</b> (target histamine-1 receptors, but also cholinergic, alpha-adrenergic, and serotonergic receptors).</li> <li>• Can have <b>substantial adverse effects</b>, especially in older patients (e.g., not recommended for use in patients &gt;65 years old).</li> <li>• Most common adverse effect is sedation. May decrease cognitive and motor skills, use with caution.</li> <li>• Some (especially in children) may have stimulating effects (e.g., insomnia, anxiety, hallucinations).</li> <li>• Can cause anti-cholinergic effects (e.g., dry mouth, dry eyes, constipation, tachycardia, etc).</li> </ul>	<ul style="list-style-type: none"> <li>• Selective (more specific to peripheral histamine-1 receptors, don't cross the blood-brain barrier).</li> <li>• Generally well-tolerated.</li> <li>• Generally, not sedating (note that cetirizine may be slightly more sedating than others).</li> <li>• Typically, more expensive than first-generation antihistamines.</li> </ul>

The chart below compares approved indications, dosing, and special considerations of the available **ORAL** second-generation antihistamines. Fexofenadine and desloratadine are sometimes also referred to as third-generation antihistamines because they are active metabolites of second-generation antihistamines. Intranasal antihistamines (e.g., levocabastine) are available by prescription and are not included in this chart. Note that second-line treatment of urticaria (i.e., not adequately controlled with initial doses [see chart below] of second-generation antihistamines) is an increase in dose of up to four-times the approved doses.<sup>4,6</sup>

Drug <sup>a</sup> and Cost <sup>b</sup>	OTC/Rx and Strength <sup>c</sup>	Indications and Oral Dosing <sup>c</sup>	Adverse Drug Reactions <sup>c,d</sup>	Comments <sup>c</sup>
<b>Bilastine</b> ( <i>Blexten</i> )  ~ \$0.84/day	Tablet (Rx): 20 mg	<b>Indications</b> <ul style="list-style-type: none"> <li>• Seasonal allergic rhinitis in patients 12 years and older.</li> <li>• Chronic spontaneous urticaria in patients 18 years and older.</li> </ul> <b>Dosing</b> <ul style="list-style-type: none"> <li>• 20 mg once daily</li> </ul>	<ul style="list-style-type: none"> <li>• dizziness ~1%</li> <li>• drowsiness ~4%</li> <li>• headache ~4%</li> <li>• gastrointestinal ~4%</li> </ul>	<ul style="list-style-type: none"> <li>• Take on an empty stomach with water. Avoid grapefruit or other fruit juices and food for two hours before and one hour after bilastine.</li> <li>• Not recommended with medications that inhibit P-glycoprotein (especially with moderate to severe renal impairment) or medications that prolong the QT interval.<sup>e</sup></li> <li>• Contraindicated with a history of prolonged QT interval or congenital long QT syndromes.</li> </ul>

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<p><b>Cetirizine</b> (<i>Reactine</i>, generics)</p> <p>10 mg/day: ~\$0.40/day (tablets) ~\$0.69/day (liquid)</p>	<p>Capsule (OTC): 10 mg</p> <p>Tablet (OTC): 5 mg, 10 mg</p> <p>Disintegrating tablet (OTC): 10 mg</p> <p>Syrup (OTC): 1 mg/mL</p> <p>Tablet (Rx): 20 mg</p>	<p><b>Indications</b></p> <ul style="list-style-type: none"> <li>• 2 to 12 years: <ul style="list-style-type: none"> <li>○ itching due to allergic reactions</li> <li>○ seasonal allergic rhinitis</li> </ul> </li> <li>• 12 years and older: <ul style="list-style-type: none"> <li>○ chronic idiopathic urticaria</li> <li>○ seasonal and perennial allergic rhinitis</li> </ul> </li> </ul> <p><b>Dosing</b></p> <ul style="list-style-type: none"> <li>• 2 to 6 years: 5 mg once daily</li> <li>• 6 to 12 years: 10 mg once daily</li> <li>• 12 to 65 years: 5 to 10 mg once daily</li> <li>• 65 years and older: 5 mg once daily</li> <li>• max daily dose: 20 mg (Rx only)</li> </ul>	<p><b>10 mg dose:</b></p> <ul style="list-style-type: none"> <li>• drowsiness ~10%</li> <li>• dry mouth ~2%</li> <li>• headache ~7%</li> </ul> <p><b>20 mg dose:</b></p> <ul style="list-style-type: none"> <li>• drowsiness ~24%</li> <li>• dry mouth ~8%</li> <li>• fatigue ~7%</li> <li>• headache ~17%</li> <li>• nausea ~3%</li> </ul>	<ul style="list-style-type: none"> <li>• Start with 5 mg once daily in patients with moderate hepatic or renal impairment.</li> <li>• Contraindicated in patients with: <ul style="list-style-type: none"> <li>○ an allergy to hydroxyzine.</li> <li>○ severe renal impairment (creatinine clearance [CrCl] less than 10 mL/min).</li> </ul> </li> <li>• Syrup is sugar-free, sweetened with sorbitol and sucralose.</li> <li>• Disintegrating tablets are available as “Fast Melt Junior” and “Rapid Dissolve” products (both are 10 mg).</li> <li>• Note that multi-ingredient <i>Reactine Complete</i> tablets each contain cetirizine 5 mg plus pseudoephedrine 120 mg.</li> </ul>
<p><b>Desloratadine</b> (<i>Aerius</i>, <i>Aerius Kids</i>, generics)</p> <p>~ \$0.13/day (tablets) ~\$0.73/day (liquid)</p>	<p>Syrup (OTC): 0.5 mg/mL</p> <p>Tablet (OTC): 5 mg</p>	<p><b>Indications</b></p> <ul style="list-style-type: none"> <li>• allergic rhinitis</li> <li>• chronic idiopathic urticaria</li> </ul> <p><b>Dosing</b></p> <ul style="list-style-type: none"> <li>• 2 to 5 years: 1.25 mg once daily</li> <li>• 6 to 11 years: 2.5 mg once daily</li> <li>• 12 years and older: 5 mg once daily</li> </ul>	<ul style="list-style-type: none"> <li>• drowsiness ~2%</li> <li>• dry mouth ~3%</li> <li>• fatigue ~2%</li> <li>• headache ~5%</li> </ul>	<ul style="list-style-type: none"> <li>• Use with caution in patients with severe hepatic or renal impairment.</li> <li>• Not recommended for use longer than 14 days in children two to 12 years, unless recommended by a prescriber.</li> <li>• Note that multi-ingredient <i>Aerius Double Action 12 Hour</i> extended-release tablets each contain desloratadine 2.5 mg plus pseudoephedrine 120 mg.</li> </ul>

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<b>Fexofenadine</b> <i>(Allegra 12-Hour, Allegra 24-Hour)</i>  ~\$0.80/day (12-Hour)  ~\$0.65/day (24-Hour)	12-hour tablet (OTC): 60 mg  24-hour tablet (OTC): 120 mg	<b>Indications</b> 12 years and older: <ul style="list-style-type: none"> <li>seasonal and perennial allergic rhinitis*</li> <li>chronic idiopathic urticaria</li> </ul> *24-hour formulation is <b>only</b> indicated for <b>seasonal</b> allergic rhinitis.  <b>Dosing</b> <ul style="list-style-type: none"> <li><i>Allegra 12-Hour:</i> 60 mg every 12 hours</li> <li><i>Allegra 24-Hour:</i> 120 mg once daily</li> </ul>	<ul style="list-style-type: none"> <li>abdominal pain ~1%</li> <li>diarrhea ~1%</li> <li>dizziness ~1%</li> <li>drowsiness ~1%</li> <li>dry eyes ~1%</li> <li>dyspepsia ~2%</li> <li>fatigue ~1%</li> <li>headache ~3% to 10%</li> <li>insomnia ~1%</li> <li>nausea ~1% to 3%</li> </ul>	<ul style="list-style-type: none"> <li>Use a dose of 60 mg once daily for patients with impaired renal function.</li> <li>Moderate to severe hepatic impairment does not appear to have any clinical effect on the pharmacokinetics of fexofenadine.</li> <li><b>Avoid</b> fruit juice or separate administration by at least four hours due to reduced absorption of fexofenadine when given together.<sup>7</sup></li> <li>Note that multi-ingredient <i>Allegra-D</i> sustained-release caplets each contain fexofenadine 60 mg plus pseudoephedrine 120 mg.</li> </ul>
<b>Loratadine</b> <i>(Allertin, Claritin, Claritin Kids, generics)</i>  ~\$0.25/day (tablets)  ~\$0.57/day (liquid)	Tablet (OTC): 10 mg  Capsule (OTC): 10 mg  Disintegrating tablet (OTC): 10 mg  Oral solution (OTC): 1 mg/mL	<b>Indications</b> <ul style="list-style-type: none"> <li>seasonal and perennial allergic rhinitis*</li> <li>chronic urticaria and other allergic dermatologic disorders</li> </ul> *Oral solution is <b>not</b> indicated for <b>perennial</b> allergic rhinitis.  <b>Dosing</b> All dosage forms: <ul style="list-style-type: none"> <li>12 years and older: 10 mg once daily</li> </ul> Oral solution: <ul style="list-style-type: none"> <li>2 to 9 years AND 30 kg or less: 5 mg once daily</li> <li>10 years and older AND over 30 kg: 10 mg once daily</li> </ul>	<ul style="list-style-type: none"> <li>drowsiness ~4% to 8%</li> <li>dry mouth ~4%</li> <li>fatigue ~3% to 4%</li> <li>headache ~8%</li> </ul>	<ul style="list-style-type: none"> <li>Disintegrating tablets should be taken on an empty stomach, immediately after opening tablet blister. Can be taken without water.</li> <li>Severe liver impairment:               <ul style="list-style-type: none"> <li>adults and children over 30 kg: 5 mg once daily <b>OR</b> 10 mg every other day.</li> <li>children 30 kg or less: 5 mg every other day.</li> </ul> </li> <li>Not recommended for use longer than 14 days in children two to 12 years unless recommended by a prescriber.</li> <li>Note that multi-ingredient <i>Claritin Allergy + Sinus</i> modified-release tablets each contain loratadine 5 mg plus pseudoephedrine 120 mg. The <b>extra-strength</b> <i>Claritin Allergy + Sinus</i> modified-release caplets each contain loratadine 10 mg plus pseudoephedrine 240 mg.</li> </ul>

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<b>Rupatadine</b> <i>(Rupall)</i>  ~ \$0.81/day	Tablet (Rx): 10 mg  Oral solution (Rx): 1 mg/mL	<b>Indications</b> <ul style="list-style-type: none"> <li>seasonal and perennial allergic rhinitis</li> <li>chronic spontaneous urticaria</li> </ul> <b>Dosing</b> 12 years and older, tablet: <ul style="list-style-type: none"> <li>10 mg once daily</li> </ul> 2 to 11 years, oral solution: <ul style="list-style-type: none"> <li>10 to 25 kg: 2.5 mg once daily</li> <li>more than 25 kg: 5 mg once daily</li> <li>Tablets are not recommended in this age group.</li> </ul>	<ul style="list-style-type: none"> <li>abdominal pain ~2%</li> <li>increased creatine phosphokinase (CPK) ~2% to 3%</li> <li>dizziness ~1%</li> <li>drowsiness ~3% to 9%</li> <li>dry mouth ~2%</li> <li>prolonged QT ~1%</li> <li>epigastric pain ~1%</li> <li>fatigue ~1% to 2%</li> <li>headache ~1% to 6%</li> <li>nausea ~2%</li> <li>vomiting ~1%</li> </ul>	<ul style="list-style-type: none"> <li>Not recommended in patients with impaired hepatic or renal function due to lack of experience.</li> <li>Contraindicated in patients with a history of prolonged QT interval, congenital long QT syndromes, or with medications that prolong the QT interval.<sup>e</sup></li> <li>Contraindicated with moderate or strong CYP3A4 inhibitors, grapefruit, and grapefruit juice.</li> <li>Use with caution with statins due to reports of increased creatine phosphokinase.</li> <li>In addition to blocking histamine, also blocks platelet-activating factor (PAF) receptor, which plays a role in allergic response.</li> </ul>

- Generics as listed in Health Canada Drug Product Database: <https://health-products.canada.ca/dpd-bdpp/>. (Accessed January 17, 2020). **Consult your local wholesaler for availability, and respective provincial/territory formulary for interchangeability status.**
- Cost based on wholesale acquisition cost (WAC), for generics when available, for the usual adult daily dose.
- From Canadian product monographs unless otherwise noted: *Blexten* (December 2018); *Reactine* (August 2019); *Aerius* (May 2019); *Allegra* (November 2019); *Claritin* (May 2019); *Rupall* (January 2017).
- Most commonly reported adverse reactions in adults during clinical trials, not necessarily statistically significantly different from placebo.
- See our chart, *Drug-induced Long QT Interval*, for comprehensive list of medications that can increase the QT interval.

*Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.*

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### References

1. Fein MN, Fischer DA, O'Keefe AW, Sussman GL. CSACI position statement: newer generation H<sub>1</sub>-antihistamines are safer than first-generation H<sub>1</sub>-antihistamines and should be the first-line antihistamines for the treatment of allergic rhinitis and urticaria. *Allergy Asthma Clin Immunol* 2019;15:61.
2. Church MK, Church DS. Pharmacology of antihistamines. *Indian J Dermatol* 2013;58:219-24.
3. Wang XY, Lim-Jurado M, Prepageran N, et al. Treatment of allergic rhinitis and urticaria: a review of the newest antihistamine bilastine. *Ther Clin Risk Manag* 2016;12:585-97.
4. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy* 2014;69:868-87.
5. Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol* 2014;133:1270-7.
6. Kanani A, Betschel SD, Warrington R. Urticaria and angioedema. *Allergy Asthma Clin Immunol* 2018;14:59.
7. Bailey DG. Fruit juice inhibition of uptake transport: a new type of food-drug interaction. *Br J Clin Pharmacol* 2010;70:645-55.

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