

Leukotriene receptor antagonists

Oral anti-inflammatory maintenance agents for asthma and allergic rhinitis that either block the cysteinyl leukotriene CysLT₁ receptor or, in the case of zileuton, inhibit 5-lipoxygenase one step earlier so the leukotrienes are never formed; none of them dilates an airway, and montelukast carries a boxed warning for serious neuropsychiatric events.

Online guide: <https://www.medguideglobal.com/pharmacology/respiratory-and-allergy/leukotriene-receptor-antagonists>

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Quick revision

One Liner: Three oral drugs interrupt one inflammatory pathway at two different points, and the reason the class is taught is not its efficacy but its safety labelling.

1. Montelukast and zafirlukast are cysteinyl leukotriene receptor antagonists; zileuton is a 5-lipoxygenase inhibitor and therefore acts upstream, blocking synthesis rather than the receptor. [1][2][3]
2. Montelukast's boxed warning names agitation, aggression, depression, sleep disturbances and suicidal thoughts and behaviour, and states that the underlying mechanisms are not well understood. [1]
3. In allergic rhinitis the montelukast label reserves treatment for patients with an inadequate response or intolerance to alternative therapies, because the benefit may not outweigh the neuropsychiatric risk. [1]
4. All three are maintenance drugs taken by mouth, and all three labels exclude them from the reversal of bronchospasm in an acute asthma attack. [1][2][3]
5. Zileuton is contraindicated in active liver disease, and serum ALT is assessed before treatment, monthly for three months, then every two to three months for the rest of the first year. [3]
6. Zafirlukast has caused fulminant hepatitis progressing to liver transplantation and death, and its absorption falls by roughly 40% when it is taken with food. [2]
7. Zafirlukast prolongs the prothrombin time in patients on warfarin, and both zafirlukast and zileuton raise theophylline exposure. [2][3]
8. Systemic eosinophilia, sometimes with the vasculitic features of Churg-Strauss syndrome, is reported with both receptor antagonists, usually as oral steroid therapy is being reduced. [1][2]

Overview

1. Leukotrienes are lipid mediators made from arachidonic acid by the enzyme 5-lipoxygenase. The cysteinyl leukotrienes among them produce, in the words of the zafirlukast label, airway edema, smooth muscle constriction, and altered cellular activity associated with the inflammatory process. Three oral drugs interrupt that pathway and are licensed in asthma. Montelukast and zafirlukast sit at the receptor; zileuton sits at the enzyme. [2][3][9]
2. The dominant fact about this class is a safety one. The montelukast boxed warning opens: "Serious neuropsychiatric (NP) events have been reported with the use of montelukast sodium. The types of events reported were highly variable, and included, but were not limited to, agitation, aggression, depression, sleep disturbances, suicidal thoughts and behavior (including suicide). The mechanisms underlying NP events associated with montelukast sodium use are currently not well understood." The label does not claim to explain the association, and a page about this class should not claim more than the label does. [1]
3. That warning is followed by a prescribing instruction rather than a caution alone: "Because of the risk of NP events, the benefits of montelukast sodium may not outweigh the risks in some patients, particularly when the symptoms of disease may be mild and adequately treated with alternative therapies. Reserve use of montelukast sodium for patients with allergic rhinitis who have an inadequate response or intolerance to alternative therapies." The benefit-risk judgement therefore depends on the indication, and it is tightest where the disease being treated is the mildest. [1]

4. The counselling obligation is written into the same warning: "Discuss the benefits and risks of montelukast sodium with patients and caregivers when prescribing montelukast sodium. Advise patients and/or caregivers to be alert for changes in behavior or new NP symptoms when taking montelukast sodium. If changes in behavior are observed, or if new NP symptoms or suicidal thoughts and/or behavior occur, advise patients to discontinue montelukast sodium and contact a healthcare provider immediately." The United Kingdom regulator reaches the same practical conclusion from its own data, having received 1,223 reports of suspected neuropsychiatric adverse reactions since authorisation in 1998. [1][5]

5. Clinically these are preventers, not relievers. The NHS medicine page states plainly that montelukast is used alongside inhalers or other asthma medicine and that a reliever inhaler, not montelukast, is what treats an attack. Where this class sits against inhaled corticosteroids is a separate question, dealt with on the inhaled corticosteroids page in this section; the labelling point that belongs here is that a leukotriene modifier is not an abrupt replacement for a steroid a patient is already taking. [6][1]

Classification and drug examples

Intro: The class splits at the point in the leukotriene pathway each drug attacks. That single distinction predicts which mediators are still active during treatment and which monitoring the label demands.

1. Name: Cysteinyl leukotriene receptor antagonists

1. Note: Competitive blockade at the CysLT1 receptor. Leukotriene synthesis continues normally; only the cysteinyl leukotriene signal is interrupted. LiverTox records that these two agents are the leukotriene receptor antagonists available in the United States and that both have been associated with rare cases of acute liver injury.

1. Name: Montelukast

Singulair

1. Route: Oral

1. Note: Binds with high affinity and selectivity to the CysLT1 receptor in preference to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or beta-adrenergic receptor. It is the only member licensed for allergic rhinitis and for prevention of exercise-induced bronchoconstriction, and the only one carrying a boxed warning. [1]

2. Name: Zafirlukast

Accolate

2. Route: Oral

2. Note: Described in its label as a selective and competitive receptor antagonist of leukotriene D4 and E4, components of slow-reacting substance of anaphylaxis. Its distinguishing problems are hepatic injury, a substantial food effect and interaction with warfarin. [2] [1][2][9]

2. Name: 5-lipoxygenase inhibitors

2. Note: Synthesis blockade rather than receptor blockade. Because the enzyme sits above the branch point, inhibition reduces the whole leukotriene output rather than the cysteinyl arm alone.

Name: Zileuton

Zyflo

Route: Oral, including an extended-release tablet

Note: An inhibitor of 5-lipoxygenase and thus an inhibitor of LTB₄, LTC₄, LTD₄ and LTE₄ formation. LiverTox describes the enzyme as the one responsible for the conversion of arachidonic acid into leukotriene A₄, which places zileuton a step above the receptor antagonists in the same pathway. [3][8] [3][8]

Mechanism of action

Summary: One pathway, two points of attack. Arachidonic acid is converted by 5-lipoxygenase to leukotriene A₄ and onward to the cysteinyl leukotrienes, which act at the CysLT1 receptor to produce airway oedema, bronchoconstriction and inflammatory cell activity. Montelukast and zafirlukast occupy that receptor; zileuton disables the enzyme that

starts the sequence.

Target: The CysLT1 receptor, and the enzyme 5-lipoxygenase upstream of it

Cidal Static: Anti-inflammatory and preventive rather than bronchodilator

Kill Kinetics: Effect depends on continued daily dosing; no immediate relief of bronchospasm

1. Step: 1

1. Title: 5-lipoxygenase generates leukotriene A4 from arachidonic acid

1. Detail: LiverTox describes 5-lipoxygenase as the enzyme responsible for the conversion of arachidonic acid into leukotriene A4. Everything else in the pathway, cysteinyl and non-cysteinyl alike, descends from that single step. [8]

2. Step: 2

2. Title: Cysteinyl leukotrienes act at CysLT1 to produce the asthmatic phenotype

2. Detail: The zafirlukast label ties leukotriene D4 and E4, components of slow-reacting substance of anaphylaxis, to airway edema, smooth muscle constriction, and altered cellular activity associated with the inflammatory process.

LiverTox adds that in allergic rhinitis these mediators are released into nasal tissue after allergen exposure. [2][9]

3. Step: 3

3. Title: Receptor antagonism: montelukast and zafirlukast occupy CysLT1

3. Detail: Montelukast binds with high affinity and selectivity to the CysLT1 receptor rather than to prostanoid, cholinergic or beta-adrenergic receptors, which is why it has no bronchodilator action of its own. Zafirlukast is a selective and competitive antagonist at the same cysteinyl arm of the pathway. [1][2]

4. Step: 4

4. Title: Synthesis inhibition: zileuton acts one step earlier

4. Detail: Zileuton is an inhibitor of 5-lipoxygenase and thus inhibits LTB4, LTC4, LTD4 and LTE4 formation. Because a CysLT1 antagonist only occupies a receptor, LTB4 continues to be produced and to signal during treatment with montelukast or zafirlukast; under zileuton it is not made in the first place. [3][1]

5. Step: 5

5. Title: The consequence is prevention, not rescue

5. Detail: Interrupting a mediator pathway reduces the inflammatory background over days of regular dosing but does nothing to relax a smooth muscle already in spasm. Each of the three labels therefore states that the drug is not indicated for reversal of bronchospasm in an acute asthma attack, and the zafirlukast label adds that it is not a bronchodilator. [1][2][3]

Major clinical uses

1. Drug: Montelukast

1. Organism: Not applicable

1. Indication: Prophylaxis and chronic treatment of asthma

1. Line: maintenance option

1. Note: The film-coated tablet label carries this indication for adults and adolescents 15 years of age and older; MedlinePlus records the medicine as preventing asthma symptoms from 12 months of age across the various formulations. [1][7]

2. Drug: Montelukast

2. Organism: Not applicable

2. Indication: Prevention of exercise-induced bronchoconstriction

2. Line: licensed use

2. Note: Indicated for prevention of exercise-induced bronchoconstriction in patients 15 years of age and older on this label. MedlinePlus states that the preventive dose is taken at least two hours before exercise, which is a property of the drug's onset rather than a rescue effect. [1][7]

3. Drug: Montelukast

3. Organism: Not applicable

3. Indication: Seasonal and perennial allergic rhinitis, restricted
3. Line: reserved
3. Note: Licensed for relief of symptoms of seasonal and perennial allergic rhinitis, with the label instruction to reserve use for patients who have an inadequate response or intolerance to alternative therapies. This restriction exists because of the neuropsychiatric risk, not because of poor efficacy. [1]
4. Drug: Zafirlukast
4. Organism: Not applicable
4. Indication: Prophylaxis and chronic treatment of asthma
4. Line: maintenance option
4. Note: Indicated in adults and children 5 years of age and older, and the label directs that it be taken regularly as prescribed even during symptom-free periods. It has no allergic rhinitis or exercise indication. [2]
5. Drug: Zileuton
5. Organism: Not applicable
5. Indication: Prophylaxis and chronic treatment of asthma
5. Line: seldom used, monitoring-heavy
5. Note: Indicated in adults and children 12 years of age and older. The scheduled liver enzyme testing its label attaches to treatment, and its contraindication in active liver disease, shape where it can be used at all. [3]
6. Drug: Montelukast
6. Organism: Not applicable
6. Indication: Add-on therapy alongside inhaled treatment for asthma
6. Line: adjunct
6. Note: The NHS medicine page frames montelukast as taken alongside inhalers or other asthma medicine rather than instead of them, and directs patients to a reliever inhaler for an attack. Ranking this class against inhaled corticosteroids is a guideline question and is not asserted here. [6]

Pharmacokinetics

1. Drug: Montelukast
1. Route: Oral
1. Absorption: Mean oral bioavailability 64%; oral bioavailability and Cmax are not influenced by a standard meal
1. Csf Penetration: Not applicable
1. Metabolism: CYP3A4, 2C8 and 2C9 are involved in vitro, with 2C8 playing a major role at clinically relevant concentrations
1. Elimination: Hepatic
1. Half Life: 2.7 to 5.5 hours in healthy young adults
1. Dose Adjust: No adjustment recommended in renal insufficiency or in mild-to-moderate hepatic insufficiency [1]
2. Drug: Zafirlukast
2. Route: Oral
2. Absorption: Food reduces mean bioavailability by approximately 40%, so the label directs administration at least 1 hour before or 2 hours after meals
2. Csf Penetration: Not applicable
2. Metabolism: Extensively metabolised; hydroxylated metabolites are formed through the CYP2C9 pathway
2. Elimination: Faecal, after hepatic metabolism
2. Half Life: Approximately 10 hours
2. Dose Adjust: Exposure is 50-60% higher in stable alcoholic cirrhosis and rises two- to three-fold in patients aged 65 and over [2]
3. Drug: Zileuton
3. Route: Oral, immediate and extended release

- 3. Absorption: Oral
- 3. Csf Penetration: Not applicable
- 3. Metabolism: Eliminated predominantly by metabolism
- 3. Elimination: Hepatic
- 3. Half Life: Mean terminal half-life about 3.2 hours
- 3. Dose Adjust: Contraindicated in active liver disease; serum ALT determines whether treatment continues [3]
- 1. This page gives no dose regimens. Choice of agent, formulation and monitoring interval belongs to the treating clinician working from a current prescribing reference, because they depend on age, indication, liver function and the rest of the patient's asthma treatment.
- 2. All three are more than 90% protein bound, montelukast and zafirlukast at more than 99% and zileuton at 93%, which matters chiefly when interpreting displacement interactions. [1][2][3]

Adverse effects

- 1. Effect: Headache
 - 1. Detail: The commonest complaint across the class. Headache was reported in 12.9% of zafirlukast-treated patients in clinical trials, and headache appears among the adverse reactions listed at 5% or more with montelukast. [2][1]
- 2. Effect: Gastrointestinal upset
 - 2. Detail: Nausea, diarrhoea and abdominal pain were each reported in a small percentage of zafirlukast recipients, and abdominal pain and diarrhoea appear in the montelukast adverse reaction list. [2][1]
- 3. Effect: Respiratory tract and ear, nose and throat events
 - 3. Detail: Montelukast's adverse reactions occurring in at least 5% of patients and more often than with placebo include upper respiratory infection, pharyngitis, cough, rhinorrhoea, sinusitis, influenza and otitis media, reflecting the paediatric and adult populations studied. [1]
- 4. Effect: Sleep disturbance and mood change at low frequency
 - 4. Detail: The UK regulator quantifies these: sleep disturbances, depression and agitation including aggressive behaviour may affect up to 1 in 100 people, and disturbances of attention or memory up to 1 in 1,000. [4]
- 1. Effect: Neuropsychiatric events with montelukast, the subject of a boxed warning
 - 1. Detail: The warning names agitation, aggression, depression, sleep disturbances and suicidal thoughts and behaviour including suicide, describes the reported events as highly variable, and states that the mechanisms are currently not well understood. The UK regulator places hallucinations and suicidal thinking and behaviour at up to 1 in 10,000 people, and concluded in April 2024 that the benefits of montelukast continue to outweigh the risks for most patients in asthma while the risk needed to be communicated better.
 - 1. Action: Monitoring for behavioural change, and the decision to continue or discontinue, rest with the treating clinician; the label directs that treatment be stopped and a healthcare provider contacted immediately if such symptoms appear. [1][4][5]
- 2. Effect: Hepatic injury with zafirlukast
 - 2. Detail: Cases of life-threatening hepatic failure have been reported, and in rare cases patients have either presented with fulminant hepatitis or progressed to hepatic failure, liver transplantation and death.
 - 2. Action: The label directs that treatment be discontinued and liver function tests, in particular serum ALT, measured immediately if liver dysfunction is suspected from signs such as right upper quadrant pain, nausea, lethargy, pruritus or jaundice. [2]
- 3. Effect: Transaminase elevation and idiosyncratic liver injury with zileuton
 - 3. Detail: ALT elevations above three times the upper limit of normal occurred in 1.9% of patients treated for at least one year against 0.2% of placebo recipients, with onset typically within four to eight weeks. LiverTox grades zileuton as a possible rare cause of clinically apparent liver injury.
 - 3. Action: Treatment is stopped and hepatic enzymes followed until normal if transaminases reach five times the upper limit of normal or symptoms of liver dysfunction appear. [8][3]

4. Effect: Eosinophilic conditions, including features of Churg-Strauss syndrome
4. Detail: Patients on montelukast may present with systemic eosinophilia, sometimes with clinical features of vasculitis consistent with Churg-Strauss syndrome. The zafirlukast label reports systemic eosinophilia, eosinophilic pneumonia or the same vasculitic picture, usually though not always in association with reduction of oral steroid therapy.
4. Action: Because the timing follows steroid withdrawal, any change to concurrent corticosteroid treatment is a clinician decision that requires the patient to be watched for these features. [1][2]
1. Drug: Montelukast
1. Effect: Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking montelukast: the drug does not confer protection in aspirin-exacerbated respiratory disease. [1]
2. Drug: Zafirlukast
2. Effect: Accumulation in the elderly and in cirrhosis. Apparent oral clearance falls with age, giving roughly two- to three-fold higher C_{max} and AUC in patients aged 65 and over, and C_{max} and AUC are about 50-60% greater in stable alcoholic cirrhosis. [2]
3. Drug: Zafirlukast
3. Effect: Neuropsychiatric events have been reported in adult, adolescent and paediatric patients, with post-marketing reports including insomnia and depression. This is a warning rather than a boxed warning. [2]
4. Drug: Zileuton
4. Effect: Post-marketing neuropsychiatric reports for zileuton include sleep disorders and behaviour changes, so the pattern is not unique to the receptor antagonists. [3]

Contraindications, precautions and interactions

1. Zileuton is contraindicated in active liver disease, and in persistent hepatic function enzyme elevations greater than or equal to three times the upper limit of normal. [3]
2. None of the three may be used to reverse bronchospasm in an acute asthma attack, including status asthmaticus; a reliever is required for that purpose. [1][2][3]
1. Before montelukast is prescribed, its benefits and risks are to be discussed with the patient and any caregiver, and both advised to be alert for changes in behaviour or new neuropsychiatric symptoms during treatment. [1]
2. The UK regulator advises that families be told what to watch for, since a patient may not recognise a change in their own mood, sleep or behaviour, and that the leaflet's list of neuropsychiatric reactions be read carefully. [4]
3. Montelukast must not be abruptly substituted for inhaled or oral corticosteroids, although the dose of an inhaled corticosteroid may be reduced gradually under medical supervision. [1]
4. Zileuton requires serum ALT before treatment begins, monthly for the first three months, every two to three months for the remainder of the first year, and periodically thereafter during long-term use. [3]
5. For zafirlukast, periodic transaminase testing has not been shown to prevent serious injury, and the label rests instead on prompt withdrawal once clinical signs of hepatic dysfunction appear. [2]
6. Higher zafirlukast exposure in older patients and in cirrhosis makes those groups the ones in whom hepatic adverse effects are most likely to matter. [2]
1. With: Warfarin
1. Effect: Coadministration of zafirlukast with warfarin produces a clinically significant increase in prothrombin time, and the label requires close prothrombin time monitoring with anticoagulant adjustment. Zileuton likewise increases warfarin levels and its label requires prothrombin time monitoring. [2][3]
2. With: Theophylline
2. Effect: Zileuton increases theophylline levels, and the label directs that the theophylline dose be reduced and levels monitored. Rare cases of raised theophylline levels, with or without signs of toxicity, have been reported when zafirlukast was added to an existing theophylline regimen. [3][2]
3. With: Propranolol and other beta-blockers
3. Effect: Zileuton increases propranolol levels and beta-blocker activity, so the combination is monitored. [3]

4. With: Erythromycin

4. Effect: Erythromycin decreased mean plasma concentrations of zafirlukast by approximately 40% through reduced bioavailability, an interaction in the opposite direction to the one students usually expect from a macrolide. [2]

5. With: Aspirin

5. Effect: Coadministration of aspirin increased mean plasma concentrations of zafirlukast by approximately 45%. [2]

6. With: Food

6. Effect: A high-fat or high-protein meal reduced mean zafirlukast bioavailability by about 40%, which is why the label separates administration from meals. Montelukast is unaffected in this respect, its bioavailability and C_{max} being uninfluenced by a standard meal. [2][1]

Comparison tables

Title: Where the three members diverge

Caption: The point of attack in the pathway drives the licensed uses, the monitoring and the signature hazard.

Selection is a clinician decision made from a current prescribing reference.

1. Key: drug

1. Label: Drug

1. Is Row Header: true

2. Key: target

2. Label: Point of attack

3. Key: licensed

3. Label: Licensed beyond asthma

4. Key: monitoring

4. Label: Monitoring the label requires

5. Key: signature

5. Label: Signature hazard

1. Drug: Montelukast

1. Target: CysLT1 receptor

1. Licensed: Exercise-induced bronchoconstriction; allergic rhinitis, reserved for inadequate response or intolerance to alternatives

1. Monitoring: Vigilance for behavioural and neuropsychiatric change, with counselling of patient and caregiver

1. Signature: Boxed warning for serious neuropsychiatric events [1]

2. Drug: Zafirlukast

2. Target: CysLT1 receptor, competitive antagonism of LTD4 and LTE4

2. Licensed: Nothing beyond asthma

2. Monitoring: No routine schedule; immediate ALT measurement and withdrawal if hepatic symptoms appear

2. Signature: Fulminant hepatitis, hepatic failure and transplantation; warfarin and theophylline interactions [2]

3. Drug: Zileuton

3. Target: 5-lipoxygenase, upstream of the receptor

3. Licensed: Nothing beyond asthma

3. Monitoring: Scheduled serum ALT before treatment, monthly for three months, then periodically

3. Signature: Transaminase elevation; contraindicated in active liver disease [3][8]

High-yield exam pearls

1. Pearl: Only montelukast carries the boxed warning, and only montelukast has the allergic rhinitis restriction attached to it.

1. Why: Examiners test whether a candidate applies a warning to a whole class by reflex. Zafirlukast and zileuton do report neuropsychiatric events, but as ordinary warnings. [1][2][3]

2. Pearl: Zileuton is not a leukotriene receptor antagonist at all, despite sitting in the same teaching class.
2. Why: It inhibits the synthesising enzyme, so LTB₄ as well as the cysteinyl leukotrienes falls. A question that contrasts synthesis inhibition with receptor blockade is asking about exactly this. [3][8]
3. Pearl: Zafirlukast is the one that must be separated from food; montelukast is not.
3. Why: A high-fat or high-protein meal cuts zafirlukast bioavailability by around 40%, whereas a standard meal changes neither montelukast's bioavailability nor its C_{max}. [2][1]
4. Pearl: Eosinophilic conditions in this class cluster around corticosteroid reduction.
4. Why: Both receptor antagonists report systemic eosinophilia and Churg-Strauss features usually associated with a fall in oral steroid dose, which is a temporal association rather than proof of causation. [1][2]
5. Pearl: Two of the three interact with warfarin and with theophylline in the same direction: more effect, more risk.
5. Why: Zafirlukast raises prothrombin time and can raise theophylline levels; zileuton raises both warfarin and theophylline exposure and also propranolol levels. [2][3]

Common exam traps

1. Trap: Treating a leukotriene modifier as something that can relieve an attack because it improves breathing over time.
1. Correction: Zafirlukast's label states it is not a bronchodilator, and each of the three excludes reversal of bronchospasm in acute asthma. The NHS page tells patients to use the reliever inhaler for an attack. [2][1][6]
2. Trap: Assuming the montelukast boxed warning explains a mechanism for the neuropsychiatric events.
2. Correction: It says the opposite: the mechanisms are currently not well understood, and a causal association with underlying conditions has not been established. A page that offers a mechanism is claiming more than the label does. [1]
3. Trap: Starting a leukotriene modifier and stopping an inhaled corticosteroid on the same day.
3. Correction: The label allows gradual reduction of inhaled corticosteroid under medical supervision, but forbids abrupt substitution. Eosinophilic complications reported in this class cluster around exactly that manoeuvre. [1][2]
4. Trap: Expecting erythromycin to raise zafirlukast levels because macrolides usually inhibit metabolism.
4. Correction: Erythromycin reduced mean zafirlukast concentrations by about 40% by decreasing its bioavailability, while aspirin raised them by about 45%. [2]
5. Trap: Answering that a leukotriene modifier is licensed for allergic rhinitis as a class.
5. Correction: Only montelukast holds that indication, and its own label reserves it for patients with an inadequate response or intolerance to alternative therapies. [1][2]

Self-test questions

1. Question: Which statement best describes how zileuton differs mechanistically from montelukast?
1. Zileuton inhibits 5-lipoxygenase and so reduces formation of the leukotrienes, whereas montelukast blocks the CysLT₁ receptor
2. Zileuton blocks the CysLT₁ receptor more selectively than montelukast does
3. Zileuton is a bronchodilator acting at beta-2 adrenoceptors
4. Zileuton inhibits cyclo-oxygenase and reduces prostaglandin formation
1. Explanation: The zileuton label describes it as an inhibitor of 5-lipoxygenase that thus inhibits LTB₄, LTC₄, LTD₄ and LTE₄ formation, while montelukast binds with high affinity and selectivity to the CysLT₁ receptor rather than to prostanoid, cholinergic or beta-adrenergic receptors. [3][1]
2. Question: A prescriber is considering montelukast purely for seasonal allergic rhinitis in a patient whose symptoms are mild and who has not tried anything else. What does the labelling require?
1. Use is reserved for patients with an inadequate response or intolerance to alternative therapies
2. Montelukast is the preferred first choice for all allergic rhinitis
3. Montelukast may be used first provided liver enzymes are checked monthly
4. Allergic rhinitis is not an indication for montelukast at any point

2. Explanation: The boxed warning states that the benefits may not outweigh the risks in some patients, particularly where symptoms are mild and adequately treated with alternatives, and reserves allergic rhinitis use for inadequate response or intolerance to alternative therapies. Liver enzyme monitoring belongs to zileuton, not montelukast. [1]
3. Question: Which monitoring requirement belongs specifically to zileuton?
 1. Serum ALT before treatment, monthly for the first three months, then every two to three months for the rest of the first year
 2. Prothrombin time measured before every dose
 3. Annual eosinophil count in all patients
 4. Serum potassium at each review
3. Explanation: That schedule is set out in the zileuton label, which also contraindicates the drug in active liver disease or persistent enzyme elevations at or above three times the upper limit of normal. Prothrombin time is monitored only where warfarin is co-prescribed. [3]
4. Question: Which of these interactions is documented for zafirlukast?
 1. A clinically significant increase in prothrombin time when given with warfarin
 2. Loss of oral contraceptive efficacy through enzyme induction
 3. A doubling of digoxin clearance
 4. Precipitation of serotonin syndrome with selective serotonin reuptake inhibitors
4. Explanation: The zafirlukast label records a clinically significant increase in prothrombin time on coadministration with warfarin and requires close monitoring with anticoagulant dose adjustment. The other three options are not described in that label. [2]

Frequently asked questions

1. Question: Why is montelukast still licensed if it carries a boxed warning?
 1. Answer: Because the regulators concluded that the balance still favours treatment in the right patients rather than in all of them. The MHRA review published in April 2024 found that the benefits continue to outweigh the risks for most patients in asthma, and responded by strengthening communication, including a warning in the patient leaflet for every UK montelukast product. The narrower judgement falls on allergic rhinitis, where the disease is milder and the label restricts use accordingly. [5][1]
2. Question: Can any of these drugs be used during an asthma attack?
 2. Answer: No. Each label excludes use in reversal of bronchospasm in an acute asthma attack, and zafirlukast's adds that it is not a bronchodilator at all. They reduce the inflammatory background with regular daily dosing, which is a different job from relieving an obstruction that is already present. [1][2][3]
3. Question: How do leukotriene modifiers relate to inhaled corticosteroids?
 3. Answer: They are given alongside inhaled treatment rather than as a swap for it: the NHS medicine page describes montelukast as taken with a patient's inhalers or other asthma medicine, and the label forbids abrupt substitution for an inhaled or oral corticosteroid while permitting gradual, supervised reduction. Any ranking of the two options in a treatment ladder is a guideline matter, covered on the inhaled corticosteroids page in this section rather than asserted here. [6][1]
4. Question: Which neuropsychiatric symptoms should raise concern, and how common are they?
 4. Answer: The UK regulator lists sleep disturbances, depression and agitation including aggressive behaviour at up to 1 in 100 people, disturbances of attention or memory at up to 1 in 1,000, and hallucinations and suicidal thinking and behaviour very rarely at up to 1 in 10,000. Its advice is that families be told what to look for, because the person affected may not notice the change themselves, and that medical attention be sought immediately if it happens. [4]
5. Question: Why is zileuton so rarely seen in practice?
 5. Answer: Its hepatic profile and the workload attached to it. ALT elevations above three times the upper limit of normal occurred in 1.9% of patients treated for at least a year against 0.2% on placebo, the drug is contraindicated in active liver disease, and the label sets a monitoring schedule running through the whole of the first year and beyond. LiverTox

nonetheless classes clinically apparent injury as rare. [8][3]

6. Question: Is the whole class interchangeable if one member causes liver injury?

6. Answer: Not by assumption. LiverTox notes that the two receptor antagonists are structurally distinct and that their patterns of liver injury differ enough that patients injured by one have tolerated the other without recurrence, but that is an observation about reported cases rather than a rule to apply at the bedside. The decision after a suspected drug-induced liver injury rests with the treating clinician. [9]

References

[1] MONTELUKAST SODIUM tablet, film coated - prescribing information, including the boxed warning. DailyMed, U.S. National Library of Medicine .

<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=97a682c2-7e00-4d07-a5ac-4436c977f842>

[2] ACCOLATE (zafirlukast) tablet, film coated - prescribing information. DailyMed, U.S. National Library of Medicine .

<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4bf90772-58d5-456d-ad1c-fc448cc5a231>

[3] ZILEUTON tablet, multilayer, extended release - prescribing information. DailyMed, U.S. National Library of Medicine .

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