Gemeinsamer Bundesausschuss

# Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

# und

# Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

## Vorgang: 2019-B-008-z Dupilumab

Stand: April 2019

# I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

**Dupilumab**
Als Zusatztherapie zur Behandlung des unzureichend kontrollierten schweren Asthmas

| **Kriterien gemäß 5. Kapitel § 6 VerfO** | |
|---|---|
| Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben. | *siehe Übersicht II:* Zugelassene Arzneimittel im Anwendungsgebiet: |
| Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein. | Nicht angezeigt |
| Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen | Beschluss des G-BA über eine Änderung der Arzneimittel-Richtlinie (AM-RL):<br>- Mepolizumab (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 21. Juli 2016)<br>- Reslizumab (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 6. Juli 2017)<br>- Benralizumab (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 2. August 2018)<br>*Hinweis:alle drei Beschlüsse nur für Erwachsene*<br>Beschluss des G-BA über eine Änderung der Arzneimittel-Richtlinie (AM-RL) - Anlage IV: Therapiehinweis zu Omalizumab (Beschluss vom 17. Dezember 2015)<br><br>DMP-Richtlinie (DMP-RL): Asthma |
| Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören. | *siehe Evidenzsynopse* |

## II. Zugelassene Arzneimittel im Anwendungsgebiet

| **Wirkstoff**<br>**ATC-Code**<br>**Handelsname** | **Anwendungsgebiet**<br>(Text aus Fachinformation) |
|---|---|
| Zu bewertendes Arzneimittel: | |
| Dupilumab | Anwendungsgebiet laut positive Opinion:<br>„Dupixent is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO (see section 5.1), who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment“ |
| **Beta-2-Sympathomimetika (inhalativ; kurzwirkend) (SABA)** | |
| Salbutamol<br>R03AC02<br>Salbutamol CT | Zur Verhütung und Behandlung von Atemwegserkrankungen mit reversibler Obstruktion, wie z. B. Asthma bronchiale oder chronische Bronchitis. Salbutamol-CT Dosieraerosol wird angewendet bei Erwachsenen, Jugendlichen und Kindern im Alter von 5 bis 12 Jahren (für die Anwendung bei Kleinkindern und Kindern unter 5 Jahren siehe Abschnitte 4.2 und 5.1).<br>Hinweis:<br>Eine längerfristige Behandlung soll symptomorientiert und nur in Verbindung mit einer entzündungshemmenden Dauertherapie erfolgen.<br>(FI Salbutamol CT, Stand 04/2015) |
| Fenoterol<br>R03AC04<br>Berotec N® | - Symptomatische Behandlung von akuten Asthmaanfällen.<br>- Prophylaxe von belastungsinduziertem Asthma bronchiale.<br>- Symptomatische Behandlung von Asthma bronchiale allergischer und nichtallergischer Ursache und/oder anderen Erkrankungen, die mit einer reversiblen Obstruktion der Atemwege einhergehen, z.B. chronisch obstruktive Bronchitis mit und ohne Lungenemphysem.<br>Hinweis:<br>- Sofern eine Dauerbehandlung erforderlich ist, soll stets eine begleitende antiinflammatorische Therapie erfolgen.<br>Dosierung:<br>Die Dosierung richtet sich nach Art und Schwere der Erkrankung. Soweit nicht anders verordnet, gelten für Erwachsene und Kinder ab 6 Jahren folgende Empfehlungen:<br>(FI Berotec, Stand 09/2015) |

## II. Zugelassene Arzneimittel im Anwendungsgebiet

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| **Beta-2-Sympathomimetika (systemisch; kurzwirkend) (SABA)** | |
| Reproterol<br>R03CC14<br>Bronchospasmin | Zur kurzfristigen Behandlung des schweren bronchospastischen Anfalls und des Status asthmaticus.<br>Aus Dosierung: Kinder (Säuglinge ab 3. Monat, Klein- und Schulkinder) […]<br>(FI Bronchospasmin, Stand 02/2016) |
| **Beta-2-Sympathomimetika (inhalativ; langwirkend) (LABA)** | |
| Salmeterol<br>R03AC12<br>Serevent®<br>Dosier-Aerosol<br>Serevent®<br>Diskus | Zur Langzeitbehandlung von Atemwegserkrankungen mit Verengung der Atemwege durch Krämpfe der Bronchialmuskulatur (obstruktive Atemwegserkrankungen), wie z. B. Asthma bronchiale (anfallsweise auftretende Atemnot durch Atemwegsverkrampfung, insbesondere nächtliches Asthma), chronische Bronchitis und Blählunge (Lungenemphysem).<br>Gleichzeitig soll beim Asthma bronchiale eine regelmäßige Therapie mit entzündungshemmenden Arzneimitteln (inhalative und/ oder orale Kortikoide) sichergestellt werden, da Serevent kein Ersatz hierfür ist. Diese Behandlung mit Kortikoiden ist regelmäßig weiterzuführen.<br>Warnhinweis:<br>Serevent Dosier-Aerosol und Serevent Diskus sollen nicht für die Akutbehandlung eines Asthmaanfalls eingesetzt werden.<br>*Aus Dosierung: Für Erwachsene und Kinder ab 4 Jahren gelten folgende Empfehlungen:*<br>*Serevent Dosier-Aerosol: Erwachsene: 2-mal täglich 2 Sprühstöße inhalieren. Bei stärkeren Beschwerden kann die Dosis auf Anweisung des Arztes auf 2-mal täglich 4 Sprühstöße erhöht werden. Kinder ab 4 Jahren: 2-mal täglich 2 Sprühstöße inhalieren.*<br>*Serevent Diskus Erwachsene: 2-mal täglich 1 Einzeldosis inhalieren. Bei stärkeren Beschwerden kann die Dosis auf Anweisung des Arztes auf 2-mal täglich 2 Einzeldosen erhöht werden. Kinder ab 4 Jahren: 2-mal täglich 1 Einzeldosis inhalieren.*<br>(FI Serevent ® Dosier-Aerosol, Stand 02/2015) |
| Formoterol<br>R03AC13<br>Formoterol CT® | - Symptomatische Langzeitbehandlung des chronischen mäßigen bis schweren Asthma bronchiale in Kombination mit einer entzündungshemmenden Dauertherapie (z. B. Kortikosteroide).<br>- […]<br>Hinweis: Bisher liegen keine Hinweise darauf vor, dass Formoterol eine Behandlung mit Kortikosteroiden ersetzen kann. Bei Asthma bronchiale muss Formoterol in jedem Fall mit Kortikosteroiden zur Inhalation kombiniert werden.<br>*Aus Dosierung: Kinder ab 6 Jahren, Jugendliche und Erwachsene (auch Ältere) gilt: Die übliche Erhaltungsdosis ist 1 Kapsel mit Pulver zur Inhalation (12 Mikrogramm) zweimal täglich.*<br>(FI Formoterol-CT, Stand 06/2015) |
| **Beta-2-Sympathomimetika (oral; kurz-, langwirkend)** | |
| Terbutalin<br>R03AC03<br>Aerodur | Atemwegserkrankungen mit Verengung der Atemwege durch Krämpfe der Bronchialmuskulatur (obstruktive Atemwegserkrankungen), wie z.B. Asthma bronchiale, chronische Bronchitis und Blählunge (Lungenemphysem).<br>*Aus Dosierung: Für Erwachsene und Kinder ab 5 Jahren gelten folgende Empfehlungen: […]* |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
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| Turbohaler® | (FI Aerodur Turbohaler, Stand 05/2017) |
| Salbutamol<br>R03CC02<br>Salbubronch® | Verhütung und Behandlung von Atemwegserkrankungen bei Erwachsenen und Kindern ab 2 Monaten, die mit einer Verengung der Atemwege durch Krämpfe der Bronchialmuskulatur einhergehen (obstruktive Atemwegserkrankungen), wie z. B. bei Asthma bronchiale, chronischer Bronchitis und Blählunge (Lungenemphysem).<br>Hinweis<br>SALBUBRONCH Elixier ist nur für Patienten, die nicht symptomorientiert mit inhalativen β2-Sympathomimetika behandelt werden können, geeignet. Eine Behandlung mit SALBUBRONCH Elixier sollte in Ergänzung zu einer entzündungshemmenden Dauertherapie mit Glukokortikoiden oder anderen entzündungshemmend wirkenden Substanzen erfolgen. (FI SALBUBRONCH® Elixier, Stand 02/2014) |
| Bambuterol<br>R03CC12<br>Bambec® | Verhütung und Behandlung von Atemwegserkrankungen, die mit einer Verengung der Atemwege durch Krämpfe der Bronchialmuskulatur einhergehen (obstruktive Atemwegserkrankungen).<br>Hinweis:<br>Bambec ist nur für Patienten, die nicht symptomorientiert mit inhalativen Beta-2-Sympathomimetika behandelt werden können, geeignet. Bei Patienten mit Asthma bronchiale sollte eine Behandlung mit Bambuterol in Ergänzung zu einer entzündungshemmenden Dauertherapie, z. B. mit Glukokortikoiden zur Inhalation oder Leukotrien- Rezeptor-Antagonisten, erfolgen.<br>*Aus Dosierung: Kinder von 6 - 12 Jahren: […]*<br>(FI Bambec®, Stand 05/2016) |
| Clenbuterol<br>R03CC13<br>Spiropent® | Symptomatische Behandlung chronisch obstruktiver Atemwegserkrankungen mit reversibler Atemwegsverengung, wie z. B. Asthma bronchiale oder chronisch obstruktive Bronchitis mit und ohne Emphysem.<br>Hinweis<br>Spiropent Tabletten sind nicht zur symptomorientierten Behandlung des akuten Asthmaanfalls geeignet. Eine Behandlung mit Spiropent Tabletten sollte in Ergänzung zu einer entzündungshemmenden Dauertherapie mit Kortikoiden oder anderen entzündungshemmend wirkenden Substanzen erfolgen.<br>*Aus Dosierung: Bei Kindern bis zu 12 Jahren ist im Allgemeinen wie in der nachfolgenden Tabelle angegeben zu dosieren: […]*<br>(FI Spiropent® Tropfen, Stand 03/2014) |
| Clenbuterol/<br>Ambroxol<br>R03CC63<br>Spasmo-<br>Mucosolvan Saft® | Akute und chronische Atemwegserkrankungen, die mit spastischen Verengungen, veränderter Sekretbildung und gestörtem Sekrettransport einhergehen, insbesondere spastische Bronchitiden, Emphysembronchitiden und Asthma bronchiale.<br>Hinweis<br>Spasmo-Mucosolvan Saft ist nicht zur symptomorientierten Behandlung des akuten Asthmaanfalls geeignet. Sofern eine Dauerbehandlung eines Asthma bronchiale mit Spasmo-Mucosolvan Saft erforderlich ist, soll stets eine begleitende antiinflammatorische Therapie (z. B. mit Kortikoiden) erfolgen.<br>*Soweit nicht anders verordnet wird, ist bei Kindern bis zu 12 Jahren im Allgemeinen wie in der folgenden Tabelle angegeben zu dosieren:[…]*<br>(FI Spasmo-Mucosolvan® Saft, Stand 03/2016) |

## II. Zugelassene Arzneimittel im Anwendungsgebiet

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| **Anticholinergika (inhalativ)** | |
| Tiotropiumbromid<br>R03BB04<br>Spiriva®<br>Respimat® | […]<br>Asthma<br>Spiriva Respimat ist indiziert als zusätzlicher dauerhaft einzusetzender Bronchodilatator bei Patienten ab 6 Jahren mit schwerem Asthma, die im Vorjahr mindestens eine schwere Exazerbation erfahren haben (siehe Abschnitte 4.2 und 5.1).<br>(FI Spiriva® Respimat®, Stand 05/2018)<br><br>Kinder und Jugendliche<br>*Asthma*<br>Die empfohlene Tagesdosis für Patienten im Alter von 6 bis 17 Jahren beträgt 5 Mikrogramm Tiotropium entsprechend der Inhalation von 2 Hüben aus dem Respimat Inhalator einmal täglich zur gleichen Tageszeit.<br><br>Bei Jugendlichen (12 - 17 Jahre) mit schwerem Asthma sollte Tiotropium zusätzlich zu inhalativen Kortikosteroiden (> 800 - 1600 µg Budesonid/Tag oder Äquivalent) und einem Controller, oder zusätzlich zu inhalativen Kortikosteroiden (400 - 800 µg Budesonid/Tag oder Äquivalent) und zwei Controllern angewendet werden.<br><br>Bei Kindern (6 - 11 Jahre) mit schwerem Asthma sollte Tiotropium zusätzlich zu inhalativen Kortikosteroiden (> 400 µg Budesonid/Tag oder Äquivalent) und einem Controller, oder zusätzlich zu inhalativen Kortikosteroiden (200 - 400 µg Budesonid/Tag oder Äquivalent) und zwei Controllern angewendet werden.<br><br>Die Sicherheit und Wirksamkeit von Spiriva Respimat ist bei Kindern und Jugendlichen im Alter von 6 bis 17 Jahren mit mittelgradigem Asthma sowie bei Kindern unter 6 Jahren nicht erwiesen. Die derzeit verfügbaren Daten sind in den Abschnitten 5.1 und 5.2 beschrieben, jedoch kann keine Dosierungsempfehlung gegeben werden. |
| **Inhalative Corticosteroide (ICS)** | |
| Beclometason<br>R03BA01<br>Junik® junior | Antientzündliche Therapie von Asthma bronchiale.<br>*Aus Dosierung:*<br>*Erwachsen: 2-mal täglich 4 – 6 Sprühstöße (entsprechend 0,4 – 0,6 mg Beclometasondipropionat/Tag).*<br>*Jugendliche ab 12 Jahre : 2-mal täglich 4 – 6 Sprühstöße (entsprechend 0,4 – 0,6 mg Beclometasondipro pionat/Tag).*<br>*Kinder von 5 bis 11 Jahre : 2-mal täglich 2 – 4 Sprühstöße (entsprechend 0,2 – 0,4mg Beclometasondipropionat/Tag).*<br>(FI Junik® junior, Stand 05/2017) |
| Budesonid<br>R03BA02 | Zur Behandlung persistierender Atemwegserkrankungen, wenn die Anwendung von Glukokortikoiden erforderlich ist, wie z.B. bei:<br>- Asthma bronchiale […] |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| Budenid Easyhaler ® | *Aus Dosierung: Erwachsene (einschließlich ältere Personen und Jugendliche von 12 bis 17 Jahren) mit leichtem, mittelschwerem und schwerem Asthma: Die übliche Erhaltungsdosis beträgt 100 – 400 µg zweimal täglich. Bei schwerem Asthma kann die Tagesdosis zeitweise bis auf 1600 µ g, aufgeteilt auf mehrere (zwei) Dosen, erhöht, und sobald sich das Asthma stabilisiert hat, wieder reduziert werden. Kinder von 6 bis 11 Jahren: Die übliche Erhaltungsdosis beträgt 100 – 200 µg zweimal täglich. Wenn nötig, kann die Tagesdosis bis auf 800 µg, aufgeteilt auf mehrere (zwei) Dosen, erhöht, und sobald sich das Asthma stabilisiert hat, wieder reduziert werden*<br>(FI budenid Easyhaler ®, Stand 03/2017) |
| Ciclesonid<br>R03BA08<br>ALVESCO® | Zur Behandlung von persistierendem Asthma bei Erwachsenen und Jugendlichen (ab 12 Jahren).<br>(FI Alvesco®, Stand 04/2016) |
| Fluticason<br>R03BA05<br>FLUTIDE® Junior 50 Diskus® | Dauerbehandlung eines persistierenden Asthma bronchiale aller Schweregrade.<br>Hinweis: Flutide Diskus ist nicht zur Akutbehandlung eines Asthmaanfalles geeignet.<br>(FI Flutide®, Stand 07/2017) |
| Mometason<br>R03BA07<br>ASMANEX® | Bei Erwachsenen und Jugendlichen ab 12 Jahren zur regelmäßigen Behandlung, um anhaltendes Asthma bronchiale zu kontrollieren.<br>(FI ASMANEX® Twisthaler®, Stand 10/2014) |
| **Corticosteroide (systemisch, oral)** | |
| Prednisolon,<br>Prednisolon ratiopharm® | […]<br>Asthma bronchiale (DS: c-a), gleichzeitig empfiehlt sich die Verabreichung von Bronchodilatatoren.<br>*Aus Dosierung: 2. Kinder:*<br>*Hochdosiert: 2 – 3 mg/kg KG/Tag*<br>*Mittlere Dosierung: 1 – 2 mg/kg KG/Tag*<br>*Erhaltungsdosis: 0,25 mg/kg KG/Tag*<br>(FI Prednisolon-ratiopharm®, Stand 08/2010) |
| Prednison,<br>Prednison ratiopharm® | […]<br>Asthma bronchiale (DS: c-a), gleichzeitig empfiehlt sich die Verabreichung von Bronchodilatatoren.<br>*Aus Dosierung: 2. Kinder*<br>*Hochdosiert: 2 – 3 mg/kg KG/Tag*<br>*Mittlere Dosierung: 1 – 2 mg/kg KG/Tag*<br>*Erhaltungsdosis: 0,25 mg/kg KG/Tag* |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| | (FI Prednison-ratiopharm®, Stand 05/2017) |
| **Weitere** | |
| Theophyllin (systemisch)<br>R03DA04<br>z.B. Theophyllin retard-ratiopharm | Bronchospasmolytikum/Antiasthmatikum<br>Behandlung und Verhütung von Atemnotzuständen aufgrund von Verengung der Atemwege (Bronchokonstriktion) bei Patienten mit persistierendem Asthma bronchiale oder mittel- bis schwergradiger obstruktiver Atemwegserkrankung (z. B. chronische Bronchitis und Lungenemphysem).<br>*Hinweis:*<br>*Es wird empfohlen die Dauertherapie dieser Erkrankungen mit Theophyllin in Kombination mit anderen die Bronchien erweiternden und entzündungshemmenden Arzneimitteln, wie z. B. lang wirksamen β-Sympathomimetika und Glukocortikoiden durchzuführen. Arzneimittel mit verzögerter Theophyllin- Freisetzung, wie Theophyllin retardratiopharm®, sind nicht zur Akutbehandlung des Status asthmaticus oder der akuten Bronchospastik bestimmt. Theophyllin sollte nicht als Mittel der ersten Wahl zur Behandlung von Asthma bei Kindern angewendet werden.*<br>(FI Theophyllin retard-ratiopharm, Stand 04/2014) |
| Omalizumab<br>R03DX05<br>Xolair® | Xolair wird angewendet bei Erwachsenen, Jugendlichen und Kindern (6 bis < 12 Jahre). Die Behandlung mit Xolair sollte nur bei Patienten in Betracht gezogen werden, bei denen von einem IgE-(Immunglobulin E-) vermittelten Asthma ausgegangen werden kann (siehe Abschnitt 4.2).<br>Erwachsene und Jugendliche (ab 12 Jahren)<br>– Erwachsene und Jugendliche (ab 12 Jahren): Xolair wird als Zusatztherapie zur verbesserten Asthmakontrolle bei Patienten mit schwerem persistierendem allergischem Asthma angewendet, die einen positiven Hauttest oder in vitro Reaktivität gegen ein ganzjährig auftretendes Aeroallergen zeigen und sowohl eine reduzierte Lungenfunktion (FEV1 < 80 %) haben als auch unter häufigen Symptomen während des Tages oder nächtlichem Erwachen leiden und trotz täglicher Therapie mit hoch dosierten inhalativen Kortikosteroiden und einem lang wirkenden inhalativen Beta2-Agonisten mehrfach dokumentierte, schwere Asthma-Exazerbationen hatten.<br>– Kinder (6 bis < 12 Jahre): Xolair wird als Zusatztherapie zur verbesserten Asthmakontrolle bei Patienten mit schwerem persistierendem allergischem Asthma angewendet, die einen positiven Hauttest oder in vitro Reaktivität gegen ein ganzjährig auftretendes Aeroallergen zeigen und unter häufigen Symptomen während des Tages oder nächtlichem Erwachen leiden und trotz täglicher Therapie mit hoch dosierten inhalativen Kortikosteroiden und einem lang wirkenden inhalativen Beta2-Agonisten mehrfach dokumentierte, schwere Asthma-Exazerbationen hatten.<br>(FI Xolair®, Stand 05/2018) |
| Mepolizumab<br>R03DX09<br>Nucala® | Nucala ist angezeigt als Zusatzbehandlung bei schwerem refraktärem eosinophilem Asthma bei erwachsenen Patienten Jugendlichen und Kindern ab 6 Jahren (siehe Abschnitt 5.1). (FI Nucala®, Stand 08/2018) |
| Reslizumab | CINQAERO wird angewendet als Zusatztherapie bei erwachsenen Patienten mit schwerem eosinophilem Asthma, das trotz hochdosierter |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
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| R03DX08<br>CINQAERO® | inhalativer Kortikosteroide plus einem anderen Arzneimittel zur Erhaltungstherapie nur unzureichend zu kontrollieren ist (siehe Abschnitt 5.1). (FI CINQAERO®, Stand 09/2018) |
| Benralizumab<br>R03DX10<br>Fasenra® | Fasenra® ist angezeigt als Add-on-Erhaltungstherapie bei erwachsenen Patienten mit schwerem eosinophilem Asthma, das trotz hochdosierter inhalativer Corticosteroide plus lang wirksame Beta-Agonisten unzureichend kontrolliert ist (siehe Abschnitt 5.1). (FI Fasenra®, Stand 01/2018) |
| **Kombinationspräparate (ICS/LABA)** | |
| Beclometason/<br>Formoterol<br>R03AK08<br>Foster® | Foster ist angezeigt für die regelmäßige Behandlung von Asthma, bei der die Anwendung eines Kombinationsprodukts (von inhalativem Kortikosteroid und langwirksamem Beta-2-Agonisten) angezeigt ist:<br>• Patienten, die mit inhalativen Kortikosteroiden und inhalativen schnellwirksamen Beta-2-Agonisten zur bedarfsweisen Inhalation nicht ausreichend eingestellt sind oder<br>• Patienten, die mit inhalativen Kortikosteroiden und langwirksamen Beta-2-Agonisten in Kombination bereits ausreichend eingestellt sind.<br>Foster wird bei Erwachsenen angewendet.<br>(FI Foster, Stand 12/2016) |
| Budesonid/<br>Formoterol<br>R03AK07<br>DUORESP<br>Spiromax® | DuoResp® Spiromax® wird nur bei Erwachsenen ab 18 Jahren angewendet. Zur regelmäßigen Behandlung von Asthma, bei der die Anwendung eines inhalativen Kortikosteroids und eines langwirksamen Beta-Agonisten in Kombination angezeigt ist: - bei Patienten, die mit inhalativen Kortikosteroiden und kurzwirksamen Beta-2-Agonisten zur bedarfsweisen Inhalation nicht ausreichend eingestellt sind, oder - bei Patienten, die bereits mit inhalativen Kortikosteroiden und langwirksamen Beta-2-Agonisten in Kombination ausreichend eingestellt sind.<br>(FI DuoResp® Spiromax®, Stand 07/2016) |
| Salmeterol/<br>Fluticason<br>R03AK06<br>Viani® | Viani Diskus ist indiziert für die regelmäßige Behandlung von Asthma bronchiale, bei der die Anwendung von langwirksamem Beta2- Agonisten und inhalativem Kortikoid in Kombination angezeigt ist: – bei Patienten, die mit inhalativen Kortikoiden und kurzwirksamen Beta2-Agonisten zur bedarfsweisen Inhalation nicht ausreichend eingestellt sind oder – bei Patienten, die mit inhalativen Kortikoiden und langwirksamen Beta2-Agonisten ausreichend eingestellt sind. Hinweis: Die Stärke Viani 50 µg/100 µg ist nicht angezeigt bei Erwachsenen und Kindern mit schwerem Asthma bronchiale.<br>*Aus Dosierung: Kinder ab 4 Jahren: […] Die für Kinder maximal zugelassene Dosis Fluticasonpropionat, abgegeben aus einem Viani Dosier-Aerosol, ist 100 Mikrogramm 2-mal täglich.*<br>(FI Viani®, Stand 04/2015) |
| Vilanterol/<br>Fluticason<br>R03AK10 | Relvar Ellipta ist angezeigt für die regelmäßige Behandlung von Asthma bei Erwachsenen und Jugendlichen ab 12 Jahren, bei denen ein Kombinationspräparat (langwirksamer Beta2-Agonist und inhalatives Kortikosteroid) angezeigt ist:<br>• Patienten, die mit inhalativen Kortikosteroiden und einer Bedarfsmedikation mit inhalativen kurzwirksamen Beta2-Agonisten nicht |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
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| Relvar® Ellipta® | ausreichend eingestellt sind.<br>(FI Relvar® Ellipta®, Stand 10/2016) |
| **Kombinationspräparate: Anticholininergika/ Beta-2-Sympathomimetikum** | |
| Ipratropiumbromid/ Fenoterol<br>R03AL01<br>Berodual N® | Zur Verhütung und Behandlung von Atemnot bei chronisch obstruktiven Atemwegserkrankungen: Asthma bronchiale allergischer und nichtallergischer (endogener) Ursache, Anstrengungsasthma und chronisch obstruktive Bronchitis mit und ohne Emphysem. Hinweis: Sofern eine Dauerbehandlung erforderlich ist, soll stets eine begleitende antiinflammatorische Therapie erfolgen.<br>*Aus Dosierung: Für Erwachsene und Kinder ab 6 Jahren gelten folgende Empfehlungen:[…]*<br>(FI Berodual®, Stand 10/2014) |

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

## Abteilung Fachberatung Medizin

# Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

## Vorgang: 2019-B-008z (Dupilumab)

| | |
|---|---|
| Auftrag von: | Abt. AM |
| Bearbeitet von: | Abt. FB Med |
| Datum: | 13. Februar 2019 |

# Inhaltsverzeichnis

# Abkürzungsverzeichnis

| | |
|---|---|
| ACQ | Asthma Control Questionnaire |
| AE | adverse events |
| AQLQ | Asthma Quality of Life Questionnaire |
| AWMF | Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften |
| BUD | budesonide |
| F | formoterol |
| FEV1 | forciertes exspiratorisches Volumen (engl. Forced Expiratory Volume in 1 second) |
| FP | fluticasone |
| FVC | Forced vital capacity |
| GIN | Guidelines International Network |
| GINA | Global Initiative for Asthma |
| GoR | Grade of Recommendations |
| HR | Hazard Ratio |
| ICS | Inhaled Corticosteroid |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen |
| KI | Konfidenzintervall |
| LABA | long-acting beta2-agonists |
| LAMA | long-acting muscarinic antagonist |
| LoE | Level of Evidence |
| NICE | National Institute for Health and Care Excellence |
| NMA | Netzwerkmetaanalyse |
| OCS | orales Glucocorticosteroid |
| PEF | Peak expiratory flow |
| OCS | Orale Corticosteroide |
| OR | Odds Ratio |
| RR | Relatives Risiko |
| SABA | short-acting beta-agonist |
| SAE | Serious adverse events |

| | |
|---|---|
| SAL | salmeterol |
| SIGN | Scottish Intercollegiate Guidelines Network |
| SiT | ’single inhaler therapy’ |
| TRIP | Turn Research into Practice Database |
| WHO | World Health Organization |

# 1 Indikation

Mittelschweres bis schweres Asthma

Für Evidenzsynopse: Mittelschweres bis schweres Asthma, das mit mittel- bis hochdosierten inhalativen Kortikosteroiden plus einem weiteren Arzneimittel zur Erhaltungstherapie nur unzureichend kontrolliert ist.

# 2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Asthma* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 27.09.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1317 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 24 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

# 3 Ergebnisse

## 3.1 G-BA Beschlüsse/IQWiG Berichte

**G-BA, 2017 [9].**

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 06. Juli 2017 - Reslizumab

**Anwendungsgebiet**

CINQAERO wird angewendet als Zusatztherapie bei erwachsenen Patienten mit schwerem eosinophilem Asthma, das trotz hochdosierter inhalativer Corticosteroide plus einem anderen Arzneimittel zur Erhaltungstherapie nur unzureichend zu kontrollieren ist

**Zweckmäßige Vergleichstherapie**

Die zweckmäßige Vergleichstherapie für die Behandlung (Add-on-Therapie) des schweren eosinophilen Asthmas bei erwachsenen Patienten, welche trotz hoher Dosen an inhalativen Corticosteroiden und einem weiteren Controller unkontrolliert sind, ist:

eine patientenindividuelle Therapieeskalation:

- der hochdosierten inhalativen Corticosteroide und der langwirksamen Bronchodilatatoren (LABA) mit Tiotropium und ggf. orale Corticosteroide* oder
- bei IgE-vermittelter Pathogenese des Asthmas ggf. Omalizumab zusätzlich zu hochdosierten inhalativen Corticosteroiden und langwirksamen Bronchodilatatoren (LABA) und ggf. orale Corticosteroide* oder
- ggf. der hochdosierten inhalativen Corticosteroide und der Bronchodilatatoren (LABA) mit oralen Corticosteroiden*

*Orale Corticosteroide sollten nur kurzzeitig und in der niedrigst-wirksamen Dosis eingesetzt werden.

**Fazit / Ausmaß des Zusatznutzens / Ergebnis**

a) Patienten mit schwerem eosinophilem Asthma, die nicht oder nur im Rahmen von akuten Exazerbationen mit oralen Corticosteroiden behandelt werden:

Ein Zusatznutzen ist nicht belegt.

b) Patienten mit schwerem eosinophilem Asthma, die auch über die Behandlung akuter Exazerbationen hinaus regelmäßig mit oralen Corticosteroiden behandelt werden:

Anhaltspunkt für einen geringen Zusatznutzen.

**G-BA, 2018 [10].**

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 02. August 2018 - Benralizumab

**Anwendungsgebiet**

Fasenra ist angezeigt als Add-on-Erhaltungstherapie bei erwachsenen Patienten mit schwerem eosinophilem Asthma, das trotz hochdosierter inhalativer Kortikosteroide plus lang wirksamer Beta-Agonisten unzureichend kontrolliert ist.

**Vergleichstherapie**

eine patientenindividuelle Therapieeskalation:

- - der hochdosierten inhalativen Corticosteroide (ICS) und der langwirksamen Beta-Agonisten (LABA) mit Tiotropium und ggf. orale Corticosteroide (OCS)[a] oder
- - bei IgE-vermittelter Pathogenese des Asthmas ggf. Omalizumab zusätzlich zu hochdosierten ICS und LABA und ggf. OCSa oder
- - ggf. der hochdosierten ICS und LABA mit OCSa,b oder
- - ggf. der hochdosierten ICS und LABA mit Mepolizumab bei Patienten, die nicht anderweitig eskaliert werden können

[a] Orale Corticosteroide sollten nur kurzzeitig und in der niedrigst-wirksamen Dosis eingesetzt werden. Bei der Behandlung des Asthmas mit OCS ist darauf zu achten, dass die Dosierung von OCS die Cushing-Schwelle möglichst nicht dauerhaft überschreitet. Eine Behandlung von Exazerbationen ist davon abzugrenzen.

[b] Eine Therapie mit OCS ist im Vergleich zu den anderen genannten Wirkstoffen - sofern diese geeignet sind - nicht als zu präferierende Therapieoption anzusehen.

**Fazit / Ausmaß des Zusatznutzens / Ergebnis**

a) Erwachsene Patienten mit schwerem eosinophilem Asthma, das trotz hochdosierter inhalativer Corticosteroide plus lang wirksamer Beta-Agonisten unzureichend kontrolliert ist und für die die weiteren Möglichkeiten der Therapieeskalation noch nicht ausgeschöpft sind:

Ein Zusatznutzen ist nicht belegt.

b) Erwachsene Patienten mit schwerem eosinophilem Asthma, das trotz hochdosierter inhalativer Corticosteroide plus lang wirksamer Beta-Agonisten unzureichend kontrolliert ist und für die die weiteren Möglichkeiten der Therapieeskalation bereits ausgeschöpft sind:

Anhaltspunkt für einen geringen Zusatznutzen.

**G-BA, 2018 [8].**

Richtlinie des Gemeinsamen Bundesausschusses zur Zusammenführung der Anforderungen an strukturierte Behandlungsprogramme nach § 137f Absatz 2 SGB V (DMP-Anforderungen-Richtlinie/DMP-A-RL) zuletzt geändert am 19. April 2018 veröffentlicht im Bundesanzeiger (BAnz AT 23. August 2018 B2) Inkrafttreten: 24. August 2018

**Fazit**

1.5.8.1 Dauertherapie bei Erwachsenen

Vorrangig sollen zur Dauertherapie die folgenden Wirkstoffgruppen verwendet werden:

1. Basistherapie

- inhalative Glukokortikosteroide,

2. als Erweiterung dieser Basistherapie kommen zusätzlich zur Gabe von inhalativen Glukokortikosteroiden in Betracht:

- inhalative lang wirksame Beta-2-Sympathomimetika
- Wenn trotz dieser erweiterten Basistherapie ein unkontrolliertes Asthma bronchiale besteht, stehen zur Modifikation bzw. Eskalation zur Verfügung: - langwirksame Anticholinergika
- systemische Glukokortikosteroide
- Leukotrien-Rezeptor-Antagonisten
- Theophyllin (Darreichungsform mit verzögerter Wirkstofffreisetzung)
- Antikörper

Bei Patientinnen und Patienten mit trotz Ausschöpfung einer erweiterten Basistherapie nicht ausreichend kontrollierbarem schwerem persistierendem Asthma bronchiale kann eine Behandlung mit Antikörpern (z. B. Anti-IgE-Antikörper oder Anti-IL-5-Antikörper) erwogen werden. Hierfür soll eine Überweisung zum qualifizierten Facharzt oder zur qualifizierten Fachärztin oder zur qualifizierten Einrichtung erfolgen.

Bei Undurchführbarkeit einer Therapie mit inhalativen Glukokortikosteroiden (z. B. Ablehnung oder Unverträglichkeit) als Basismedikation ist vor Verordnung einer unterlegenen alternativen antientzündlichen Therapie ein Aufklärungsgespräch über Risiken dieser Therapieoptionen zu führen.

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**G-BA, 2015 [7].**

Anlage IV zum Abschnitt H der Arzneimittel-Richtlinie Verordnungseinschränkungen und -ausschlüsse in der Arzneimittelversorgung Therapiehinweise gemäß § 92 Abs. 2 Satz 7 SGB V i. V. m. § 17 AM-RL zur wirtschaftlichen Verordnungsweise von Arzneimitteln.

**Zugelassene Anwendungsgebiete**

Omalizumab ist zugelassen als Zusatztherapie zur verbesserten Asthmakontrolle bei:

<u>Erwachsenen und Jugendlichen (ab 12 Jahren)</u>

- mit schwerem persistierendem allergischem Asthma,
- die einen positiven Hauttest oder In-vitro-Reaktivität gegen ein ganzjährig auftretendes Aeroallergen zeigen und
- sowohl eine reduzierte Lungenfunktion (FEV1 < 80%) haben
- als auch unter häufigen Symptomen während des Tages oder nächtlichem Erwachen leiden und

- trotz täglicher Therapie mit hochdosierten inhalativen Kortikosteroiden und einem lang wirkenden inhalativen Beta-2-Agonisten mehrfach dokumentierte, schwere Asthma - exazerbationen hatten.
- Die Behandlung mit Omalizumab sollte nur bei Patienten in Betracht gezogen werden, bei denen von einem IgE-vermittelten Asthma ausgegangen werden kann.

Empfehlungen zur wirtschaftlichen Verordnungsweise:

Der Therapiehinweis bezieht sich ausschließlich auf die Indikation Asthma bronchiale.

Die Verordnung von Omalizumab ist als Zusatztherapie bei Jugendlichen ab 12 Jahren und Erwachsenen nur wirtschaftlich, die kumulativ folgende Voraussetzungen erfüllen:

- schweres persistierendes allergisches Asthma,
- reduzierte Lungenfunktion (FEV1 < 80%),
- positiver Hauttest oder In-vitro-Reaktivität gegen ein ganzjährig auftretendes und vom Patienten nicht vermeidbares Aeroallergen,
- das Asthma ist IgE-vermittelt mit IgE-Werten zwischen ≥ 76 und ≤ 1500 I.E./ml vor Beginn der Behandlung,
- häufige dokumentierte Symptome während des Tages oder nächtliches Erwachen,
- trotz täglicher Therapie mit hochdosierten inhalativen Kortikosteroiden (entsprechend > 1000 µg pro Tag Beclometason oder Äquivalent) und mindestens einem lang wirkenden inhalativen Beta-2-Agonisten als Kontroller traten
- in den letzten 12 Monaten mindestens zwei unabhängige, dokumentierte schwere Asthmaexazerbationen, die mit systemischen Kortikosteroiden behandelt wurden, oder
- eine Exazerbation, die systemische Kortikosteroidgabe notwendig machte und zur Krankenhausaufnahme bzw. Notfallbehandlung führte, auf.
- das Körpergewicht liegt innerhalb der Grenzen der Dosierungstabelle also ≥ 20 kg und ≤ 150 kg.
- Nichtraucher

## 3.2 Cochrane Reviews

**Farne HA et al., 2017 [6].**

Anti-IL5 therapies for asthma

**Fragestellung**

We considered in this review whether taking the new drugs mepolizumab, reslizumab or benralizumab in addition to standard treatment (e.g. inhaled steroids and combination inhalers) are better than a placebo for people with asthma.

**Methodik**

Population:

- adults and children with a diagnosis of asthma. We focused on collating data from people who had been reported as having eosinophilic asthma to analyse these individuals as a subgroup

Intervention:

- anti-IL-5 therapy

Komparator:

- placebo

Endpunkte:

- primary: 'Clinically significant' asthma exacerbation, as defined by treatment with a course (three days or more) of systemic corticosteroids (with or without hospital admission); secondary: 1. Asthma exacerbation requiring hospital admission, 2. HRQoL (as measured by a validated questionnaire e.g. ACQ, AQLQ, SGRQ), 3. Measures of lung function (e.g. FEV1), 4. Serious adverse events, 5. 'Clinically significant' adverse events, as defined by those that prompted discontinuation of the intervention and withdrawal from the study, 6. Eosinophil counts in peripheral blood Reporting one or more of the outcomes listed here in the trial was not an inclusion criterion for the review.

Recherche/Suchzeitraum:

- The search was first conducted in 11/2013 and was updated in 11/2014 and 03/2017

Qualitätsbewertung der Studien:

- risk of bias for each study using the criteria outlined intheCochraneHandbook for Systematic Reviews of Interventions

**Ergebnisse**

Anzahl eingeschlossener Studien:

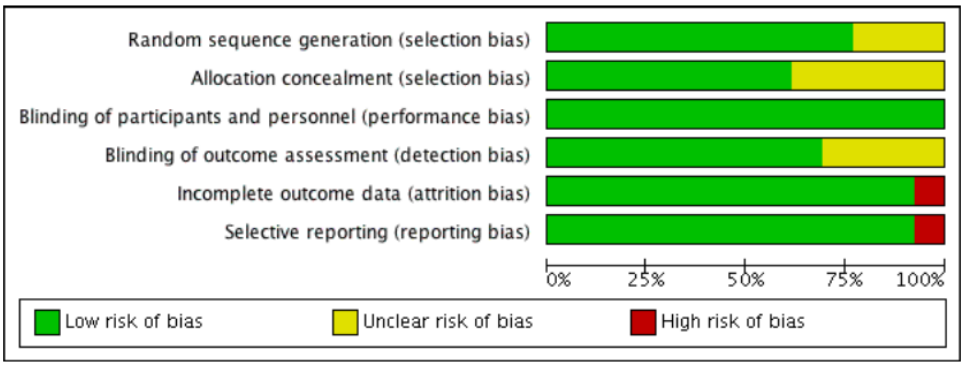
- 13 studies included in the qualitative synthesis; 12 studies included in the quantitative synthesis

Charakteristika der Population:

-

Qualität der Studien:

- The evidence included in this review is provided by very well-designed studies. We consider these studies to be at low risk of bias in the following important respects: the procedure that determined who received which treatment, the blinding processes and the clarity of detail concerning participants who did not complete the study. Overall the evidence was high to moderate quality.




Studienergebnisse:

- four included studies comparing mepolizumab versus placebo (N=1809)
- four included studies comparing reslizumab versus placebo (N=1764)
- five studies comparing benralizumab versus placebo (N=3232)

**Mepolizumab (SC) compared to placebo for asthma**

**Patient or population:** people with asthma
**Setting:** community
**Intervention:** mepolizumab (SC)
**Comparison:** placebo

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with placebo | Risk with mepolizumab (SC) | | | | |
| Rate of exacerbations requiring systemic corticosteroids<br>Follow-up: range 24 to 32 weeks | The mean rate in the placebo group was 1.48 events per participant per year[a] | The mean rate in the intervention group was 0.81 fewer events per participant per year (95% CI 0.66 fewer to 0.94 fewer) | Rate ratio 0.45 (0.36 to 0.55) | 936 (2 RCTs) | ⊕⊕⊕⊕ High | |
| Rate of exacerbations requiring emergency department treatment or admission<br>Follow-up: range 24 to 32 weeks | The mean rate in the placebo group was 0.15 events per patient per year[b] | The mean rate in the intervention group was 0.10 fewer events per participant per year (95% CI 0.05 fewer to 0.12 fewer) | Rate ratio 0.36 (0.20 to 0.66) | 936 (2 RCTs) | ⊕⊕⊕⊕ High | |
| Health-related quality of life (ACQ)<br>Scale from: 0 to 6 (lower is better)<br>Follow-up: range 24 to 32 weeks | The mean change in the placebo group ranged from −0.4 to −0.5 units | The mean in the intervention group was -0.42 units fewer (-0.56 fewer to -0.28 fewer) | - | 936 (2 RCTs) | ⊕⊕⊕◯ Moderate[c] | A change of ≥ 0.5 is considered the minimum clinically significant difference |

| | | | | | | |
|---|---|---|---|---|---|---|
| Health-related quality of life (SGRQ)<br>Scale from: 0 to 100 (lower is better)<br>Follow-up: range 24 to 32 weeks | The mean change in the placebo group ranged from −7.9 to −9.0 units | The mean change in the intervention group was -7.4 units fewer (-9.5 fewer to -5.29 fewer) | - | 936<br>(2 RCTs) | ⊕⊕⊕⊕<br>High | A change of ≥ 4 is considered the minimum clinically significant difference |
| Pre-bronchodilator $FEV_1$ (L)<br>Follow-up: range 24 to 32 weeks | The mean change in the placebo group ranged from 0.086 L (± 0.031 L) to 0.120 L (0.047 to 0.192 L) | The mean difference from placebo was a further 0.11 L (0.06 L to 0.17 L) | - | 936<br>(2 RCTs) | ⊕⊕⊕⊕<br>High | |
| Adverse events leading to discontinuation<br>Follow-up: range 24 to 32 weeks | 15 per 1000 | 7 per 1000<br>(2 to 27) | Risk ratio 0.45<br>(0.11 to 1.80) | 936<br>(2 RCTs) | ⊕⊕⊕◯<br>Moderate[d] | |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**ACQ**: Asthma Control Questionnaire; **CI:** confidence interval; **$FEV_1$** : forced expiratory volume in 1 second; **RR:** risk ratio; **SC**: subcutaneous; **SGRQ**: St. George's Respiratory Questionnaire

**GRADE Working Group grades of evidence**
**High quality:** we are very confident that the true effect lies close to that of the estimate of the effect
**Moderate quality:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low quality:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
**Very low quality:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Rounded mean of the rate in the placebo group of the two studies: 1.21 and 1.74.
[b] Rounded mean of the rate in the placebo group of the two studies: 0.10 and 0.20.
[c] The mean difference (-0.42) is smaller than the minimum clinically significant difference (a reduction of 0.5 points).
[d] The 95% CI crosses the line of no effect, thus we downgraded the quality of evidence to moderate because of imprecision.

**Reslizumab (IV) compared to placebo for asthma**

**Patient or population:** people with asthma
**Setting:** community
**Intervention:** reslizumab (IV)
**Comparison:** placebo

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with placebo | Risk with reslizumab (IV) | | | | |
| Rate of exacerbations requiring systemic corticosteroids<br>Follow-up: 52 weeks | The mean rate in the placebo group was 1.54 events per participant per year | The mean rate in the intervention groups was 0.93 fewer events per participant per year (1.09 fewer to 0.73 fewer) | Rate ratio 0.43<br>(0.33 to 0.55) | 953<br>(2 RCTs) | ⊕⊕⊕⊕<br>High | |
| Rate of exacerbations requiring emergency department treatment or admission<br>Follow-up: 52 weeks | The mean rate in the placebo group was 0.12 events per participant per year | The mean rate in the intervention groups was 0.04 fewer events per participant per year (0.07 fewer to 0.02 more) | Rate ratio 0.67<br>(0.39 to 1.17) | 953<br>(2 RCTs) | ⊕⊕⊕⊕<br>High | |
| Health-related quality of life (AQLQ)<br>Scale from: 1 to 7 (higher is better)<br>Follow -p: range 16 weeks to 52 weeks | The mean change in the placebo group ranged from 0.779 to 0.89 units | MD 0.28 higher<br>(0.17 higher to 0.39 higher)[a] | - | 1164<br>(3 RCTs) | ⊕⊕⊕⊕<br>High | A change of ≥ 0.5 is considered the minimum clinically significant difference |
| Health-related quality of life (ACQ)<br>Scale from: 0 to 6 (lower is better)<br>Follow-up: range 16 | The mean change in the placebo group ranged from −0.368 to −0.80 units | MD -0.25 lower<br>(-0.33 lower to -0.17 lower)[b] | - | 1652<br>(4 RCTs) | ⊕⊕⊕⊕<br>High | A change of ≥ 0.5 is considered the minimum clinically significant difference |

| | | | | | |
|---|---|---|---|---|---|
| weeks to 52 weeks | | | | | |
| Pre-bronchodilator $FEV_1$ (L) Follow-up: range 16 weeks to 52 weeks | The mean change in the placebo group ranged from 0.002 L (± 0.1216 L) to 0.215 (± 0.0484 L) | MD 0.11 L higher (0.07 L higher to 0.15 L higher) | - | 1652 (4 RCTs) | ⊕⊕⊕⊕ High |
| Serious adverse events Follow-up: range 16 weeks to 52 weeks | 91 per 1000 | 72 per 1000 (51 to 102) | RR 0.79 (0.56 to 1.12) | 1656 (4 RCTs) | ⊕⊕⊕⊕ High |
| Adverse events leading to discontinuation Follow-up: range 16 weeks to 52 weeks | 58 per 1000 | 38 per 1000 (25 to 59) | RR 0.66 (0.43 to 1.02) | 1659 (4 RCTs) | ⊕⊕⊕⊕ High |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

**ACQ**: Asthma Control Questionnaire; **AQLQ**: Asthma Quality of Life Questionnaire; **CI:** confidence interval; **$FEV_1$** : forced expiratory volume in 1 second; **MD**: mean difference; **IV**: intravenous; **RR:** risk ratio

**GRADE Working Group grades of evidence**
**High quality:** We are very confident that the true effect lies close to that of the estimate of the effect
**Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
**Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] The mean difference (0.28) is smaller than the minimum clinically significant difference (a reduction of 0.5 points).
[b] The mean difference (-0.25) is smaller than the minimum clinically significant difference (a reduction of 0.5 points)

**Benralizumab (SC) compared to placebo for asthma**

**Patient or population:** people with asthma
**Setting:** community
**Intervention:** benralizumab (SC)
**Comparison:** placebo

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with placebo | Risk with benralizumab (SC) | | | | |
| Rate of exacerbations requiring systemic corticosteroids Follow-up: range 48 weeks to 56 weeks | The mean rate in the placebo group was 0.98 events per participant per year[a] | The mean rate in the intervention groups was 0.37 fewer events per participant per year (0.44 fewer to 0.29 fewer) | Rate ratio 0.62 (0.55 to 0.70) | 2456 (3 RCTs) | ⊕⊕⊕⊕ High | |
| Rate of exacerbations requiring emergency department treatment or admission Follow-up: range 48 weeks to 56 weeks | The mean rate in the placebo group was 0.11 events per participant per year[b] | The mean rate in the intervention groups was 0.04 fewer events per participant per year (0.06 fewer to 0.002 fewer) | Rate ratio 0.68 (0.47 to 0.98) | 1537 (2 RCTs) | ⊕⊕⊕◯ Moderate[c] | There is greater heterogeneity ($I^2$ = 43%) owing to inclusion of less severe participants in FitzGerald 2016 (a larger proportion who had only suffered one exacerbation the previous year, with correspondingly less potential for exacerbation) |
| Health-related quality of life (AQLQ) Scale from: 1 to 7 (higher is better) Follow-up: range 48 weeks to 56 weeks | The mean change in the placebo group ranged from 0.98 to 1.31 units | MD 0.23 higher (0.11 higher to 0.35 higher)[c] | - | 1541 (3 RCTs) | ⊕⊕⊕⊕ High | A change of ≥ 0.5 is considered the minimum clinically significant difference |

| | | | | | | |
|---|---|---|---|---|---|---|
| Health-related quality of life (ACQ) Scale from: 0 to 6 (lower is better) Follow up: range 48 weeks to 56 weeks | The mean change in the placebo group ranged from −1.19 to −0.76 units | MD -0.20 lower (-0.29 lower to -0.11 lower)[d] | - | 2359 (3 RCTs) | ⊕⊕⊕⊕ High | A change of ≥ 0.5 is considered the minimum clinically significant difference |
| Pre-bronchodilator $FEV_1$ (L) Follow-up: range 48 weeks to 56 weeks | The mean change in the placebo group ranged from -0.01 L to 0.239 L | MD 0.10 L higher (0.05 L higher to 0.14 L higher) | - | 2355 (3 RCTs) | ⊕⊕⊕⊕ High | |
| Serious adverse events Follow-up: range 48 weeks to 56 weeks | 135 per 1000 | 109 per 1000 (89 to 136) | RR 0.81 (0.66 to 1.01) | 2648 (4 RCTs) | ⊕⊕⊕⊕ High | |
| Adverse events leading to discontinuation Follow-up: range 48 weeks to 56 weeks | 9 per 1000 | 19 per 1000 (9 to 41) | RR 2.15 (1.02 to 4.57) | 2597 (3 RCTs) | ⊕⊕⊕⊕ High | |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**ACQ:** Asthma Control Questionnaire; **AQLQ:** Asthma Quality of Life Questionnaire; **CI:** confidence interval; **$FEV_1$** : forced expiratory volume in 1 second; **MD:** mean difference; **IV:** intravenous; **RR:** risk ratio

**GRADE Working Group grades of evidence**
**High quality:** we are very confident that the true effect lies close to that of the estimate of the effect
**Moderate quality:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low quality:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
**Very low quality:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Rounded mean of the rate in the placebo group of the eosinophilic and non-eosinophilic arms (as applicable) or the three studies: 1.33, 1.21, 0.68, 0.49, 0.93, 1.21.
[b] Rounded mean of the rate in the placebo group of the two studies: 0.18 and 0.04.
[c] The mean difference (0.23) is less than the minimum clinically significant difference (≥ 0.5).

### Anmerkung/Fazit der Autoren

We found that participants with severe asthma, who had high numbers of a certain type of inflammatory cell (eosinophils) in the blood, benefited from taking mepolizumab, reslizumab or benralizumab through reduced asthma attacks. There were small improvements in quality of life and breathing tests, but these may be too small to be detected by patients. We agree with international guidelines that say that these treatments can be added to standard treatment for people with severe asthma. However, we think that further research is needed to clarify some aspects, such as how to assess treatment response and how long to give treatment for.

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**Kew KM et al., 2015 [13].**

Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus addition of long-acting $beta_2$- agonists (LABA) for adults with asthma (Review)

### Fragestellung

To assess the efficacy and safety of adding a LAMA to ICS compared with adding a LABA for adults whose asthma is not well controlled on ICS alone.

### Methodik

Population: adults (aged 18 years or older) whose asthma is not well controlled with ICS alone

Intervention: LAMA add-on

Komparator: LABA add-on

→ Studies involving the addition of the following LAMAs at any dose:

tiotropium (Spiriva HandiHaler or Respimat);

aclidinium bromide (Eklira Genuair);

glycopyrronium bromide (Seebri Breezhaler).

→ Eligible comparison groups were randomised to receive the same dose of ICS as the intervention group, with the addition of any of the following LABAs:

formoterol 12 or 24 mcg twice daily

salmeterol 50 mcg twice daily

vilanterol 22 mcg once daily

Endpunkte:

(1) primäre Endpunkte: Exacerbations requiring oral corticosteroids; Quality of life (measured on a validated asthma scale, e.g. Asthma Quality of Life Questionnaire, AQLQ); Any serious adverse event.

(2) sekundäre Endpunkte: Exacerbations requiring hospital admission; Lung function (in particular, trough forced expiratory volume in one second (FEV1)); Asthma control (measured on a validated scale, e.g. Asthma Control Questionnaire (ACQ), Asthma Control Test); Any adverse events

Suchzeitraum (Aktualität der Recherche): bis April 2015

Anzahl eingeschlossene Studien/Patienten (Gesamt): 4 RCTs (n= 2049)

Qualitätsbewertung der Studien: Cochrane Risk of Bias Tool; geplante Sensitivitätsanalyse für die primären Endpunkte unter Ausschluss von Studien mit hohem Verzerrungspotential, nicht-publizierten Daten

Heterogenität: $I^2$ nach Higgins/Thompson (greater than 30% → they reported it and explored possible causes by pre-specified subgroup analysis)

→ a priori definierte Subgruppen:

Duration of therapy (six months or less, more than six months).

Corticosteroid dose (according to GINA 2014 – defined low, medium and high cut-offs).

Dose and type of LABA (e.g. formoterol 24 mcg, salmeterol 50 mcg).

Dose and type of LAMA (e.g. tiotropium HandiHaler 18 mcg, tiotropium Respimat 5 mcg).

**Ergebnisse**

- 4 Studien eingeschlossen

Patientencharakteristika

- Baseline characteristics, with the exception of percentagemale and mean age, were generally poorly reported across studies.Mean percentage predicted FEV1 at baseline was between 66% and 76% in the three studies reporting it (NCT00350207; NCT00565266; Rajanandh 2014; Rajanandh 2015). Mean ages were all between

- 37 and 45 years.The proportion ofmen and women was fairly balanced within studies reporting this information, and across studies the percentage of men ranged between 33% (NCT00565266) and 65% (LAMA group of Rajanandh 2014).
- All of the studies compared the LAMA, tiotropium, to salmeterol or formoterol, both used as an add-on drug to ICS. NCT01172808 and NCT01172821 were multi-arm twin trials that included separate arms for two doses of tiotropium Respimat, 2.5mcg daily and 5mcg daily.NCT00350207 used tiotropium at 5 mcg daily; NCT00565266, NCT01290874, Rajanandh 2014, and Rajanandh 2015 used tiotropium HandiHaler 18 mcg daily, but only one of these contributed data to at least one meta-analysis.

Qualitätsbewertung: several studies were given high risk of bias ratings, particularly in the blinding domains and selective reporting, and there was some uncertainty in others, mostly due to insufficient reporting. However, most of the high risk of bias judgements were associated with studies that did not contribute data to the metaanalyses.

Studienergebnisse

**Comparison 1. Long-acting muscarinic antagonists (LAMA) add-on versus long-acting beta$_2$-agonists (LABA) add-on**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Exacerbations (oral corticosteroid) | 2 | | Odds Ratio (Random, 95% CI) | 1.05 [0.50, 2.18] |
| 2 Asthma Quality of Life Questionnaire (AQLQ) total | 4 | | Mean Difference (Random, 95% CI) | -0.12 [-0.18, -0.05] |
| 3 Serious adverse events (all) | 4 | | Odds Ratio (Random, 95% CI) | 0.84 [0.41, 1.73] |
| 4 Exacerbations (hospital) | 4 | | Odds Ratio (Random, 95% CI) | 0.72 [0.18, 2.92] |
| 5 Trough forced expiratory volume in 1 second ($FEV_1$) (L) | 4 | | Mean Difference (Random, 95% CI) | 0.05 [0.01, 0.09] |
| 6 Peak $FEV_1$ (L) | 3 | | Mean Difference (Random, 95% CI) | Totals not selected |
| 7 Trough peak expiratory flow (PEF) (L/min) | 4 | | Mean Difference (Random, 95% CI) | 5.78 [0.86, 10.71] |
| 8 Trough forced vital capacity (FVC) (L) | 3 | 1745 | Mean Difference (IV, Random, 95% CI) | 0.03 [-0.02, 0.07] |
| 9 Peak FVC (L) | 2 | 1483 | Mean Difference (IV, Random, 95% CI) | -0.00 [-0.04, 0.03] |
| 10 Asthma Control Questionnaire (ACQ) total | 3 | | Mean Difference (Random, 95% CI) | 0.06 [0.00, 0.13] |
| 11 ACQ response | 2 | 1563 | Odds Ratio (M-H, Random, 95% CI) | 0.91 [0.73, 1.13] |
| 12 Adverse events AEs (all) | 3 | 1839 | Odds Ratio (IV, Random, 95% CI) | 1.11 [0.92, 1.35] |
| 13 AEs classified as asthma | 3 | 1839 | Odds Ratio (M-H, Random, 95% CI) | 0.95 [0.74, 1.22] |

**Comparison 3. Long-acting muscarinic antagonists (LAMA) dose head-to-head**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Exacerbations (oral corticosteroid) | 1 | 1036 | Odds Ratio (M-H, Fixed, 95% CI) | 0.69 [0.40, 1.22] |
| 2 Asthma Quality of Life Questionnaire (AQLQ) total | 2 | 973 | Mean Difference (IV, Random, 95% CI) | 0.01 [-0.09, 0.10] |
| 3 Serious adverse events (SAEs) (all) | 2 | 1036 | Odds Ratio (M-H, Random, 95% CI) | 1.09 [0.47, 2.49] |

**Comparison 4. Sensitivity analysis excluding the cross-over trial**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Exacerbations (oral corticosteroid) | 1 | | Odds Ratio (IV, Random, 95% CI) | Totals not selected |
| 2 Asthma Quality of Life Questionnaire (AQLQ) total | 3 | 1745 | Mean Difference (IV, Random, 95% CI) | -0.11 [-0.19, -0.03] |
| 3 Serious adverse events (SAEs) (all) | 3 | 1839 | Odds Ratio (IV, Random, 95% CI) | 0.79 [0.30, 2.07] |

- Studies reporting exacerbations requiring OCS showed no difference between the two add-ons, but our confidence in the effect was low due to inconsistency between studies and because the confidence intervals (CI) included significant benefit of either treatment (odds ratio (OR) 1.05, 95%CI 0.50 to 2.18; 1753 participants; 3 studies);
- People taking LAMA scored slightly worse on two scales measuring quality of life (Asthma Quality of Life Questionnaire; AQLQ) and asthma control (Asthma Control Questionnaire; ACQ); the evidence was rated high quality but the effects were small and unlikely to be clinically significant (AQLQ: mean difference (MD) -0.12, 95% CI -0.18 to -0.05; 1745 participants; 1745; 4 studies; ACQ: MD 0.06, 95% CI 0.00 to 0.13; 1483 participants; 3 studies).
- some evidence support small benefits of LAMA over LABA on lung function, including on our pre-specified preferred measure trough forced expiratory volume in one second (FEV1) (MD 0.05 L, 95% CI 0.01 to 0.09; 1745 participants, 4 studies). However, the effects on other measures varied, and it is not clear whether the magnitude of the differences were clinically significant.
- More people had adverse events on LAMA but the difference with LABA was not statistically significant.

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**Kew KM et al., 2016 [12].**

Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta$_2$-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma (Review)

**Fragestellung**

To assess the effects of adding a long-acting muscarinic antagonist (LAMA) to combination long-acting beta$_2$-agonists (LABA) and inhaled corticosteroids (ICS) in adults whose asthma is not well controlled by LABA/ICS

**Methodik**

Population:

- studies in adults (aged 18 years or older) with asthma who were taking LABA/ICS combination therapy

Intervention / Komparator:

- (1) LAMA add-on to any dose of LABA/ ICS combination therapy versus the same dose of LABA/ICS alone
- (2) LAMA versus placebo (if they required participants to be taking LABA/ICS combination therapy for inclusion in the trial)
- (3) We included studies involving the addition of the following LAMA at any dose.
- Tiotropium (Spiriva Handihaler or Respimat).
- Aclidinium bromide (Eklira Genuair).
- Glycopyrronium bromide (Seebri Breezhaler).
- (4) allowed participants to continue using additional short- or long-acting medications (e.g. salbutamol, terbutaline and ipratropium, leukotriene receptor antagonists), provided they were not part of the randomised treatment.

Endpunkte:

- primäre Endpunkte: Exacerbations requiring oral corticosteroids; Quality of life (measured on a validated asthma scale, e.g. Asthma Quality of Life Questionnaire, AQLQ); Serious adverse events (all causes)
- sekundäre Endpunkte: Exacerbations requiring hospital admission; Lung function (preferably trough forced expiratory volume in one second, or $FEV_1$); Asthma control (measured on a validated scale, e.g. Asthma Control Questionnaire (ACQ), Asthma Control Test); Any adverse events

Recherche/Suchzeitraum:

- bis Januar 2016

Qualitätsbewertung der Studien:

Cochrane Risk of Bias Tool; geplante Sensitivitätsanalyse für die primären Endpunkte unter Ausschluss von Studien mit hohem Verzerrungspotential, nicht-publizierten Daten und Cross-over-Studien

- Heterogenität: $I^2$ nach Higgins/Thompson

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 3 completed RCTs (n=1197)

Charakteristika der Population:

- Four studies met the inclusion criteria, one of which was withdrawn prior to enrolment (NCT02127697).The other three studies were all multicentre, parallel, double-blind, double-dummy randomised controlled trials sponsored by Boehringer-Ingelheim.

- Kerstjens 2012a and Kerstjens 2012b randomised patients to one of two groups, tiotropium Respimat at a dose of 5 µg once daily or placebo. Ohta 2014 was a three-arm study randomising people to receive one of two doses of tiotropium Respimat, 2.5 µg or 5 µg daily, or placebo.
- Inclusion criteria that were commonacross the trials were that patients were aged between 18 and 75years, diagnosed with asthma before age 40 as confirmed at screening with a range of similar lung function requirements, and had a score of at least 1.5 on the ACQ to confirm that it was symptomatic.
- The twin trials were more stringent with criteria relating to the duration and severity of asthma, requiring participants to have at least a five-year history of asthma, at least one exacerbation needing treatment with systemic glucocorticoids in the previous year, and stable high doses of LABA/ICS.
- Ohta 2014 required only a 12-week history of symptomatic asthma, and crucially that participants could be taking stablemediumdoses of ICS, “alone or in a fixed combination with a LABA, for at least four weeks”.

Qualität der Studien:

- low risk of bias across domains
  - 4 double-blind, double-dummy trials comparing LAMA to placebo, including 1197 people with asthma taking combination LABA/ICS
    - für die quanititative Analyse wurden 3 Studien eingeschlossen

**Studienergebnisse:**

LAMA + LABA/ICS vs LABA/ICS

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Exacerbations requiring oral corticosteroids (patients with at least one) | 2 | 907 | Odds Ratio (M-H, Random, 95% CI) | 0.76 [0.57, 1.02] |
| 2 Exacerbations requiring oral corticosteroids (number per patient) | 2 | 907 | Rate Ratio (Random, 95% CI) | 0.79 [0.53, 1.17] |
| 3 Time to first exacerbation requiring oral corticosteroids | 2 | 907 | Hazard Ratio (Random, 95% CI) | 0.80 [0.63, 1.01] |
| 4 Quality of life (AQLQ) | 2 | 907 | Mean Difference (IV, Random, 95% CI) | 0.09 [-0.03, 0.20] |
| 5 Serious adverse events | 3 | 1197 | Odds Ratio (M-H, Random, 95% CI) | 0.60 [0.24, 1.47] |
| 6 Exacerbations requiring hospital admission | 3 | 1191 | Risk Difference (M-H, Random, 95% CI) | -0.01 [-0.04, 0.01] |
| 7 Lung function (change in trough $FEV_1$ L) | 3 | 1191 | Mean Difference (IV, Random, 95% CI) | 0.07 [0.03, 0.11] |
| 8 Lung function (change in trough FVC) | 3 | 1191 | Mean Difference (IV, Random, 95% CI) | 0.07 [0.02, 0.13] |
| 9 Asthma control (ACQ) | 2 | 907 | Mean Difference (IV, Random, 95% CI) | -0.13 [-0.23, -0.02] |
| 10 Asthma control (ACQ responder) | 2 | 1192 | Odds Ratio (M-H, Random, 95% CI) | 1.42 [0.88, 2.29] |
| 11 Any adverse events | 3 | 1197 | Odds Ratio (M-H, Random, 95% CI) | 0.70 [0.52, 0.94] |
| 12 Quality of life (AQLQ) by timeframe | 2 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 12.1 24-26 weeks | 2 | 907 | Mean Difference (IV, Random, 95% CI) | 0.11 [-0.03, 0.24] |
| 12.2 48-52 weeks | 2 | 907 | Mean Difference (IV, Random, 95% CI) | 0.09 [-0.03, 0.20] |

- People randomised to take a LAMA add-on had fewer exacerbations requiring oral corticosteroids than those continuing to take LABA/ICS alone, although the confidence intervals included no difference (OR 0.76, 95% CI 0.57 to 1.02) = moderate quality

- Over 48 weeks, 328 out of 1000 people taking their usual LABA/ICS would have to take oral corticosteroids for an exacerbation compared with 271 if they took a LAMA as well (95%CI 218 to 333 per 1000).
- Quality of life (AQLQ) was no better for those taking LAMA add-on than those taking LABA/ICS alone when considered in light of the 0.5 minimal clinically important difference on the scale (MD 0.09, 95% CI − 0.03 to 0.20)
- evidence for whether LAMA increased or decreased serious adverse events in this population was inconsistent (OR 0.60, 95% CI 0.24 to 1.47; I2 = 76%).
- high quality evidence showing benefits to lung function (trough FEV1 and FVC) and potentially small benefits to asthma control. People taking a LAMA add-on were less likely to experience non-serious adverse events.

**Anmerkung/Fazit der Autoren**

Tiotropium add-on may have additional benefits over LABA/ICS alone to reduce the need for rescue oral steroids in people with severe asthma. The effect was imprecise, and there was no evidence for other LAMA preparations. Possible benefits on quality of life were negligible, and evidence for the effect on serious adverse events was inconsistent. There are likely to be small added benefits of tiotropium Respimat 5 µg daily on lung function and asthma control over LABA/ICS alone, and fewer non-serious adverse events. The benefit of tiotropium add-on on the frequency of hospital admission is not yet known, despite year-long trials.

*Kommentare zum Review*

- The studies added tiotropium Respimat to LABA/ICS therapy; however the exact LABA/ICS combination was not specified
- all of the studies were funded by industry

## 3.3 Systematische Reviews

**Sobieraj DM et al., 2018 [20].**

Association of Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists With Asthma Control in Patients With Uncontrolled, Persistent Asthma A Systematic Review and Meta-analysis

+

**Sobieraj DM et al., 2018 [21].**

Intermittent Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists for Asthma

**Fragestellung**

To conduct a systematic review and meta-analysis of the effects associated with LAMA vs placebo or vs other controllers as an add-on therapy to inhaled corticosteroids and the use of a LAMA as add-on therapy to inhaled corticosteroids and long-acting β-agonists (LABAs; hereafter referred to as triple therapy) vs inhaled corticosteroids and LABA in patients with uncontrolled, persistent asthma

**Methodik**

Population:

- patients 12 years and older with uncontrolled, persistent asthma

Intervention vs Komparator:

- LAMA vs placebo or vs another controller as an add-on therapy to inhaled corticosteroids or that compared triple therapy vs inhaled corticosteroids and LABA

Endpunkte:

- asthma exacerbations (systemic corticosteroid use, hospitalization, emergency department visits, intensive care or intubation, or as defined by the study)
- mortality (all cause or asthma-specific),
- spirometry (measuredas peak, trough,andarea under the curve [AUC] values for forced expiratory volume in the first second [FEV1], forced vital capacity [FVC], and FEV1/FVC);
- asthma control (Asthma Control Test [ACT] or Asthma Control Questionnaires [ACQs; 5-,6-, or 7-item]), asthma-related quality of life (Asthma Quality of Life Questionnaire [AQLQ], MiniAQLQ,and AQLQ for 12 y and older [AQLQ +12]),
- health care utilization (additional medication use, additional health resource use related to the intervention)

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, Cochrane databases, and clinical trial registries (earliest date through November 28, 2017).

Qualitätsbewertung der Studien:

- Cochrane Collaboration’s Risk of BiasTool forRCTs

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 15 RCTs (n=7122)

Charakteristika der Population:

- All trials enrolled adults 18 years or older with the exception of 2 trials22,28 that were exclusively focused on children and adolescents aged 12 to 17 years.
- Sample sizes for individual studies ranged from 21029 to 1071 participants.18 Eight RCTs compared LAMA vs placebo as add-on therapy to inhaled corticosteroids.17-22,29
- Five of these trials17-19,29 also included a LABA group andwere also used to evaluate the effect of LAMA vs LABA as add-on therapy to inhaled corticosteroids. An additional 3 trials23-25 compared LAMA with another controller, including LABA, doxofylline, and montelukast. Four RCTs evaluated triple therapy vs inhaled corticosteroids and LABA. Trials ranged from15 days19 to 18 months25 in duration.
- Trials included in this systematic review defined uncontrolled asthma based on the ACQ score. However, this is only 1 of many criteria recommended for assessment.1 Likewise, although all patients were considered to have persistent asthma given their use of inhaled corticosteroids maintenance therapy, whether patients had mild, moderate, or severe persistent asthma was left to the reporting of the study authors.

Qualität der Studien:

- Most RCTs had a low risk of bias for random sequence generation (13 [86.7%]), allocation concealment (12 [80%]), incomplete data reporting (14 [93.3%]), selective reporting (12 [80%]), and other types of bias (15 [100%]). Three studies (20%) had a high risk of bias for blinding of participants and personnel and 2 studies (13.3%) for blinding of study outcomes.

**Studienergebnisse:**

LAMA vs Other Controllers as Add-on Therapy to Inhaled Corticosteroids

- Comparing LAMA with LABAas add-on therapy to inhaled corticosteroids, there was no statistically significant association of LAMA with
  - the risk of exacerbation requiring systemic corticosteroid (RR,0.87 [95% CI, 0.53 to 1.42]; RD, 0.00 [95% CI, −0.02 to 0.02])
  - in asthma worsening (RR, 1.00 [95% CI, 0.84 to 1.20]; RD, 0.00 [95% CI, −0.05 to 0.04]), or in the composite outcome including oral steroid use or increase in asthma medication (RR,0.60[95%CI,0.15 to2.42];RD,−0.03 [95%CI,−0.12 to 0.06]).
- No deaths occurred in 3 RCTs and in the fourth trial 3 of 532 participants (0.6%) died in the LAMAgroup, 2 of these deaths were considered asthma-related (0.4%) whereas no deaths occurred in the LABA group.
- LAMA had no significant associations with ACQ scores with 1 trial reportingACQ-6score, 2 trials reportingACQ-7 scores, and 2 trials reportingACQ-7 responder analysis.
- No significant associations were found in measures of spirometry including the most frequently reported lung function measures of FEV1 trough, FEV1% predicted, and FVC trough with LAMA use

- No significant associations were found for AQLQ score

Triple Therapy vs Inhaled Corticosteroids and LABA

- Triple therapy was not significantly associated with the risk of exacerbation requiring systemic corticosteroids vs inhaled corticosteroidsandLABAwhenthe inhaled corticosteroid dose remained the same (RR, 0.84 [95%CI, 0.57 to 1.22];RD, −0.01[95% CI, −0.08 to 0.07]) (Figure 2A)
- it was significantly associated with a lower risk of asthma worsening (RR, 0.78 [95%CI, 0.72 to 0.86];RD, −0.01 [95%CI, −0.22 to 0.01])
- (eFigure 3 in the Supplement) (Table 3).
- Two studies reported exacerbations requiring hospitalization and neither found a significant association at 48 weeks.
- No deaths occurred in the 3 trials included in this analysis, 2 of which were 48 weeks in duration and the third being 12weeks in duration.
- No significant associations with ACQ-7 scores were found with triple therapy vs inhaled corticosteroids and LABA (Figure 2B). No consistent association for triple therapy on ACQ response was mseen across studies (Table 3).
- Triple therapy was associated with improvements in some measures of spirometry, including FEV1 trough (MD, 0.07 [95%CI, 0.01 to 0.14]) and measures of FVC (peak MD, 0.11 [95% CI, 0.05 to 0.17]; trough MD, 0.09 [95% CI, 0.03 to 0.15]; AUC MD, 0.10 [95% CI, 0.04 to 0.17]) (Figure 3A, eFigures 6-10 in the Supplement).
- No significant association with AQLQ score or AQLQ score response was seen with triple therapy.
- Triple therapy was not significantly associated with improvements in rescue medication use vs combined inhaled corticosteroids and LABA therapy (Figure 3B).

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**Anmerkung/Fazit der Autoren**

The association of LAMAwith benefitmay not be greater than that with LABA. Triple therapy was not associated with a lower risk of exacerbations.

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**Tian, B. P.et al., 2017 [22].**

Efficacy and safety of benralizumab for eosinophilic asthma: A systematic review and meta-analysis of randomized controlled trials

**Fragestellung**

We conducted a systematic review of the literatures to provide a summary ofthe relevant studies and to assess the efficacy and safety of administering benralizumab on clinicai exacerbation, lung function, life quality, and adverse events (AEs) in asthma patients.

**Methodik**

Population:

- Eosinophilic asthma patients

Intervention:

- benralizumab

Komparator:

- placebo

Endpunkte:

- symptom control, lung function or AEs

Recherche/Suchzeitraum:

- PubMed» Embase, and Cochrane Controlled Trials Register databases until May 31, 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 7 articles on 9 RCTs (n=2321 patients)

Charakteristika der Population:

- The subjects were patients with uncontrolled severe or severe asthma in five articles [21, 29-32], asthma exacerbation in one articte 119], and eosinophilic asthma in two studies from one articie [20].
- Participants received intravenous benralizumab in two studies [20, 2I], and the others received subcutaneous injections.

Qualität der Studien:

Table 2. Risk of bias of the included studies.

| Source | Random sequence generation | Allocation concealment | Blinding of participants & personal | Blinding of outcomes assessment | Incomplete outcome data | Selective reporting |
|---|---|---|---|---|---|---|
| Laviolette (2013) | | | | | | |
| Cohort 1 | Yes | Yes | Yes | Yes | Yes | Yes |
| Cohort 2 | Yes | Yes | Yes | Yes | Yes | Yes |
| Castro (2014) | Yes | Yes | Yes | Yes | Yes | Yes |
| Nowak (2015) | Yes | Unclear | Yes | Yes | Yes | Yes |
| Park (2016) | Yes | Unclear | Yes | Yes | Yes | Yes |
| FitzGerald (2016) | Yes | Yes | Yes | Yes | Yes | Yes |
| Bleecker (2016) | Yes | Yes | Yes | Yes | Yes | Yes |
| Nair (2017) | Yes | Yes | Yes | Yes | Yes | Yes |

**Studienergebnisse:**

Asthma Exacerbations.

- All six studies defined asthma exacerbation based on the unscheduled use of rescue medication.
- Among them, five studies defined asthma exacerbation äs the use or increase dose ofsystemic steroids for at least three days [28-32], and one defined the criterion äs an uncontrolled Symptom after the use ofrescue albuterol or corticosteroids within 2 h, and required a visit to the emergency room [19].

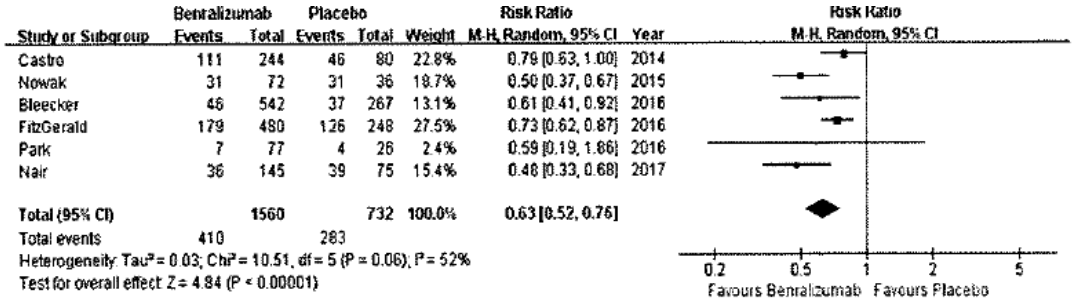


Figure 2. The effect of benralizumab versus placebo on exacerbations.

FEV1% changes from basefine

- Three studies assessed the responsiveness ofFEVl (forced expiratory volume in l sec) % of predicted value

- No significant difFercnce was observed between the benralizumab and placebo groups in changes from baseline of FEV1% of the predicted value (SMD: -0. 10, 95% CI: -0.31 to 0. 10, p = 0. 33). No statistical heterogeneity was observed {I == 0%, p == 0.38).
- Notably, two phase 3 studies (FitzGerald, CALIMA & Bleecker, SIROCCO) suggested that eosinophilic asthma subjects who were treated with benralizumab exhibited significant increases in the pre-bronchodilator FEV1 compared to placebo for patients receiving high-dosage ICSs plus LABA with baseline blood eosinophil counts of at least 300 cells//xL on both the Q4W (30 mg, every 4 weeks) and Q8W (30 mg, every 8 weeks) therapeutic schedules [29,30].
- For patients with baseline eosinophil counts lower than 300 cells/^L, an improvement in FEV1 after benralizumab treatment was noted in Castro et al.s study (100 mg) bu£ not in the trials conducted by FitzGerald elal. And Bleecker et al. [21, 29, 30].
- For the severe asthma, benralizumab treatment significantly increased the FEV1 at 20 weeks but not at aver the entire 28-week trial period versus placebo [31 ].

Asthma Control Questionnaire IACQ) score

- Although several trials described the ACQ scores, the ACQ data of four RCTs with 755 participants (544 in the benralizumab treatment group and 217 in the placebo-control group) could be analyzed together [19, 21, 31, 32].
- The findings from the meta-analysis suggested similar outcomes for the ACQ changes from baseüne between the benralizumab and control groups (SMD: -0. 10, 95% CI: -0.26 to 0. 06, p = 0.22) in eosinophilic asthmatics.
- No significan£ heterogeneity was observed among the studies (I2 = 32%, f = 0.22) (Figure S2).

Asthma control and Quality ofLife Assessment (AQLQ)

- In the eosinophilic asthma subpopulations, life quaäity was assessed using the AQLQ questionnaire [19, 21].
- The results from the pooled statistical analysis from these two studies showed no obvious improvement for the AQLQ score in the benralizumab arm compared to the placebo arm (SMD: -0. 11, 95% CI:-0.32 to 0. 10, p == 0. 3), and statistical heterogeneity was not found (/2 0%, p == 0. 58).
- However, äs reported by three phase three dinical trials [29-31], health-related quality oflife benefited from benralizumab treatment for the 30 mg Q8 schedule but not for the 30 mg Q4W schedule.

Adverse events

- Although seven studies included AEs, six studies reported total AEs that could be analyzed [20, 21, 29-32).
- A total of 1,216 of l ,646 patients suffered AEs in the benralizumab arms compared to 622 ofthe 847 controls in asthmatics who had a peripheral blood eosinophil count of at least 300 cells/ytL, with a RR of 1.00 (95% CI: 0. 95-1.05, p = 0.96).
- Statistical heterogeneity was not observed among the studies (/ ^ 40%, p == 0. 13).

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30. FitzGerald )M, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M> et ai. Benratizumab, aii anti-interleukin-5 receptor alpha monoclonal antibody, äs add-on treatment for patients with severe, uncontrolled, eosinophiiic asthma (CALIMA): a randomised, double-blind, placebocontrolled phase 3 trial. Lanccl. 2016; 388(10056); 2128-2141.
31. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et ai. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. N Engl) Med. 2017; 376 (25):2448-2458.

**Anmerkung/Fazit der Autoren**

In summary, we found that the use of benralizumab, a humanized monoclonal antibody against IL-5Ro', appears to be safe for controlling exacerbations but may not improve the lung function, ACQ or AQLQ score. These findings provided a foundation for the reasonable use Of benralizumab for asthma patients. Additionally, larger samples and more high-quality studies are required to further investigate the efficacy and safety ofbenralizumab in asthma.

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**Wang F.P. et al., 2018 [24].**

Anti-interleukin 5 Therapy for Eosinophilic Asthma: a Meta-analysis of Randomized Clinical Trials

**Fragestellung**

We conducted a meta-analysis of randomized controlled trials (RCTs) to assess the overall efficacy and safety of anti-interleukin 5 treatments on eosinophilic asthma.

**Methodik**

Population:

- adults/ adolescents (12 years or older) with a diagnosis of eosinophilic asthma,
- eosinophilic inflammation was shown by one or more criteria at study entry or in the previous year: a sputum eosinophil count ≥2.5 % or the eosinophil/lymphocyte and eosinophil/neutrophil (ELEN; a surrogate blood-based marker of sputum eosinophilia) index was positive, an exhaled nitric oxide concentration (FENO) ≥50 ppb, and an asthma-related peripheral blood eosinophil count ≥300 µL

Intervention:

anti-interleukin 5 therapy at any dose

Komparator:

others

Endpunkte:

lung function, asthma exacerbations, asthma control and quality-of-life scores, and adverse events

Recherche/Suchzeitraum:

PubMed, Embase, the Cochrane Library, and the Chinese Biological Medicine (CBM) database for articles published up to June 2016

Qualitätsbewertung der Studien:

Cochrane risk of bias

**Ergebnisse**

Anzahl eingeschlossener Studien:

12 RCTs (3340 patients)

Charakteristika der Population:

- The sample sizes ranged from 20 to 621 subjects.
- Of these, five studies used mepolizumab [7–11], four reslizumab [19–22], and three benralizumab [12, 23, 24].
- Treatment duration ranged from 1 day to 52weeks and follow-up ranged from 12 to 52 weeks.
- The mean age of patients was 46.8 years old. […]
- Five studies included severe eosinophilic asthmatics [8–11, 19], three studies included refractory or uncontrolled eosinophilic asthmatics [7, 20, 22], and the remaining studies did not specify asthma severity [12, 21, 23, 24].

Qualität der Studien:

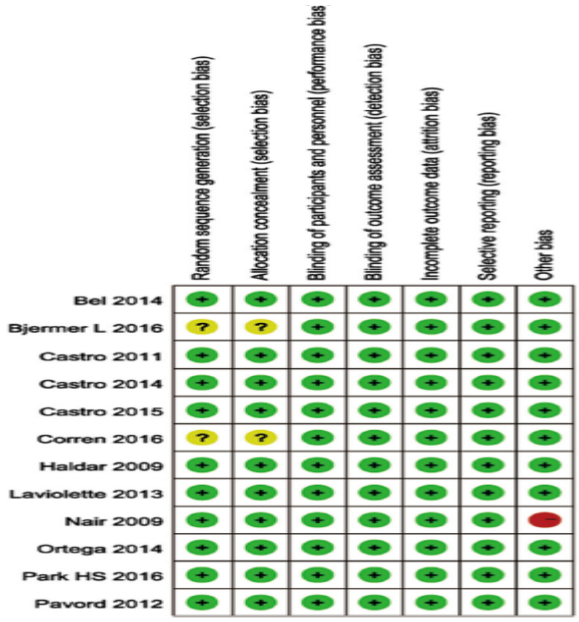


Fig. 8 Risk of bias summary of included studies

**Studienergebnisse:**

FEV1

- Nine trials reported the data on FEV1.
- Mepolizumab was used in four studies showed significant effect on FEV1 (MD = 0.09; 95 % CI, 0.03 to 0.14; P = 0.002).
- Reslizumab was reported in four studies, also could significantly improve FEV1 (MD=0.15, 95 % CI, 0.09 to 0.22; P < 0.001).
- Benralizumab was used in only one study (MD = 0.14, 95 % CI, 0.02 to 0.26; P = 0.02).
- Overall, anti-interleukin 5 treatment were associated with significant improvements in FEV1 (MD = 0.12; 95 % CI, 0.08 to 0.16; P < 0.001) (Fig. 2), with minimal heterogeneity (I2 = 15 %, P = 0.3),

Asthma Quality-of-Life Questionnaire (AQLQ)

- Five trials provided data about AQLQ scores.
- The pooled analysis showed anti-interleukin 5 treatment was associated with a significant increase in AQLQ scores (MD = 0.23; 95 % CI, 0.13–0.34; P < 0.001), with no significant heterogeneity (I2 = 0 %; P = 0.81).
- AQLQ scores improved both in
  - mepolizumab treatment (MD = 0.18; 95 % CI, 0.01–0.36; P = 0.04)
  - reslizumab (MD = 0.27; 95 % CI, 0.13–0.42; P < 0.001).
  - Benralizumab only used in one study (MD = 0.21; 95 % CI, −0.12–0.54; P = 0.22).

Asthma Exacerbations

- Six studies were included.
- Overall, compared with placebo, asthma exacerbations risk was significantly decreased with anti-interleukin 5 treatment (RR = 0.52; 95 % CI, 0.46 to 0.59; P < 0.001), and there was no heterogeneity among studies (I2 = 0 %, P = 0.5).
- When looking at subgroups, mepolizumab (RR = 0.55; 95 % CI, 0.47 to 0.64; P < 0.001) and reslizumab (RR = 0.46; 95 % CI, 0.37 to 0.58; P < 0.001) were also linked to markedly lower asthma exacerbations.

Adverse Events

- Eight studies mentioned adverse events.
- Anti-interleukin 5 treatment was associated with a trend of lower adverse events incidence (RR = 0.93; 95 % CI, 0.89 to 0.97; P = 0.001), with no heterogeneity (I2 = 0 %, P = 0.55).
- In subgroup analysis, however, we found no significant differences in both mepolizumab (RR = 0.96; 95 % CI, 0.9–1.03; P = 0.3) and benralizumab treatment groups (RR = 0.91; 95 % CI, 0.81–1.02; P = 0.09).
- Only treatment with reslizumab was associated with a trend of lower adverse events incidence (RR = 0.92; 95 % CI, 0.87–0.97; P = 0.003)
- The incidence of serious adverse events was low in the antiinterleukin 5 treatment group (1–16 %). Common adverse events were nasopharyngitis, headache, asthma worsening, injection-site reactions and upper respiratory tract infection

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Park HS, Kim MK, Imai N, Nakanishi T, Adachi M, Ohta K (2016) A phase 2a study of benralizumab for patients with eosinophilic asthma in South Korea and Japan. Int Arch Allergy Immunol 169(3):135–145. doi: 10.1159/000444799

### Anmerkung/Fazit der Autoren

In summary, the current meta-analysis indicated that antiinterleukin 5 treatment was well tolerated and could significantly improve FEV1, quality of life, and reduced asthma exacerbation risk in patients with eosinophilic asthma. Therefore, the humanized anti-interleukin 5 monoclonal antibodies may be effective and safe for eosinophilic asthma. The results highlight the importance of selection asthma phenotypes could derive clinical benefit from anti-interleukin 5 therapy. Nasopharyngitis was the most frequently reported adverse event in either study involving anti-interleukin 5 treatments, and benralizumab needs more data to support its safety profile.

**Li J et al., 2017 [14].**

### Fragestellung

The efficacy and safety of reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: A systematic review and meta-analysis

### Methodik

Population:

inadequately controlled, eosinophilic asthma

Intervention vs Komparator:

Reslizumab vs. others

Endpunkte:

Asthma exacerbation, a forced expiratory volume in 1 s (FEV1), Asthma Control Questionnaire (ACQ) score, blood eosinophil counts, the proportion of individuals who withdrawn due to adverse event (AE) and Upper respiratory AEs.

Recherche/Suchzeitraum:

Medline, Embase and Cochrane Controlled Trials Register databases until May 2016

Qualitätsbewertung der Studien:

Cochrane risk of bias

### Ergebnisse

Anzahl eingeschlossener Studien:

4 articles [16–19], reporting data from a total of 5 RCTs that compared reslizumab with placebo

Charakteristika der Population:

**Table 1.** Study and patient characteristics.

| Study | Therapy in experimental group | Therapy in control group | Country | Sample size | | Administration method | Duration of treatment | Dosage (mg) | Inclusion population |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Experimental | Control | | | | |
| Castro M 2015 [16] | Reslizumab | Placebo | Asia, Australia, North America, South America, South Africa, and Europe | 245/232 | 244/232 | intravenous | 16 weeks | (3.0 mg/kg) | Patients aged 12–75 with at least one blood eosinophil count of 400 cells per μL or higher and inadequately controlled asthma |
| Castro M 2011 [17] | Reslizumab | Placebo | United States and Canada | 53 | 53 | intravenous | 15 weeks | (3.0 mg/kg) | Patients aged 18–75 with asthma was poorly controlled associated with induced sputum eosinophils of 3% or more |
| Corren J 2016 [18] | Reslizumab | Placebo | United States | 77 | 19 | intravenous | 16 weeks | (3.0 mg/kg) | Patients aged 18–65 years with asthma inadequately controlled |
| Bjermer L 2016 [19] | Reslizumab | Placebo | Sweden | 106 | 105 | Intravenous | 16 weeks | (3.0 mg/kg) | Patients aged 12–75 years with inadequately controlled asthma and had at least one blood eosinophil count of ≥400 cells/μL |

Qualität der Studien:

**Table 2.** Quality assessment of individual study.

| Study | Allocation sequence generation | Allocation concealment | Blinding | Loss to follow-up | Calculation of sample size | Statistical analysis | ITT analysis | Level of quality |
|---|---|---|---|---|---|---|---|---|
| Castro M 2015 [16] | A | A | A | 7 | YES | analysis of covariance | YES | A |
| Castro M 2011 [17] | A | A | A | 0 | YES | analysis of covariance | YES | A |
| Corren J 2016 [18] | A | A | A | 1 | YES | linear regression analysis | NO | A |
| Bjermer L 2016 [19] | A | A | A | 3 | YES | stratified Cochran-Mantel-Haenszel test | NO | A |

*Note.* A - all quality criteria met (adequate): low risk of bias. B - one or more of the quality criteria only partly met (unclear): moderate risk of bias. C - one or more criteria not met (inadequate or not used): high risk of bias.

Studienergebnisse:

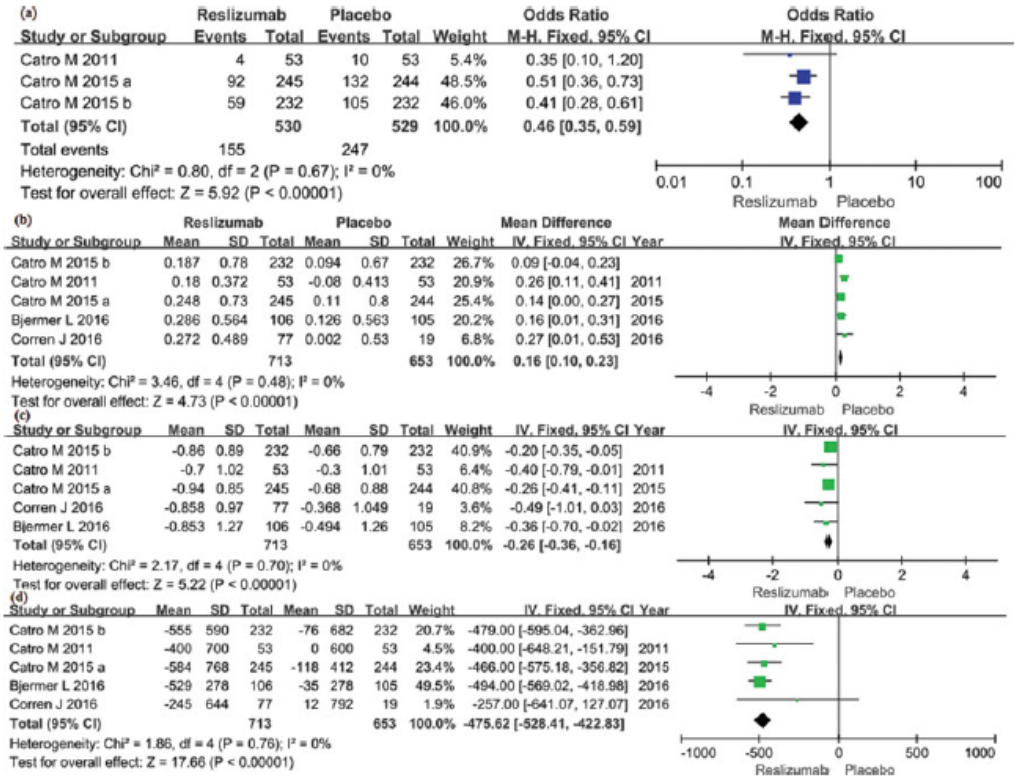


**Figure 3.** Forest plots showing changes in (a) asthma exacerbation, (b) $FEV_1$, (c) ACQ score and (d) blood eosinophil counts in the treatment studies. FEV1: a forced expiratory volume in 1 second; ACQ: Asthma Control Questionnaire; SD: standard deviation, IV: inverse variance; CI: confidence interval, MH: mantel haenszel.

The proportion of individuals who withdrawn due to AE

- Five RCTs included the proportion of individuals who withdrawn due to AE data representing a cohort of 1365 participants (713 in the reslizumab group and 652 in the placebo group)
- The fixed-effects estimate of the OR was 0.86, and the 95% CI was 0.68 to 1.10 (p= 0.24). The result suggests that reslizumab and placebo were similar in terms of the incidence of withdrawn due to AE.

Upper respiratory AEs

- Five RCTs included the upper respiratory AEs data representing a cohort of 1365 participants (713 in the reslizumab group and 652 in the placebo group).
- The heterogeneity test showed P = 0.94, so we adopted the fixed-effects model (Figure 4), the OR was 0.67, and the 95% CI was 0.38 to 1.17 (p = 0.16).
- The result suggests that reslizumab and placebo were similar in terms of the incidence of upper respiratory AEs.

16. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 2015;3(5):355–66.

17. Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am Respir Crit Care Med 2011;184(10):1125–32.

18. Corren J,Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 Study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. Chest. in press.

19. Bjermer L, Lemiere C,Maspero J,Weiss S, Zangrilli J, Germinaro M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: A randomized phase 3 study. Chest. in press.

**Anmerkung/Fazit der Autoren**

This meta-analysis indicates reslizumab to be an effective and safe treatment for eosinophilic asthma.

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**Cockle SM et al., 2017 [5].**

Comparative effectiveness of mepolizumab and omalizumab in severe asthma: An indirect treatment comparison

**Fragestellung**

To collect all publicly available RCTs to support an indirect treatment comparison of mepolizumab and omalizumab in severe asthma

**Methodik**

Bayesian network meta-analysis (Details in Appendix B). A Frequentist network meta-analysis was also conducted.

Population:

- patients ≥12 years of age, with severe asthma (patients receiving >1000 mg/day beclomethasone dipropionate equivalent plus ≥1 additional controller, and with a documented history of exacerbations).
- This population definition was then further refined to incorporate treatment eligibility for mepolizumab and omalizumab, as far as data availability allowed. Two populations were defined,
  - 1) the Overlap population, which aimed to include patients eligible for both mepolizumab AND omalizumab, and
  - 2) the Trial population, which aimed to include patients eligible for either mepolizumab OR omalizumab

Intervention:

- mepolizumab and omalizumab

Komparator:

- placebo, in addition to SoC

Endpunkte:

- Primary pre-specified endpoints were the rate of clinically significant exacerbations and the rate of exacerbations requiring hospitalization.
- Pre-specified secondary endpoints included the change from baseline in health-related quality of life (HRQoL), measured by the St George's Respiratory Questionnaire or Asthma Quality of Life Questionnaire; change from baseline in lung function ($FEV_1$), or postbronchodilator $FEV_1$, or $FEV_1$% predicted, or morning peak expiratory flow (PEF; L/min) when these data were unavailable; change from baseline in asthma control measured by the Asthma Control Questionnaire; and the proportion of patients with any adverse events (AEs), serious AEs (SAEs), withdrawals due to AEs or fatal AEs

Recherche/Suchzeitraum:

- A systematic literature review was conducted on August 5, 2014, and updated on July 8, 2015

Qualitätsbewertung der Studien:

- Eigene Kriterien in Anlehnung an NICE: Randomisierung angemessen, allocation concealment, Gruppen vergleichbar hinsichtlich prognostisch relevanter Faktoren, Verblindung, Unterschiede bzgl. drop-outs zwischen den Gruppen, selektives Berichten von Endpunkten, ITT-Analyse

**Ergebnisse**

Anzahl eingeschlossener Studien:

- The systematic literature review identified seven mepolizumab publications corresponding to three distinct RCTs and 29 omalizumab publications, corresponding to 19 distinct RCTs
- Upon application of the ITC inclusion/exclusion criteria (PICOS), of the 22 identified RCTs, one mepolizumab study (…) and three omalizumab studies (…) were eligible for inclusion in the primary ITC analysis
  - OMA: N=527
  - Mepa: N=1298

Charakteristika der Population:

**Table 2**
Key characteristics of double-blind, randomized controlled trials included in the ITC.

| | Study duration (weeks) | Treatment arms[a] | Key inclusion criteria | Number of patients | Included in Overlap population[b] analysis | Included in Trial population[c] analysis |
|---|---|---|---|---|---|---|
| **Mepolizumab-included studies** | | | | | | |
| MENSA [12][d] | 32 | • Mepolizumab 100 mg SC every 4 weeks (n = 194)<br>• Placebo (n = 191) | • Blood eosinophil counts≥150 cells/μL at initiation of treatment or≥300 cells/μL in previous 12 months<br>• ≥2 asthma exacerbation in previous 12 months | 527 | ✓ | ✓ |
| **Omalizumab-included studies** | | | | | | |
| INNOVATE [16][d] | 28 | • Omalizumab administered every 2 or 4 weeks to provide dose of ≥0.016 mg/kg per IU/mL of IgE (n = 209)<br>• Placebo (n = 210) | • Persistent allergic asthma despite high doses of corticosteroids and long-acting $\beta_2$ agonists<br>• ≥2 asthma exacerbation (or 1 severe exacerbation) in previous 12 months | 419 | ✓ | ✓ |
| Chanez et al., 2010 [9][e] | 16 | • Omalizumab administered every 2 or 4 weeks as per EU prescribing information [9] (n = 20)<br>• Placebo (n = 11) | • Persistent allergic asthma despite high doses of corticosteroids and long-acting $\beta_2$ agonists<br>• ≥2 severe asthma exacerbations in previous 12 months | 31 | ✓ | ✓ |
| EXTRA [18][f] | 48 | • Omalizumab ≥0.008 mg/kg per IU/mL of IgE every 2 weeks or ≥0.016 mg/kg of IgE every 4 weeks (n = 427)<br>• Placebo (n = 421) | • Severe allergic asthma despite high doses of corticosteroids and long-acting $\beta_2$ agonists<br>• ≥1 asthma exacerbation in previous 12 months | 848 | – | ✓ |

IgE, immunoglobulin E; ITC, indirect treatment comparison; SCS, systemic corticosteroids.
[a] For patients included in the base case meta-analysis only.
[b] Including patients potentially eligible for both mepolizumab and omalizumab.
[c] Including all patients eligible for mepolizumab regardless of their eligibility for omalizumab.
[d] Provided data for all efficacy and safety endpoints in the primary Bayesian network meta-analysis of the Overlap and Trial populations.
[e] Provided data for all safety endpoints in the primary Bayesian network meta-analysis of the Overlap and Trial populations.
[f] Provided data for exacerbations and safety endpoints in the primary Bayesian network meta-analysis of the Trial population.

Qualität der Studien:

- die 4 ausgewerteten RCTs erfüllten fast alle Qualitätskriterien

**Studienergebnisse:**

- Although asthma control and QoL were pre-specified as efficacy endpoints for the ITC, feasibility assessment demonstrated there was insufficient data in the included studies for endpoint analysis.
- In the Overlap population, no differences between treatments in clinically significant exacerbations and exacerbations requiring hospitalization were found, although trends favored mepolizumab.
- In the Trial population, mepolizumab treatment produced greater reductions in clinically significant exacerbations (RR: 0.63 [95% CrI: 0.45,0.89]) but not exacerbations requiring hospitalization compared with omalizumab, although the trend favored mepolizumab.
- Both treatments had broadly comparable effects on lung function, and similar tolerability profiles

9 Genetech. XOLAIR® Summary of Product Characteristics. ; 2009 (accessed May 2016) - http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000606/WC500057298.pdf
12 Ortega, H.G., Liu, M.C., Pavord, I.D. et al, Mepolizumab treatment in patients with severe eosinophilic asthma. N. Engl. J. Med. 2014;371:1198–1207.
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18 Hanania, N.A., Alpan, O., Hamilos, D.L. et al, Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. Ann. Intern. Med. 2011;154:573–582.

**Anmerkung/Fazit der Autoren**

In summary, this ITC compared the efficacy and tolerability of mepolizumab and omalizumab. Restrictions in terms of data availability led to a number of study limitations, which have been acknowledged and which were partially tested by additional scenarios and sensitivity analyses. These additional analyses supported the results from the primary analysis, which suggested that in patients with severe asthma eligible to receive both treatments, mepolizumab seems to be at least as efficacious as omalizumab at reducing exacerbations and improving lung function, and that the tolerability profiles of the two treatments do not seem to meaningfully differentiate.

*Kommentare zum Review*

- This study was funded by GlaxoSmithKline, alle Autoren sind Angestellte bei GSK
- asthma control and HRQoL could not be included in the analysis; different measures were used in the mepolizumab and omalizumab trials, preventing comparison
- differences in the length of time between clinical visits may influence patient recall of AEs, and the existence of an extension study for the mepolizumab population may have influenced the rate of withdrawals
- average patient age was greater in the mepolizumab MENSA trial (~50 years of age) than in the omalizumab INNOVATE and EXTRA trials (43e45 years of age). consequently, the number of asthma comorbidities in these patients may have differed, suggesting that the comparison of treatment AE profiles between RCTs should be interpreted with caution.

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**Cabon Y et al., 2017 [3].**

Comparison of anti-interleukin-5 therapies in patients with severe asthma: global and indirect meta-analyses of randomized placebo controlled trials

**Fragestellung**

Inconsistent results have been reported regarding IL-5 blockade treatment in asthma. There were no direct between-treatment comparisons.

**Methodik**

- A meta-analysis was first conducted to assess the efficacy of the IL-5 blockade strategy overall
- An indirect network meta-analysis was then performed to compare each anti-IL5 mAb efficacy and safety result using the Bayesian framework according to Cochrane's collaboration guidelines

*Hinweis*: Further eosinophilic subgroup analysis and sensitivity analysis were also conducted in case of heterogeneity.

Population:

- patients with severe asthma

Intervention:

- anti-interleukin-5 therapies (benralizumab, reslizumab and mepolizumab)

Komparator:

- Placebo (als Brückenkomparator)

Endpunkte:

- annual exacerbation rates, $FEV_1$ change from baseline and variations in asthma symptoms assessed by changes in the ACQ-5

Recherche/Suchzeitraum:

- from 1990 to September 2015

Qualitätsbewertung der Studien:

- Metaanalyse: Cochrane tool / NMA: R-AMSTAR criteria were assessed to check the overall data quality

**Ergebnisse**

Anzahl eingeschlossener Studien:

- Of the 11 clinical trials identified, 10 were considered eligible for the meta-analysis, reported in six separate publications and two publications describing two different trials each (total: 3421 patients)

Charakteristika der Population:

- The defined exacerbation and population characteristics were quite similar in the eight studies consisting of 10 trials, which involved a total of 3421 patients (59.6% females, average age 47.3 years, average BMI 28.0 kg/ $m^2$

Qualität der Studien:

- 7 RCTs with high quality, 3 RCTs with moderate quality

**Studienergebnisse:**

Metaanalyse:

- The annual exacerbation rate ratio of the three aggregated anti-IL-5 mAbs vs. placebo was 0.60 [0.50, 0.71], P < 0.01. This effect was assessed by a random effect model due to heterogeneity ($I^2$ = 0.61).
- The heterogeneity noted in the exacerbation rate ratios was due to the combined rate reduction in eosinophilic and non-eosinophilic 2014 Castro's studies. When these two trials were excluded, the exacerbation rate estimates based on the fixed effect model were 0.52 [0.45, 0.60] (P < 0.01, $I^2$ = 0).
- The FEV1 change from baseline vs. placebo was 0.09 L [0.05; 0.12], P < 0.01, using a fixed effect model ($I^2$ = 0.28).
- The meta-analysis indicated an overall ACQ-5 change from baseline of -0.31 [-0.41, -0.21], P < 0.01, based on a fixed effect model ($I^2$ = 0.11) involving seven studies only, because of missing values in three studies.

Subgruppenanalyse:

- A specific meta-analysis was performed in the eosinophilic patient subgroup (> 300 mm3/L). For this subgroup, including five studies, the annual exacerbation rate ratio was 0.57 [0.47,

0.69], P < 0.01, I2 = 0.54. FEV1 increased by 0.10 L [0.06, 0.14] (P < 0.01, $I^2$ = 0) in this subgroup. ACQ-5 changed by -0.33 [-0.45, -0.21] (P < 0.01, $I^2$ = 0.21).

Netzwerkemetaanalyse:

- Accordingly, the top three treatments with the greatest probability of being ranked first for reducing the exacerbation rate were reslizumab 3 mg/kg with P1 = 51%, followed by mepolizumab 750 mg (P1 = 22%) and mepolizumab 100 mg (P1 = 13%).
- Corresponding rate ratio reductions regarding the exacerbation rate vs. placebo were 0.46 [0.3, 0.69] for reslizumab 3 mg/kg, 0.51 [0.35, 0.77] for mepolizumab 750 mg and 0.55 [0.37, 0.83] for mepolizumab 100 mg. As expected, benralizumab 2 mg did not significantly differ from placebo.
- Regarding the asthma control questionnaire (ACQ-5) findings, benralizumab 20 mg had the greatest probability of being ranked first (mean difference vs. placebo -0.38 [-0.97, 0.18], P1 = 27%). Reslizumab 3 mg/kg (0.14 L [0.05, 0.24], P1 = 37%) had the best likelihood of being ranked first for FEV1 improvement. Regarding safety concerns, we analysed non-severe adverse events first. Benralizumab 20 mg had the greatest probability of being ranked as the safest (RR = 0.94 [0.57, 1.54], P1 = 28%), which was also in favour of the treatment. For severe adverse events, reslizumab was ranked as the best SAE reducer compared to placebo (RR = 0.81 [0.22, 3.03], P1 = 37%), again in favour of the treatment.

Subgruppenalanyse:

- In the eosinophilic subgroup, the top three drugs for exacerbation rate reduction were reslizumab 3 mg/kg with a 0.46 [0.26, 0.81] rate ratio regarding the annual exacerbation rate vs. placebo, with a probability of being the best treatment P1 = 41%.
- This treatment was followed by mepolizumab 750 mg with 0.49 [0.23, 1.02] (P1 = 27%) vs. placebo, and then mepolizumab 100 mg with a 0.54 [0.31, 0.97] (P1 = 11%) rate ratio regarding the annual exacerbation rate vs. placebo.
- On average, benralizumab 20 mg had the highest probability of being the best treatment for improving the FEV1 value (0.15L [0.30, 0.60], P1 = 29%) and decreasing the ACQ-5 score (-0.36 [-2.28, 1.56], P1 = 18%).

12 Castro M, Mathur S, Hargreave F et al Reslizumab for poorly controlled, eosinophili asthma: a randomized, placebo controlled study. Am J Respi Crit Care Med 2011; 184:1125–32.
13 Castro M, Wenzel SE, Bleecker ERet al. Benralizumab, an anti-interleuki 5 receptor a monoclonal antibody versus placebo for uncontrolled eosinophili asthma: a phase 2b randomise dose-ranging study. Lance Respir Med 2014; 2:879–90.
15 Castro M, Zangrilli J, Wechsler ME et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo- controlled, phase 3 trials. Lancet Respir Med 2015; 3:355–66.
16 Bel EH, Wenzel SE, Thompson PJ et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 2014; 371:1189–97.
17 Ortega HG, Liu MC, Pavord ID et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med 2014; 371:1198–207.
18 Pavord ID, Korn S, Howarth P et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 2012; 380:651–9.
19 Flood-Page P, Swenson C, Faiferman Iet al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. Am J Respir Crit Care Med 2007; 176:1062–71.
20 Haldar P, Brightling CE, Hargadon B et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med 2009; 360:973–84.

**Anmerkung/Fazit der Autoren**

In conclusion, anti-IL-5 treatment had significant effects in severe asthma patients with frequent exacerbations and evidence of eosinophilic inflammation. Reslizumab appeared to be the most

effective mAb in reducing exacerbation rates and improving FEV1. Nonetheless, mepolizumab 100 mg and benralizumab 20 mg appeared to be excellent alternatives. No clear significant differences between treatments in terms of efficacy and safety were found due to the limited number of studies available.

Long-term effects, best duration of treatment and the risk of relapse after withdrawal are important issues that should be addressed in further studies. A clear definition of the satisfactory clinical response and the ideal response time for its assessment would also be warranted.

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**Wang F_P et al., 2016 [23].**

Efficacy and Safety of Anti-Interleukin- Therapy in Patients with Asthma A Systematic Review and Meta-Analysis

**Fragestellung**

We conducted a meta-analysis of randomized, controlled trials (RCTs) to assess whether anti-IL-5 monoclonal antibodies therapy is safe and effective in patients (more than 12 years) with asthma.

**Methodik**

Population:

adults/adolescents (12 years) with diagnosis of asthma

Intervention:

anti-interleukin-5 monoclonal antibody therapy at any dose

Komparator:

placebo-controlled or standard therapy

Endpunkte:

Primary outcomes: lung function [first second forced expiratory volume (FEV1), FEV1% of predicted value, peak expiratory flow (PEF), histamine PC20], the Asthma Quality of Life Questionnaire (AQLQ) scores, and asthma exacerbation

Secondary outcomes: adverse events and efficacy outcomes [blood eosinophil count, sputum eosinophils (%), short-acting β-agonist (SABA) rescue use].

Recherche/Suchzeitraum:

PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for articles published from 1946 to October 2016

Qualitätsbewertung der Studien:

Cochrane risk of bias

**Ergebnisse**

Anzahl eingeschlossener Studien:

20 RCTs

Charakteristika der Population:

Sample sizes ranged from 19 to 1306 subjects.

Nine, five, and six trials used mepolizumab [18-26], reslizumab [27-31], and benralizumab [32-37], respectively.

Treatment duration ranged from 1 day to 56 weeks and follow-up ranged from 12 to 56 weeks.

Nine studies involved patients with severe/refractory asthma [22-28, 36, 37]; four studies included patients with mild, mild to moderate, or moderate asthma [18-21]; the remaining studies did not specify asthma severity [29±35]. Corren et al. [30] and Castro et al. [33] studied patients with noneosinophilic asthma.

Qualität der Studien:

Most trials had low risk of bias across the six domains. The allocation sequence was adequately generated and concealed in fourteen trials, [22±29,32±37]. The randomization techniques included computer generated randomization codes and minimization. The remaining trials did not report the method used, and we were unable to obtain this information. All but one study was described as double-blinded [20]. Almost all RCTs reported complete outcome data, only one trial reported on attrition insufficiently [27].

Studienergebnisse:

Subgroup analysis of asthma exacerbation and FEV1 in RCTs.

| Stratification | asthma exacerbation | | | | $FEV_1$ | | | |
|---|---|---|---|---|---|---|---|---|
| | No. of Patients (Studies) | RR(95% CI) | *P* Value | $I^2$, % | No. of Patients (Studies) | MD(95% CI) | *P* Value | $I^2$, % |
| **Subgroup analysis** | | | | | | | | |
| **Effects model** | | | | | | | | |
| random-effects model | 6072(13) | 0.66(0.59–0.73) | <0.001 | 51 | 6725(14) | 0.09(0.06–0.12) | <0.001 | 10 |
| fixed effects model | 6072(13) | 0.63(0.59–0.67) | <0.001 | 51 | 6725(14) | 0.09(0.06–0.12) | <0.001 | 10 |
| **Asthma severity** | | | | | | | | |
| mild or moderate asthma | 362(1) | 0.85(0.51–1.43) | 0.55 | … | 365(2) | -0.02(-0.2–0.15) | 0.8 | 0 |
| severe asthma | 4090(8) | 0.59(0.53–0.65) | <0.001 | 23 | 3901(7) | 0.11(0.07–0.14) | <0.001 | 35 |
| mixed asthma | 1620(4) | 0.73(0.65–0.82) | <0.001 | 18 | 2459(5) | 0.08(0.04–0.12) | <0.001 | 0 |

Studies including patients with severe/referactory asthma

**22.** Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med. 2009; 360(10):973±84. doi: 10.1056/ NEJMoa0808991

**23.** Nair P, Pizzichini MMM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Engl J Med. 2009; 360(10):985±93. doi: 10. 1056/NEJMoa0805435

**24.** Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): A multicentre, double-blind, placebo-controlled trial. The Lancet. 2012; 380 (9842):651±9. doi: 10.1016/S0140-6736(12)60988-X

**25.** Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoidsparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014; 371(13):1189±97. doi: 10. 1056/NEJMoa1403291

**26.** Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014; 371(13):1198±207. doi: 10.1056/ NEJMoa1403290 PMID: 25199059.

**27.** Kips JC, O'Connor BJ, Langley SJ, Woodcock A, Kerstjens HA, Postma DS, et al. Effect of SCH55700, a humanized anti-human interleukin-5 antibody, in severe persistent asthma: a pilot study. Am J Respir Crit Care Med. 2003; 167(12):1655±9. Epub 2003/03/22. doi: 10.1164/rccm.200206-525OC PMID: 12649124.

**28.** Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med. 2011; 184 (10):1125±32. Epub 2011/08/20. doi: 10.1164/rccm.201103-0396OC PMID: 21852542.

Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety o benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroid Anti-Interleukin-5 Therapy for Asthma and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3
trial. Lancet. 2016. doi: 10.1016/S0140-6736(16)31324-1 PMID: 27609408.

**37.** FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin- 5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016. doi: 10.1016/S0140-6736(16)31322-8 PMID: 27609406.

**Anmerkung/Fazit der Autoren**

Our study indicates that anti-interleukin-5 therapy is safe and may reduce asthma exacerbation risk, slightly improve FEV1, FEV1%, and quality of life; and decrease blood and sputum eosinophil levels, although PEF, PC20 were not improved or SABA rescue use reduced. Antiinterleukin-5 therapy may therefore be beneficial as adjunct asthma therapy, particularly in severe and eosinophilic asthma.

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**Rodrigo GJ et al., 2016 [18].**

Once-daily fluticasone furoate and vilanterol for adolescents and adults with symptomatic asthma. A systematic review with meta-analysis

**Fragestellung**

The objective of this systematic review was to assess the efficacy and safety of fluticasone furoate-vilanterol compared with ICS monotherapy or twice daily ICS-LABA formulations.

**Methodik**

Population:

- patients with asthma (12 years or older) with documented use of an ICS with or without a LABA

Intervention:

- Fluticasone furoate evilanterol

Komparator:

- ICS monotherapy or ICS-LABA twice-daily combinations

Endpunkte:

- pulmonary function (forced expiratory volume in 1 second [$FEV_1$] or peak expiratory flow rate [PEF]) as a primary outcome
- rescue medication use, health status (Asthma Quality of Life Questionnaire [AQLQ] total score), asthma control, number of patients with at least 1 severe asthma exacerbation (defined as a deterioration of asthma requiring the use of systemic corticosteroids for ≥3 days or a hospitalization or emergency department visit due to asthma), withdrawals,
- safety of treatment (adverse events [AEs], serious adverse events [SAEs], cardiac events, and pneumonia). A SAE was defined as any untoward medical occurrence that sometimes results in death, is life-threatening, requires inpatient hospitalization, or results in persistent or significant disability or incapacity

Recherche/Suchzeitraum:

- bis Januar 2016

Qualitätsbewertung der Studien:

- risk of bias assessment according to recommendations outlined in the Cochrane Handbook

Heterogenität: Statistical heterogeneity was measured by the I2 test (<25% absence, 26%-39% unimportant, 40%-60% moderate, and 60%-100% substantial).

Subruppen: a priori subgroup analysis, we explored the influence of the dose of fluticasone furoate-vilanterol (100/25 mg vs 200/25 mg once daily). Subgroups were compared using the residual $Chi^2$ test from the Peto odds ratios

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 7 RCTs (N=5.668)

Charakteristika der Population:

Characteristics of the Included Studies

| Study | Duration, ek | Patients, No. (% female) | Mean age (range), y | Racial characteristics | Mean baseline $FEV_1$, % predicted | Primary outcome | Selected comparisons |
|---|---|---|---|---|---|---|---|
| Bateman et al[24] | 24–78 | 2019 (67) | 42 (≥12) | W, 74%; A, 11%; AA, 5% | 68 | Asthma exacerbations | Fluticasone furoate–vilanterol, 100/25 μg once daily, vs fluticasone furoate, 100 μg once daily |
| Bernstein et al[25] | 12 | 1039 (61) | 46 (≥12) | W, 88%; A, <1%; AA, <1% | 68 | Weighted mean $FEV_1$ | Fluticasone furoate–vilanterol, 100/25 μg once daily, vs fluticasone furoate –vilanterol, 200/25 μg once daily, vs fluticasone furoate, 100 μg once daily |
| Bleecker et al[26] | 12 | 609 (58) | 40 (≥12) | W, 84%; A, 8%; AA, <1% | 68 | Trough $FEV_1$ and @weighted mean $FEV_1$ | Fluticasone furoate–vilanterol, 100/25 μg once daily, vs fluticasone furoate, 100 μg once daily |
| Busse et al[27] | 52 | 503 (63) | 38 (≥12) | W, 67%; A, 25%; AA, 7% | 74 | AEs, SAEs Asthma exacerbations | Fluticasone furoate–vilanterol, 100/25 μg once daily, vs fluticasone furoate –vilanterol, 200/25 μg once daily, vs fluticasone propionate, 500 μg twice daily |
| Lin et al[28] | 12 | 309 (59) | 48 ( ≥12) | | 63 | PM PEF | Fluticasone furoate–vilanterol, 200/25 μg once daily, vs fluticasone propionate, 500 μg twice daily |
| O'Byrne et al[29] | 24 | 586 (59) | 46 (≥12) | W, 84%; A, 9%; AA, 7% | 67 | Trough $FEV_1$ and weighted mean $FEV_1$ | Fluticasone furoate–vilanterol, 200/25 μg once daily, vs fluticasone furoate, 200 μg once daily, vs fluticasone propionate, 500 μg twice daily |
| Woodcock et al[30] | 24 | 806 (61) | 43 (≥12) | W, 59%; A, 31%; AA, 10% | 64 | Weighted mean $FEV_1$ | Fluticasone furoate–vilanterol, 100/25 μg once daily, vs fluticasone propionate –salmeterol, 250/50 μg twice daily |

Abbreviations: A, Asian; AA, African American; AE, adverse event; ICS, inhaled corticosteroids; $FEV_1$, forced expiratory volume in 1 second; PEF, peak expiratory flow; SAE, serious adverse event; W, white.

Qualität der Studien:

- Qualitätsbewertung: the studies had a high methodologic quality

**Studienergebnisse:**

Fluticasone furoate-vilanterol vs. fluticasone furoate, 100 mg (3 Studien) (no statistical heterogeneity among studies)

- fluticasone furoate-vilanterol significantly increased the percentage of patients symptom free and reduced the use of rescue medication. Fluticasone furoate-vilanterol also reduced significantly the number of patients with at least 1 severe asthma exacerbation (9.1% vs 13.2%, NNTB ¼ 24).

- no statistical significant differences in the rate of AEs, SAEs, pneumonia, or cardiac events (1.4% vs 1.3%) among both groups

Fluticasone Furoate-Vilanterol Group vs Fluticasone Propionate, 500 mg (3 Studien[27-29])

- fluticasone furoate-vilanterol significantly increased the percentage of patients symptom free and reduced the number of patients with at least 1 severe asthma exacerbation (1.3% vs 2.4%, NNTB ¼ 88).
- No statistical difference in health status. Safety outcomes revealed no significant differences in AEs (1.4% vs 2.4%) or in the occurrence of pneumonia (0.4% vs 0.2%)
- fluticasone furoate-vilanterol group had a nonsignificant small increase in the frequency of cardiac events (6.4% vs 1.8%) compared with fluticasone propionate (Ergebnis von einer Studie[27])

Fluticasone FuroateeVilanterol, 100/25 mg, vs Fluticasone Propionatee Salmeterol, 250/50 mg (1 Studie[30])

- At 24 weeks, there were no differences in trough FEV1, asthma control, health status, and safety across both treatment groups.

[24] Bateman ED, O'Byrne PM, Busse WW, et al. Once-daily fluticasone furoate (FF)/vilanterol reduces risk of severe exacerbations in asthma versus FF alone. Thorax. 2014;69:312e319.
[25] Bernstein DI, Bateman ED, Woodcock A, et al. Fluticasone furoate (FF)/vilanterol (100/25mg or 200/25 mg) or FF (100 mg) in persistent asthma. J Asthma. 2015;52:1073e1083.
[26] Bleecker ER, Lötvall J, O'Byrne PM, et al. Fluticasone furoate-vilanterol 100-25 mg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. J Allergy Clin Immunol Pract. 2014;2:553e561.
[27] Busse WW, O'Byrne PM, Bleecker ER, et al. Safety and tolerability of the novel inhaled corticosteroid fluticasone furoate in combination with the b2 agonist vilanterol administered once daily for 52 weeks in patients 12 years old with asthma: a randomised trial. Thorax. 2013;68:513e520.
[28] Lin J, Kang J, Lee SH, et al. Fluticasone furoate/vilanterol 200/25 mg in Asian asthma patients: a randomized trial. Respir Med. 2015;109:44e53.
[29] O'Byrne PM, Bleecker ER, Bateman ED, et al. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. Eur Respir J. 2014;43:773e782.
[30] Woodcock A, Bleecker ER, Lötvall J, et al. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. Chest. 2013;144:1222e1229.

**Anmerkung/Fazit der Autoren**

In conclusion, according to the data from this systematic review, the use of once-daily fixed fluticasone furoate-vilanterol combination revealed a slight increase in terms of lung function compared with ICS monotherapy (fluticasone furoate and fluticasone propionate). However, the significance of advantages in other outcomes was unclear. The lack of therapeutic advantage and a trend toward an increased risk of cardiac events do not support the use of fluticasone furoate-vilanterol, 200/25 µg, and require close and careful monitoring. Future studies should focus on comparison of fluticasone furoate-vilanterol and other combination therapies for safety and efficacy in larger and racially diverse cohorts and studies conducted for a longer duration.

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**Rodrigo GJ et al., 2015 [17].**

What Is the Role of Tiotropium in Asthma? A Systematic Review With Meta-analysis

**Fragestellung**

The aim of this systematic review was to assess the efficacy and safety of tiotropium in patients with asthma.

**Methodik**

Population:

- adults and adolescents aged >12 years with symptomatic stable asthma of any severity and receiving inhaled corticosteroids (ICSs) or an ICS plus long-acting b 2 -agonist (LABA)

Intervention:

- tiotropium

Komparator:

- any treatment

Endpunkte:

- primäre Endpunkte: $FEV_1$ and morning and evening peak expiratory flow (PEF)
- sekundäre Endpunkte: rescue medication use (puffs/d), asthma symptom-free days per week, quality of life (Mini-Asthma Quality of Life Questionnaire [AQLQ] total score), asthma control (Asthma Control Questionnaire 7 [ACQ-7] total score), ACQ-7 responder rate determined by the percentage of patients with an improvement (decrease) in the ACQ-7 total score of at least 0.5 points, asthma exacerbations (number of patients with one or more episodes that required the use of systemic corticosteroids), withdrawals (total and due to AEs), and safety (AEs and serious adverse events [SAEs]) as secondary outcomes

Recherche/Suchzeitraum:

- Medline, Embase, CINAHL, Scopus, and CENTRAL (Cochrane Central Register of Controlled Trials) September 2014

Qualitätsbewertung der Studien:

Cochrane Risk of bias tool

- Heterogenität: $I^2$ test (≤25%, absent; 26%-39%, unimportant; 40%-60%, moderate; 60%-100%, substantial).

**Ergebnisse**

Anzahl eingeschlossener Studien:

- 13 RCTs (n=4966)

Charakteristika der Population:

- The selected studies were grouped into three treatment protocols:
  - (1) tiotropium OD as add-on to ICS in patients with mild to moderate asthma, 6,18,21-28
  - (2) tiotropium OD added to ICS vs bid LABA plus ICS in patients with moderate asthma, 6,18,26,27
  - (3) tiotropium OD as add-on to LABA plus ICS vs LABA plus ICS in patients with severe asthma. 4,19,20
- Severity was determined according GINA (Global Initiative for Asthma) criteria. 2
- Th e duration of studies ranged between 4 and 52 weeks.
- Only one study was not sponsored by a pharmaceutical company. 6

Qualität der Studien:

- All but one of the studies showed a low risk of bias in the six items of the Cochrane instrument; the one study 4 had an unclear sequence generation, and concealment was judged to have a high risk of bias.

Studienergebnisse:

- Tiotropium Plus ICS vs LABA Plus ICS (4 Studien)
  - All included patients with moderate asthma
  - Tiotropium significantly improved morning PEF more than LABA, although the magnitude of the increase was small (6.6 L/min).
  - no significant difference in evening PEF between groups
  - no significant differences in peak and trough FEV 1
  - On the contrary, patients receiving LABA experienced a significant reduction in the use of rescue medication (-0.2 puffs/d) and an improved AQLQ total score (0.12 units) but without reaching the MCID.
  - no significant differences in asthma symptom-free days; ACQ-7 total score and responder rate; number of patients with at least one asthma exacerbation; and withdrawals, AEs (67.6% vs 72.8%), and SAEs (1.9% vs 2.5%).
- Tiotropium as Add-on to LABA Plus ICS (3 Studien)
  - in symptomatic patients with severe asthma
  - Tiotropium as add-on to LABA plus ICS was associated with signifi cant improvements in morning and evening PEF (16 [P< .0004] and 20 L/min [P< .00001], respectively), heterogeneity among studies was moderate, and there was no evidence of systematic bias (P = .15 and P = .68).
  - triple therapy increased peak and trough $FEV_1$ significantly by a magnitude of 120 and 80 mL, respectively, compared with LABA plus ICS
  - combination of tiotropium, LABA, and ICS resulted in significant increases in AQLQ and ACQ-7 total scores, they did not reach the MCDI.
  - tiotropium showed a greater likelihood of achieving an MCID in ACQ-7 score (58.1% vs 45.1%), with an NNTB of 8.
  - Triple therapy showed a significant reduction in the number of patients who experienced at least one asthma exacerbation (18.2% vs 24.0%), with an NNTB of 17. no significant differences between groups in the remainder of outcomes.

TABLE 4 ] Tiotropium as Add-on to ICS Plus LABA vs ICS Plus LABA on Asthma Outcomes (Severe Asthma)

| Outcome | Studies[a] | No. | Estimate | Effect (95% CI) | $I^2$ % ($P$ Value) |
|---|---|---|---|---|---|
| $FEV_1$ peak (change from baseline) L | 4, 19, 20[1], 20[2] | 1,169 | MD | 0.12 (0.09 to 0.16) | 26 (.00001) |
| $FEV_1$ trough (change from baseline) L | 19, 20[1], 20[2] | 1,119 | MD | 0.08 (0.04 to 0.11) | 20 (.00001) |
| Rescue medication use, puffs/d | 20[1], 20[2] | 912 | MD | −0.16 (−0.44 to 0.13) | 0 (.28) |
| AQLQ (change from baseline) | 4, 19, 20[1], 20[2] | 1,169 | MD | 0.12 (0.05 to 0.18) | 26 (.003) |
| ACQ-7 (change from baseline) | 20[1], 20[2] | 912 | MD | −0.20 (−0.25 to −0.09) | 73 (.98) |
| ACQ-7 (responder rate) | 20[1], 20[2] | 907 | RR | 1.29 (1.13 to 1.46) | 0 (.0001) |
| | | | NNTB | 8 (5 to 15) | |
| No. patients with at least one episode of asthma exacerbation | 19, 20[1], 20[2] | 1,119 | RR | 0.70 (0.53 to 0.94) | 0 (.02) |
| | | | NNTB | 17 (9 to 99) | |
| Total withdrawals | 19, 20[1], 20[2] | 1,119 | RR | 0.96 (0.64 to 1.44) | 22 (.85) |
| Withdrawals due to worsening asthma | 19, 20[1], 20[2] | 1,119 | RR | 0.55 (0.18 to 1.66) | 0 (.29) |
| Any AE | 19, 20[1], 20[2] | 1,119 | RR | 0.77 (0.59 to 1.01) | 15 (.06) |
| SAE | 19, 20[1], 20[2] | 1,119 | RR | 0.71 (0.32 to 1.55) | 55 (.39) |

See Table 1-3 legends for expansion of abbreviations.
[a]20[1], 20[2] = trials 1 and 2 from Kerstjens et al.[20]

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**Anmerkung/Fazit der Autoren**

Tiotropium resulted noninferiorly to salmeterol and superiorly to placebo in patients with moderate to severe asthma who were not adequately controlled by ICS or ICS/ salmeterol. Major benefits were concentrated in the increase in lung function and in the case of patients with severe asthma, in the reduction of exacerbations.

In conclusion, this systematic review suggests that tiotropium is noninferior to salmeterol and superior to placebo in patients with moderate to severe asthma

Major benefits are concentrated in lung function and, in patients with severe asthma, an increase in control and a decrease in exacerbations. Thus, tiotropium might be an alternative to LABA in patients with mild to moderate asthma whose symptoms are not well controlled by ICS alone or as an add-on therapy in patients with severe asthma not controlled with available medications, including ICS plus LABA

*Kommentare zum Review*

- Patientenpopulation umfasst u.a. Studien mit Patienten ab 12 Jahren
- Beide Autoren haben Interessenkonflikte

## 3.4 Leitlinien

**Bundesärztekammer (BÄK), 2018 [1].**

Nationale VersorgungsLeitlinie 3. Auflage, 2018 Asthma – Langfassung

+

**Bundesärztekammer (BÄK), 2018 [2].**

Nationale VersorgungsLeitlinie Asthma: Leitlinienreport; 3. Auflage [online].

**Leitlinienorganisation/Fragestellung**

die Sicherung der bestmöglichen Lebensqualität und sozialen Teilhabe für Betroffene durch eine individuell optimierte medikamentöse und nicht-medikamentöse Therapie unter Berücksichtigung von Komorbiditäten mit dem Ziel des Erhalts der bestmöglichen Lungenfunktion, der Minimierung von Nebenwirkungen und Langzeitfolgen und der Förderung der Adhärenz

**Methodik**

Grundlage der Leitlinie

Primär werden die Mitgliedsgesellschaften der AWMF, die in den jeweiligen Themenbereichen aktiv sind sowie die Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) angesprochen. Zusätzlich werden Patientenvertreter nach einem festgelegten Verfahren eingeladen. Die Repräsentativität der Leitliniengruppe zur Entwicklung der NVL wird in der Auftaktsitzung durch die Leitlinien-gruppe geprüft.

Die Koordination der NVL-Entwicklung obliegt dem ÄZQ. Jede neue NVL und jede Überarbeitung einer NVL wird bei der AWMF angemeldet.

Die Recherche kann abhängig von der Fragestellung, den vorhandenen Ressourcen und der Evidenzlage auf drei verschiedenen Ebenen (Leitlinien, Aggregierte Evidenz, Primärliteratur) erfolgen.

Die systematische Berücksichtigung der Evidenz zur Formulierung und Graduierung der Empfehlungen orientiert sich an GRADE. Für die endgültige Formulierung und Graduierung von Empfehlungen bei einer Präsenzveranstaltung wurde die Technik des Nominalen Gruppenprozesses

Für die Fälle, in denen Interessenkonflikte durch bezahlte Berater- oder Gutachtertätigkeit, bezahlte Vortragstätigkeit, Geschäftsanteile und Aktien oder Drittmittel durch die Industrie bezüglich eines Themas vorlagen, wurden Enthaltungen beschlossen

Recherche/Suchzeitraum:

- Cochrane, Medline
  - Wirksamkeit und Sicherheit von Anti-IL-5-Antikörpern bei Patienten mit Asthma 28.03.2017
  - Wirksamkeit und Sicherheit von Benralizumab 26.04.2018
- Reviews: 26.03. 2016

- Leitlinien: bis 29.01.2016

LoE

- Bewertung des Biasrisikos (Risiko systematischer Fehler) in klinischen Studien: ein Manual für die Leitlinienerstellung

GoR

Tabelle 1: Einstufung von Leitlinien-Empfehlungen in Empfehlungsgrade (Grades of Recommendation) [8]

| Empfehlungsgrad | Beschreibung | Formulierung | Symbol |
|---|---|---|---|
| A | Starke Positiv-Empfehlung | soll | ⇑⇑ |
| B | Abgeschwächte Positiv-Empfehlung | sollte | ⇑ |
| 0 | Offene Empfehlung | kann | ⇔ |
| B | Abgeschwächte Negativ-Empfehlung | sollte nicht | ⇓ |
| A | Starke Negativ-Empfehlung | soll nicht | ⇓⇓ |

**Empfehlungen**

Definition schweres Asthma

| Empfehlungen/Statements | Empfehlungs-grad |
|---|---|
| **1-1 \| ERWACHSENE**<br>Bei Erwachsenen liegt ein schweres Asthma vor, wenn unter Therapie mit inhalativen Corticosteroiden (ICS) in Höchstdosis (siehe Tabelle 6) und mindestens einem zusätzlichen Langzeitmedikament (Langwirkendes Beta-2-Sympathomimetikum oder Montelukast) oder oralen Corticosteroiden (OCS) > 6 Monate/Jahr mindestens einer der folgenden Punkte zutrifft bzw. bei Reduktion der Therapie zutreffen würde:<br>• Atemwegsobstruktion: FEV1 < 80% des Sollwertes (FEV1/FVC < LLN);<br>• häufige Exazerbationen: ≥ 2 corticoidsteroidpflichtige Exazerbationen in den letzten 12 Monaten;<br>• schwere Exazerbationen: ≥ 1 Exazerbation mit stationärer Behandlung oder Beatmung in den letzten 12 Monaten;<br>• teilweise kontrolliertes oder unkontrolliertes Asthma (siehe Abbildung 2). | **Statement** |

**Stufenschema**

**Medikamentöses Stufenschema | ERWACHSENE**

| | Stufe 1 | Stufe 2 | Stufe 3 | Stufe 4 | Stufe 5 |
|---|---|---|---|---|---|
| Langzeittherapie | – ICS niedrigdosiert | | – ICS niedrigdosiert + LABA (bevorzugt) oder – ICS mitteldosiert | – ICS mittel- bis hochdosiert + LABA (bevorzugt) oder – ICS mittel- bis hochdosiert + LABA + LAMA* | – ICS in Höchstdosis + LABA + LAMA* – Vorstellung bei einem in der Behandlung von schwerem Asthma erfahrenen Pneumologen und – Anti-IgE- oder Anti-IL-5-(R)-Antikörper |
| **Alternativen in begründeten Fällen:** | | | | | |
| | – ICS niedrigdosiert | – LTRA | – ICS niedrigdosiert + LAMA* oder – ICS niedrigdosiert + LTRA | – ICS mittel- bis hochdosiert + LABA + LTRA oder – ICS mittel- bis hochdosiert + LAMA* | – OCS (zusätzlich oder alternativ) |
| Bedarfstherapie | – SABA | | – SABA oder – Fixkombination aus ICS und Formoterol, wenn diese auch die Langzeittherapie darstellt | | |

Asthmaschulung, Allergie-/Umweltkontrolle, Beachtung von Komorbiditäten

Spezifische Immuntherapie (bei gegebener Indikation)

Im Stufenschema werden zur besseren Übersicht übergeordnete Arzneimittelkategorien und keine einzelnen Präparate genannt. Nicht alle Präparate und Kombinationen sind für die jeweilige Indikation zugelassen (siehe Fachinformationen), teilweise handelt es sich um einen Off-Label-Use (siehe Kapitel 4 Medikamentöse Therapie).

* aus der Gruppe der LAMA ist Tiotropium für die Behandlung des Asthmas zugelassen (Stand: September 2018)

ICS: Inhalative Corticosteroide, IgE: Immunglobulin E, IL-5: Interleukin 5, LABA: Langwirkende Beta-2-Sympathomimetika, LAMA: Langwirkende Anticholinergika, LTRA: Leukotrienrezeptorantagonisten, OCS: Orale Corticosteroide, SABA: Kurzwirkende Beta-2-Sympythomimetika

## 4.2 Allgemeine Therapieprinzipien innerhalb des Stufenschemas

| Empfehlungen/Statements | Empfehlungs-grad |
|---|---|
| **4-3**<br>Ein geringer Bedarf an kurzwirkenden Beta-2-Sympathomimetika (SABA) ist ein wichtiges Ziel und ein Kriterium für den Erfolg der Therapie. | **Statement** |
| **4-4 \| ERWACHSENE**<br>Die Therapie mit inhalativen Corticosteroiden (ICS) soll bei Erwachsenen in den Therapiestufen 2 bis 5 die Basis der Langzeittherapie sein. | ⇑⇑ |

### Therapieintensivierung

| | |
|---|---|
| **4-10**<br>Bei unkontrolliertem Asthma soll eine Intensivierung der Therapie den Stufenschemata folgend empfohlen werden. | ⇑⇑ |
| **4-11**<br>Bei teilweise kontrolliertem Asthma sollte eine Intensivierung der Therapie den Stufenschemata folgend erwogen werden. | ⇑ |
| **4-12**<br>Nach einer Intensivierung der Langzeittherapie gemäß Stufenschema soll die Asthmakontrolle innerhalb von drei Monaten überprüft werden. | ⇑⇑ |

### Empfehlungen zu Stufe 4

| Empfehlungen/Statements | Empfehlungs-grad |
|---|---|
| **4-29 \| ERWACHSENE**<br>Bei Erwachsenen soll in Stufe 4 bevorzugt die Kombination aus einem ICS im mittleren oder hohen Dosisbereich und einem LABA angewandt werden. | ⇑⇑ |

Eine systematische Übersichtsarbeit [107] verglich die Kombinationstherapie von ICS plus LABA mit einer Dreifachkombination aus ICS, LABA und langwirksamen Anticholinergika (LAMA). Exazerbationen, die mit OCS be-handelt werden mussten, traten bei Patienten, die die Dreifachkombination erhielten, seltener auf (271/1 000 vs. 328/1 000). Der Unterschied war jedoch nicht signifikant (OR 0,76 (95% KI 0,57; 1,02); $I^2$ = 1%, 2 RCTs, n = 907, Datenqualität moderat). Ebenfalls nicht signifikant waren die Unterschiede im Gruppenvergleich hinsichtlich der Lebensqualität, der schweren unerwünschten Effekte und der Exazerbationen, die eine Hospitalisierung erforder-lich machten. Die Asthmakontrolle, erhoben mit dem Asthma-Control-Questionnaire (ACQ-9), war zugunsten der Dreifachkombination verbessert (MD -0,13 (95% KI -0,23; -0,02); $I^2$ = 0%, n = 907, 2 RCTs, Datenqualität hoch). Zudem waren jegliche unerwünschte Effekte bei Erhalt der Dreifachkombination seltener (OR 0,70 (95% KI 0,52; 0,94); $I^2$ = 0%, 3 RCTs, n = 1 197, Datenqualität hoch). [107]

Die Autoren sehen eine additive Behandlung mit LAMA zu einer bereits bestehenden Medikation aus ICS in mitt-lerer oder hoher Dosis plus LABA als Therapiealternative für Patienten mit Asthma in Stufe 4. Wichtig ist, dass in der Stufe 4 alle verfügbaren Therapieoptionen ausgereizt werden, bevor die Therapie zur Stufe 5 eskaliert wird. Dabei entscheidet der Arzt individuell mit dem Patienten (siehe Kapitel 3.1 Gemeinsame Entscheidungsfindung), ob er zunächst die ICS-Dosis erhöht oder zu einer Dreifachkombination übergeht.

**Alternative in begründeten Fällen in Stufe 4 bei Erwachsenen**

In begründeten Fällen, insbesondere wenn Kontraindikationen gegen die bisher verwendeten Medikamente vor-liegen oder unerwünschte Wirkungen bei deren Anwendung auftreten, empfehlen die Autoren auch die Kombina-tion aus ICS mittel- bis hochdosiert, LABA und LTRA oder ICS mittel- bis hochdosiert und LAMA. In der systema-tischen Recherche wurden keine Metaanalysen identifiziert, die die Wirksamkeit und Sicherheit der Dreifachkom-bination evaluierten.

### Empfehlung zu Stufe 5

| Empfehlungen/Statements | Empfehlungs-grad |
|---|---|
| **4-32 \| ERWACHSENE**<br>Die Indikation zur Therapie mit monoklonalen Antikörpern sollte erst gestellt werden, wenn selbst unter dreimonatiger maximaler inhalativer antiobstruktiver Kombinationstherapie mit einem ICS in Höchstdosis, einem LABA und einem LAMA (Tiotropium) keine Asthmakontrolle erreicht wird. | ⇑ |

Darüber hinaus weist die Leitliniengruppe darauf hin, dass die Therapie mit monoklonalen Antikörpern in Stufe 5 sehr aufwändig und über einen längeren Zeitraum mit hohen Kosten verbunden ist. Vor diesem Hintergrund er-achten sie es als notwendig, dass die in der Empfehlung 4-32 genannte Dreifachkombination mit ICS höchstdo-siert (siehe Tabelle 6) über drei Monate evaluiert wird, bevor die Therapie mit monoklonalen Antikörpern initiiert wird. Der Eindruck aus der Versorgungssituation ist, dass die Kombination ICS plus LABA plus LAMA vor einer weiteren Therapieeskalation häufig nicht ausgeschöpft wird, da es sich um ein eher neueres Therapiekonzept handelt.

| Empfehlungen/Statements | Empfehlungs-grad |
|---|---|
| **4-33 \| ERWACHSENE**<br>Ein Therapieversuch mit Omalizumab für mindestens vier Monate soll bei Erwachsenen in Stufe 5 empfohlen werden, wenn folgende Kriterien vorliegen:<br>• schweres IgE-vermitteltes allergisches Asthma und<br>• positiver Hauttest oder in-vitro Reaktivität gegen ein ganzjährig auftretendes Aeroallergen und<br>• IgE-Serumkonzentration unter Berücksichtigung des Körpergewichts im therapierbaren Bereich und<br>• erfolgte Eliminierung vermeidbarer Allergenexpositionen. | ⇑⇑ |

Im Cochrane-Review von Normansell et al. [115] senkte Omalizumab während der kontinuierlichen Corticostero-idgabe das Risiko für eine oder mehr Exazerbationen im Vergleich zu Placebo (OR 0,55 (95% KI 0,46; 0,65); $I^2$ = 50%, 10 RCTs, n = 3 261, moderate Datenqualität) und die Häufigkeit von Hospitalisierungen (OR 0,16 (95% KI 0,06; 0,42); $I^2$ = 0%, 4 RCTs, n = 1 824, moderate Datenqualität). Bei schwererer Erkrankung war der Effekt von Omalizumab hinsichtlich der Exazerbationen nicht mehr signifikant [115].

Die Daten zur Sicherheit wurden für die steroidstabile und die Ausschleichphase gemeinsam ausgewertet [115]. Schwere unerwünschte Wirkungen waren in der Gruppe der mit Omalizumab behandelten Patienten weniger wahrscheinlich (OR 0,72 (95% KI 0,57; 0,91); $I^2$ = 7%, 15 RCTs, n = 5 713, Datenqualität moderat). Hinsichtlich jeglicher unerwünschter Wirkungen und Mortalität ergab sich kein Unterschied. Reaktionen an der Injektionsstelle waren unter Omalizumab höher (OR 1,72 (95% KI 1,33; 2,24); $I^2$ = 42%; 9 RCTs, n = 3 577, Datenqualität mode-rat). [115]

Die gepoolten Auswertungen von Daten aus Studien mit einer Dauer von 52 bis 60 Wochen von Lai et al. zeigten ähnliche Tendenzen für die oben genannten Endpunkte [118].

| Empfehlungen/Statements | Empfehlungs-grad |
|---|---|
| **4-34 \| ERWACHSENE**<br>Ein Therapieversuch mit Mepolizumab, Reslizumab oder Benralizumab für mindestens vier Monate sollte bei Erwachsenen in Stufe 5 erwogen werden, wenn folgende Kriterien vorliegen:<br>• schweres eosinophiles Asthma und<br>• zweimaliger Nachweis einer Konzentration von > 300 Eosinophilen pro µl Blut außerhalb von Exazerbationen in den vergangenen zwei Jahren. | ⇑ |

Im Vergleich zu Placebo senkte die subkutanen Gabe von Mepolizumab in einem Studienzeitraum von 32 Wo-chen (MENSA) die Rate klinisch relevanter Exazerbationen (0,83 vs. 1,74; Rate Ratio 0,47 (95% KI 0,35; 0,63); 1 RCT, n = 385, Datenqualität moderat) und die Anzahl der Exazerbationen, die das Aufsuchen einer Notaufnahme oder eine Hospitalisierung nach sich zogen [122]. Des Weiteren verbesserten sich die Lebensqualität und die Symptome signifikant, letztere allerdings nicht klinisch relevant [122].

Ein RCT (SIRIUS) [123] mit 135 Teilnehmern berichtet, dass durch die subkutane Applikation von Mepolizumab über einen Zeitraum von 24 Wochen im Vergleich zu Placebo mehr OCS eingespart werden konnten (OR 2,39 (95% KI 1,25; 4,56)). Auch die jährlich Exazerbationsrate verbesserte sich durch Mepolizumab trotz der OCS-Reduktion (Rate Ratio 0,68 (95% KI 0,47; 0,99) [123]. Die niedrige Fallzahl und die fehlende Verblindung der Er-gebnisevaluation stellen allerdings ein Risiko für eine Verzerrung dar.

Die Phase-III-Studie von Corren et al. [125] prüfte die Abhängigkeit der Wirksamkeit und Sicherheit von Reslizu-mab von der Eosinophilenzahl im Blut bei Patienten der Altersgruppe von 18 bis 65 Jahren über einen Zeitraum von 16 Wochen. Bei der Ausgangserhebung wiesen 20% der eingeschlossenen Patienten eine Eosinophilenzahl ≥ 400/µl auf. Eine klinisch relevante Verbesserung der Asthmakontrolle, gemessen mit dem ACQ-7, war unter Reslizumab häufiger als in der

Placebogruppe. Je höher die Eosinophilenzahl war, desto deutlicher war die Ver-besserung der Asthmakontrolle. Die Fallzahl für diese Subgruppenanalyse war jedoch gering und die Power der Studie genügte nicht, um repräsentative Ergebnisse zu generieren. [125]

Gestützt werden die Aussagen von Corren et al. [125] durch eine weitere Phase-III-Studie [126], bei der eine mindestens einmalige Erhöhung der Eosinophilenzahl auf ≥ 400/µl eines der Einschlusskriterien war. Untersucht wurden die Dosierungen 0,3 mg/kg Körpergewicht (KG) und 3,0 mg/kg KG im Vergleich zu Placebo. Sowohl die Asthmasymptome als auch die Asthmakontrolle, erhoben mit dem ACQ, verbesserten sich in beiden Interventi-onsgruppen im Vergleich zu Placebo. Die Verbesserung der Lebensqualität, gemessen mit dem AQLQ, wurde nur bei der höheren Dosierung ersichtlich, war jedoch klinisch nicht relevant (delta of least square mean 0,359 (95% KI 0,047; 0,670). [126] Die Qualität der Studie ist durch ein unklares Risiko für Selektionsbias, Performance bias, Detection bias und ein hohes Risiko für Attrition bias limitiert.

Die subkutane Anwendung von Benralizumab bei schwerem Asthma wurde in zwei Phase-III-Studien (SIROCCO und CALIMA) untersucht, die sehr ähnliche Studiendesigns, jedoch leicht differierende Beobachtungszeiträume hatten [127,128]. In der Studie CALIMA führte die subcutane Gabe von Benralizumab im 4-Wochen-Intervall (Rate Ratio 0,64 (95% KI 0,49; 0,85) und im 8-Wochen-Intervall (Rate Ratio 0,72 (95% KI 0,54; 0,95)) über einen Zeitraum von 56 Wo-chen im Vergleich zu Placebo zur Reduktion der jährlichen Exazerbationsrate [127]. In der Studie SIROCCO führte die subcutane Gabe von Benralizumab im 4-Wochen-Intervall (Rate Ratio 0,55 (95% KI 0,42; 0,71) und im 8-Wochen-Intervall (Rate Ratio 0,49 (95% KI 0,37; 0,64)) über einen Zeitraum von 48 Wochen im Vergleich zu Placebo zur Reduktion der jährlichen Exazerbationsrate [128]. Die Asthmasymptome verbesserten sich im Vergleich zu Placebo in beiden Studien nur in der Gruppe der im 8-Wochen-Intervall behandelten Patienten [127,128]. Unklar bleibt, ob die Ergebnisevaluation in den Studien ver-blindet erfolgte.

Eine weitere Phase-III-Studien (BISE) untersuchte die Wirksamkeit und Sicherheit von Benralizumab im Vergleich zu Placebo bei Patienten mit mildem bis moderatem Asthma: Hier ergaben sich hinsichtlich des Symptomscores und der asthmabezogenen Lebensqualität keine signifikanten Unterschiede zwischen der Interventions- und der Placebogruppe [129].

Überdies untersuchte die Studie ZONDA [130] den corticosteroidsparenden Effekt von Benralizumab über einen Zeitraum von 28 Wochen. Die Chance einer Reduktion von OCS war bei der Gabe von Benralizumab im 4-Wochen-Intervall OR 4,09 (95% KI 2,22; 7,57) und im 8-Wochen-Intervall OR 4,12 (95% KI 0,22; 7,63) höher als bei der Gabe von Placebo [130].

Ein Wirksamkeitsvergleich zwischen den einzelnen monoklonalen Antikörpern wurde in der systematischen Re-cherche nicht identifiziert.

Zu Sicherheitsaspekten von Mepolizumab, Reslizumab und Benralizumab stehen bisher nur die Zulassungsstu-dien bzw. teilweise deren Verlängerungen zur Verfügung. In einigen Studien floss der nicht näher bzw. ungenau definierte Endpunkt „Verschlechterung des Asthmas“ als unerwünschte Wirkung ein: Hier blieb meist unklar, ob zum Beispiel auch die Effektivitätsendpunkte Exazerbationen oder Symptome mit ausgewertet wurden [123–126]. Teilweise wurde in den identifizierten Studien ersichtlich, dass es sich dabei auch um Exazerbationen handelt [127–130,139]. Vor diesem Hintergrund lassen sich ähnliche oder erhöhte Raten an unerwünschten und schwe-ren unerwünschten Nebenwirkungen in der Placebogruppe erklären [122–130].

| Empfehlungen/Statements | Empfehlungs-grad |
|---|---|
| **4-38 \| ERWACHSENE**<br>Die Langzeittherapie mit systemischen Corticosteroiden soll bei Erwachsenen in Stufe 5 wegen der Gefahr schwerer Nebenwirkungen nicht empfohlen werden, es sei denn, die Asthmakontrolle ist trotz des kombinierten Einsatzes der verschie-denen Therapieoptionen der vorherigen Stufe sowie zusätzlich monoklonaler Anti-körper (sofern indiziert und wirksam) unzureichend. | ⇓⇓ |

Auch wenn zum aktuellen Zeitpunkt nur begrenzte Langzeiterhebungen für die Sicherheit der verschiedenen monoklonalen Antikörper vorliegen (siehe Empfehlun-gen 4-33, 4-34 bis 4-37), werden die unerwünschten Langzeitwirkungen von systemischen Corticosteroiden als so erheblich eingeschätzt, dass die Leitliniengruppe OCS als nachrangige Therapieoption für die Langzeittherapie in Stufe 5 einordnen.

**National Institute for Health and Care Excellence (NICE), 2017 [16].**

Asthma: diagnosis, monitoring and chronic asthma management

**Leitlinienorganisation/Fragestellung**

NICE has produced guidance on the components of good patient experience in adult NHS services.

**Methodik**

Grundlage der Leitlinie

This guideline will contain recommendations for the management of symptoms in adults, young people and children who have been diagnosed with asthma. Specific consideration will be given to subgroups based on age: children under 5 years; children aged 5–16 years; and adults and young people over 16 years of age.

Update: Following publication, and in accordance with the NICE guidelines manual, NICE will undertake a review of whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

Recherche/Suchzeitraum:

- 09/2016

LoE/GoR

Overall quality of outcome evidence in GRADE

| Level | Description |
|---|---|
| High | Further research is very unlikely to change our confidence in the estimate of effect |
| Moderate | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate |
| Low | Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate |
| Very low | Any estimate of effect is very uncertain |

**Empfehlungen**

Treatment in patients not on regular preventers

*Review question: What is the clinical and cost effectiveness of using ICS + LABA as preventer and reliever therapy compared to using ICS + LABA as preventer and a SABA as reliever therapy?*

20. If asthma is uncontrolled in adults (aged 17 and over) on a low dose of ICS and a LABA, with or without an LTRA, as maintenance therapy, offer to change the person's ICS and LABA maintenance therapy to a MART regimen with a low maintenance ICS dose.

21. If asthma is uncontrolled in adults (aged 17 and over) on a MART regimen with a low maintenance ICS dose, with or without an LTRA, consider increasing the ICS to a moderate maintenance dose (either continuing on a MART regimen or changing to a fixed-dose of an ICS and a LABA, with a SABA as a reliever therapy).

22. If asthma is uncontrolled in children and young people (aged 5 to 16) on a paediatric low dose of ICS and a LABA as maintenance therapy, consider changing their ICS and LABA

maintenance therapy to a MART regimen10 with a paediatric low maintenance ICS dose. Ensure that the child or young person is able to understand and comply with the MART regimen.

23. If asthma is uncontrolled in children and young people (aged 5 to 16) on a MART regimen11 with a paediatric low maintenance ICS dose, consider increasing the ICS to a paediatric moderate maintenance dose (either continuing on a MART regimen or changing to a fixed-dose of an ICS and a LABA, with a SABA as a reliever therapy).

Quality of the clinical evidence:

The quality of the evidence ranged from High to Very Low quality. The majority of the evidence was either Moderate or High quality.

There was limited evidence regarding the total steroid dose, with only one study, one of the smaller studies, reporting this particular outcome.

The committee noted that 2 of the studies163 ,185 compared MART versus ICS + LABA as maintenance and SABA as reliever where the doses were in the same category (i.e. low dose ICS + LABA) but there were differences in precise dosing or within class drug choice. The conclusions of these studies were similar to the overall body of evidence.

*Review question: What is the most clinically and cost-effective drug (class or combination of drug classes) for the management of children, young people and adults with asthma who are currently taking optimal preventer therapy beyond ICS low dose when this fails to provide adequate control?*

24. If asthma is uncontrolled in adults (aged 17 and over) on a moderate maintenance ICS dose with a LABA (either as MART or a fixed dose regimen) with or without an LTRA, consider:

- increasing the ICS to a high maintenance dose (this should only be offered as part of a fixed-dose regimen, with a SABA used as a reliever therapy) or
- a trial of an additional drug (for example, a long-acting muscarinic receptor antagonist or theophylline) or
- seeking advice from a healthcare professional with expertise in asthma.

Quality of the clinical evidence:

The quality of the evidence for this review ranged from Very Low to High quality. The majority of the evidence was either Low or Moderate quality. Most of the studies compared adding a new agent or increasing ICS dose against continuing on previous treatment with or without a placebo. The majority of the evidence was in people uncontrolled on ICS moderate dose. None of the evidence addressed the addition of treatment in people uncontrolled on ICS and LTRA.

Studies were found in which the baseline population were on treatment not recommended by the committee in this guideline. This included studies in people who were using a high or moderate dose ICS (without first adding in a LABA or LTRA). The committee included this population as it represents a group who are uncontrolled despite preventer treatment beyond the first line of low dose ICS, and because there will be patients currently on this treatment.

Trade-off between clinical benefits and harms

Uncontrolled on ICS moderate dose, adults

Possible interventions identified in the evidence at this stage included the addition of a LABA, addition of a LABA and conversion to MART, increasing ICS dose, addition of an LTRA, addition of a LAMA and addition of a theophylline. Any one of the additional preventers could be accompanied by an increase or decrease in steroid dose simultaneously.

Consistent with the review of interventions for those uncontrolled on ICS low dose, the addition of a LABA appeared to have the greatest benefit for critical outcomes like severe exacerbations. Again consistent with the previous review there was little difference between addition of a LABA and addition of an LTRA when compared directly, although the addition of an LTRA had less benefit than addition of a LABA when compared to continuing on ICS moderate dose. Consistent with the evidence in the population uncontrolled on ICS + LABA, the use of MART appeared to have clinically important benefits over ICS + LABA + SABA when required.

Uncontrolled on ICS high dose, adults

Possible interventions identified in the evidence at this stage included the addition of a LABA, addition of a LABA and conversion to MART and addition of an LTRA. Any one of the additional preventers could be accompanied by a change in steroid dose.

There was evidence of a clinically important benefit of addition of LABA compared to continuation on ICS high dose in terms of reliever medication use. The direct comparison between addition of LABA and conversion to MART as opposed to just addition of LABA showed a clinically important benefit for MART in terms of severe exacerbations

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**Global Initiative for Asthma (GINA), 2018 [11].**

*GINA – Global Initiative for Asthma*

Global strategy for asthma management and prevention; updated 2018

**Methodik**

Grundlage der Leitlinie:

- LL-Committee: members are recognized leaders in asthma research and clinical practice with the scientific expertise
- Jährliches Update der LL
- Vor jedem Treffen des LL-Committee: PubMed search is performed for the previous year using filters established by the Committee
- After initial screening by the Program Director and Chair of the Science Committee, each publication identified by the above search is reviewed for relevance and quality by members of the Science Committee. Each publication is allocated to at least two Committee members, but all members receive a copy of all of the abstracts and have the opportunity to provide comments
- During Committee meetings, each publication that was assessed by at least one member to potentially impact on the GINA report is discussed. Decisions to modify the report or its references are made by consensus by the full Committee, or, if necessary, by an open vote of the full Committee
- The Committee makes recommendations for therapies that have been approved for asthma by at least one regulatory agency, but decisions are based on the best available peer-reviewed evidence and not on labeling directives from government regulators
- GINA conducts an ongoing twice-yearly update of the evidence base for its recommendations.
- Levels of evidence are assigned to management recommendations where appropriate.

**LITERATURE REVIEWED FOR GINA 2017 UPDATE**

The GINA report has been updated in 2017 following the routine twice-yearly review of the literature by the GINA Science Committee. The literature searches for 'clinical trial' publication types (see above) and meta-analyses identified a total of 304 publications, of which 190 were screened out for relevance and/or quality. The remaining 114 publications were reviewed by at least two members of the Science Committee, and 66 were subsequently discussed at a face-to-face meeting (37 'clinical trials' and 29 meta-analyses). A list of key changes in GINA 2017 can be found on p.10, and a tracked changes copy of the 2016 report is archived on the GINA website.

LoE : Abbildung

| Evidence level | Sources of evidence | Definition |
|---|---|---|
| A | Randomized controlled trials (RCTs) and meta-analyses. Rich body of data. | Evidence is from endpoints of well designed RCTs or meta-analyses that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants. |
| B | Randomized controlled trials (RCTs) and meta-analyses. Limited body of data. | Evidence is from endpoints of intervention studies that include only a limited number of patients, post hoc or subgroup analysis of RCTs or meta-analysis of such RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, they were under-taken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent. |
| C | Nonrandomized trials. Observational studies. | Evidence is from outcomes of uncontrolled or non-randomized trials or from observational studies. |
| D | Panel consensus judgment. | This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories. The Panel Consensus is based on clinical experience or knowledge that does not meet the above listed criteria. |



Sonstige methodische Hinweise

keine Angabe des GoR.

## Empfehlungen

**STEP 4: Two or more controllers plus as-needed reliever medication**

→ Preferred option (adults/adolescents): combination low dose ICS/formoterol as maintenance and reliever treatment, OR combination medium dose ICS/LABA plus as-needed SABA

The selection of Step 4 treatment depends on the prior selection at Step 3. Before stepping up, check for common problems such as incorrect inhaler technique, poor adherence, and environmental exposures, and confirm that the symptoms are due to asthma (Box 2-4, p22).

For adult and adolescent patients with ≥1 exacerbations in the previous year, combination low dose ICS/formoterol as maintenance and reliever treatment is more effective in reducing exacerbations than the same dose of maintenance ICS/LABA or higher doses of ICS **(Evidence A).** This regimen can be prescribed with low dose budesonide/formoterol or beclometasone/formoterol as in Step 3; the maintenance dose may be increased if necessary. For patients taking low dose maintenance ICS/LABA with as-needed SABA, whose asthma is not adequately controlled, treatment may be increased to medium dose ICS/LABA **(Evidence B);** combination ICS/LABA medications are as for Step 3.

Other options:

Tiotropium (long-acting muscarinic antagonist) by mist inhaler may be used as add-on therapy for adult or adolescent patients with a history of exacerbations; it modestly improves lung function (Evidence A) and modestly increases time to severe exacerbation.

Combination high-dose ICS/LABA may be considered in adults and adolescents, but the increase in ICS dose generally provides little additional benefit **(Evidence A),** and there is an increased risk of side-effects. A high dose is recommended only on a trial basis for 3–6 months when good asthma control cannot be achieved with medium dose ICS plus LABA and/or a third controller (e.g. LTRA or sustained-release theophylline **(Evidence B).**

For medium or high dose budesonide, efficacy may be improved with dosing four times daily **(Evidence B),** but adherence may be an issue. For other ICS, twice-daily dosing is appropriate **(Evidence D).** Other options for adults or adolescents that can be added to a medium- or high-dose ICS but that are less efficacious than adding LABA, include LTRA **(Evidence A**), or low dose sustained-release theophylline **(Evidence B).**

**STEP 5: Higher level care and/or add-on treatment**

→ Preferred option: referral for specialist investigation and consideration of add-on treatment

Patients with persistent symptoms or exacerbations despite correct inhaler technique and good adherence with Step 4 treatment and in whom other controller options have been considered, should be referred to a specialist with expertise in management of severe asthma **(Evidence D)**

Treatment options that may be considered at Step 5 (if not already tried) are described in Box 3-14 (p.72). They include:

- Add-on tiotropium (long-acting muscarinic antagonist) in patients aged ≥12 years whose asthma is not well-controlled with ICS/LABA. Add-on tiotropium (mostly 5µg once daily by mist inhaler) modestly improves lung function (Evidence A) and modestly increases the time to severe exacerbation requiring oral corticosteroids (Evidence B).[199] There is no evidence for other LAMA preparations.[199]
- Add-on anti-immunoglobulin E (anti-IgE) (omalizumab) treatment: for patients aged ≥6 years with moderate or severe allergic asthma that is uncontrolled on Step 4 treatment[209,210] (Evidence A).
- Add-on anti-interleukin-5 treatment (subcutaneous mepolizumab for patients aged ≥12 years; intravenous reslizumab for ages ≥18 years) or anti-interleukin 5 receptor treatment (subcutaneous benralizumab for ages ≥12 years), with severe eosinophilic asthma that is uncontrolled on Step 4 treatment (Evidence A).[211-214]
- Sputum-guided treatment: for patients with persisting symptoms and/or exacerbations despite high-dose ICS or ICS/LABA, treatment may be adjusted based on eosinophilia (>3%) in induced sputum. In severe asthma, this strategy leads to reduced exacerbations and/or lower doses of ICS[152] (Evidence A).
- Add-on low dose oral corticosteroids (≤7.5 mg/day prednisone equivalent): may be effective for some adults with severe asthma[131] (Evidence D); but are often associated with substantial side effects[215,216] (Evidence B). They should only be considered for adults with poor symptom control and/or frequent exacerbations despite good inhaler technique and adherence with Step 4 treatment, and after exclusion of other contributory factors. Patients should be counseled about potential side-effects (Evidence D).[216] They should be assessed and monitored for risk of corticosteroid-induced osteoporosis, and those expected to be treated for ≥3 months should be provided with relevant lifestyle counselling and prescription of therapy for prevention of osteoporosis (where appropriate).[217]



**Stepping up asthma treatment**

- Asthma is a variable condition, and periodic treatment adjustments by the clinician and/or the patient may be needed.
- *Sustained step up (for at least 2–3 months)*: some patients may fail to respond adequately to initial treatment. A step up in treatment may be recommended (Box 3-5, p31) if the symptoms are confirmed to be due to asthma; inhaler technique and adherence are satisfactory; and modifiable risk factors such as smoking have been addressed (Box 3-8, p38). Any step-up should be regarded as a therapeutic trial, and the response reviewed after 2–3 months. If there is no response, treatment should be reduced to the previous level, and alternative treatment options or referral considered.
- *Short-term step up (for 1–2 weeks)*: an occasional short-term increase in maintenance ICS dose for 1–2 weeks may be necessary; for example, during viral infections or seasonal allergen exposure. This may be initiated by the patient according to their written asthma action plan (Box 4-2, p61), or by the health care provider.

- Day-to-day adjustment: for patients prescribed combination budesonide/formoterol or beclometasone/formoterol as maintenance and reliever treatment, the patient adjusts the number of as-needed doses of ICS/formoterol from day to day according to their symptoms, while continuing the maintenance dosage.

**Difficult-to-treat and severe asthma**

Although the majority of patients can achieve the goal of well controlled asthma, some patients' asthma will not be well controlled even with optimal therapy.[115] The term *'difficult-to-treat' asthma* is used for patients in whom ongoing factors such as comorbidities, poor adherence, and allergen exposure interfere with achieving good asthma control. *'Treatment-resistant' or 'refractory' asthma* refers to patients with a confirmed diagnosis of asthma, whose symptoms or exacerbations remain poorly controlled despite high-dose ICS plus a second controller such as LABA (and/or systemic corticosteroids) and management of comorbidities, or whose asthma control deteriorates when this treatment is stepped down. *Severe asthma* includes patients with refractory asthma, and those in whom response to treatment of comorbidities is incomplete.[131]

**Management of severe asthma**

Very few patients are completely resistant to corticosteroids, so ICS remain the mainstay of therapy for difficult-to-treat asthma. Additional therapeutic options include:

- **Optimization of ICS/LABA dose**: some patients may respond to higher doses of ICS than are routinely recommended for general use[363] (Evidence B). However, this carries the risk of systemic side-effects;[357] after some months dose optimization should be pursued by stepping down slowly at 3–6 month intervals; see Box 3-7 (p.50) (Evidence D).
- **Oral corticosteroids**: some patients with severe asthma may benefit from low dose maintenance OCS treatment[357] (Evidence D), but the potential long-term side-effects should be taken into account.[216] Patients should be monitored for risk of corticosteroid-induced osteoporosis, and those expected to be treated for ≥3 months should be provided with relevant lifestyle counselling and prescription of therapy for prevention of osteoporosis (where appropriate).[217]
- **Add-on treatments without phenotyping**: In patients selected for uncontrolled symptoms and persistent airflow limitation despite moderate-high dose ICS and LABA, add-on treatment with the long-acting muscarinic antagonist bronchodilator, tiotropium, showed improved lung function and increased time to first exacerbation.[364] Other add-on controller medications such as theophylline and LTRAs, although suggested for severe asthma, appear in the small number of available studies to be of limited benefit.
- **Sputum-guided treatment**: in centers with specific expertise in inducing and analyzing sputum, adjusting treatment for severe asthma on the basis of sputum eosinophils may allow corticosteroid dose and/or exacerbation frequency to be reduced[152] (Evidence A).
- **Phenotype-guided add-on treatment**: patients with severe asthma, uncontrolled on Step 4 treatment, may benefit from phenotyping into categories such as severe allergic, aspirin-exacerbated or eosinophilic asthma.[6,7,148,357] Patients ≥6 years with severe allergic asthma with elevated IgE levels may benefit from omalizumab (anti-IgE) therapy[209,210] (Evidence A), those with severe eosinophilic asthma may benefit from anti-IL5 therapy (subcutaneous mepolizumab ≥12 yrs; intravenous reslizumab ≥18 yrs) or anti-IL5 receptor therapy (subcutaneous benralizumab, ≥12 yrs)[365] (Evidence A), and LTRAs may be helpful for patients found to be aspirin sensitive[354] (Evidence A).



*Anmerkung zu Empfehlungen: Stufenschema siehe Anhang*

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**National Asthma Council Australia, 2017 [15].**

Australian asthma handbook: australia's national guidelines for asthma management; Version 1.3

**Leitlinienorganisation/Fragestellung**

The Australian Asthma Handbook aims to improve health outcomes and quality of life for people with asthma by providing clear guidance for the health professionals involved in their care. It

gives evidence-based, practical guidance to primary care health professionals on the most effective strategies in the diagnosis and management of asthma in adults and children.

**Methodik**

Grundlage der Leitlinie

We used the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument as a benchmark for our guideline development process and reporting.1 We also referred to the NHMRC standard for clinical practice guidelines,2 including the NHMRC system for grading evidence-based recommendations.3

We convened 17 multidisciplinary working groups in 2011. For some topics, clinical expert consultants provided advice to the working group. For topics that involved a systematic review, a methodology consultant provided advice to the working group on evidence synthesis and the development of evidence-based recommendations.

The Committee and working groups developed recommendations and considered evidence using a consensus model.

Any potential conflicts were managed by the respective working group Chairs within the discussion process. Further steps would have been to exclude the conflicted contributor from voting on finalisation of the recommendation or to involve the Guidelines Committee Chair in resolving the issue; however, these steps were not needed.

Updates von 1.2. zu 1.3.:

- prevention and management of thunderstorm asthma
- managing allergic rhinitis in people with asthma
- treatment for asthma–COPD overlap

Recherche/Suchzeitraum:

- Cochrane Database of Systematic Reviews, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects – Version 1.2.: September 2016

LoE

- NHMRC levels of evidence

**Table 1 Body of evidence matrix**

| Component | A | B | C | D |
|---|---|---|---|---|
| | Excellent | Good | Satisfactory | Poor |
| Evidence base[1] | one or more level I studies with a low risk of bias or several level II studies with a low risk of bias | one or two level II studies with a low risk of bias or a SR/several level III studies with a low risk of bias | one or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias | level IV studies, or level I to III studies/SRs with a high risk of bias |
| Consistency[2] | all studies consistent | most studies consistent and inconsistency may be explained | some inconsistency reflecting genuine uncertainty around clinical question | evidence is inconsistent |
| Clinical impact | very large | substantial | moderate | slight or restricted |
| Generalisability | population/s studied in body of evidence are the same as the target population for the guideline | population/s studied in the body of evidence are similar to the target population for the guideline | population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population[3] | population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population |
| Applicability | directly applicable to Australian healthcare context | applicable to Australian healthcare context with few caveats | probably applicable to Australian healthcare context with some caveats | not applicable to Australian healthcare context |

GoR

| Grade of recommendation | Description |
|---|---|
| A | Body of evidence can be trusted to guide practice |
| B | Body of evidence can be trusted to guide practice in most situations |
| C | Body of evidence provides some support for recommendation(s) but care should be taken in its application |
| D | Body of evidence is weak and recommendation must be applied with caution |

## Empfehlungen

**Table. Definition of levels of recent asthma symptom control in adults and adolescents (regardless of current treatment regimen)**

| *Good control* | *Partial control* | *Poor control* |
|---|---|---|
| All of:<br>• Daytime symptoms ≤2 days per week<br>• Need for reliever ≤2 days per week†<br>• No limitation of activities<br>• No symptoms during night or on waking | One or two of:<br>• Daytime symptoms >2 days per week<br>• Need for reliever >2 days per week†<br>• Any limitation of activities<br>• Any symptoms during night or on waking | Three or more of:<br>• Daytime symptoms >2 days per week<br>• Need for reliever >2 days per week†<br>• Any limitation of activities<br>• Any symptoms during night or on waking |

† Not including SABA taken prophylactically before exercise. (Record this separately and take into account when assessing management.)

Note: Recent asthma symptom control is based on symptoms over the previous 4 weeks.

## Options for adjusting medicines in a written asthma action plan for adults

| *Usual treatment* | | *Options for adjustments when asthma worsening* | |
|---|---|---|---|
| | | *Option 1* | *Option 2 ** |
| *ICS/LABA combination* | *Budesonide/formoterol* (Symbicort) *maintenance-and-reliever regimen* | Take extra doses of budesonide/formoterol as needed to relieve symptoms, up to a maximum of 72 mcg formoterol per day (12 actuations of 100/6 mcg or 200/6 mcg via dry-powder inhaler or 24 actuations of 50/3 mcg or 100/3 mcg via pressurised metered-dose inhaler per day)<br><br>No more than 6 actuations at one time | Start short course prednisone (e.g. 37.5–50 mg each morning for 5–10 days) in addition to usual budesonide/formoterol regimen |
| | *Budesonide/formoterol* (Symbicort) *conventional maintenance regimen* | Increase dose of budesonide/formoterol up to a maximum of 72 mcg formoterol daily for 7–14 days | Start short course prednisone (e.g. 37.5–50 mg each morning for 5–10 days) in addition to usual dose of budesonide/formoterol |
| | *Fluticasone furoate/vilanterol* (Breo) | If using medium dose (100/25 mcg): Replace with highest strength formulation of same medicine (fluticasone furoate/vilanterol 200/25 mcg one inhalation once daily) for 7–14 days | Start short course prednisone (e.g. 37.5–50 mg each morning for 5–10 days) in addition to usual dose of fluticasone furoate/vilanterol |
| | *Fluticasone propionate/formoterol* (Flutiform) | **If using 50/5 mcg:** Replace with highest strength formulation of same medicine (fluticasone propionate/formoterol 250/10 mcg) for 7–14 days<br><br>**If using 125/5 mcg:** Increase dose (e.g. multiply dose by 2) to achieve equivalent of highest strength formulation of same medicine (fluticasone propionate/formoterol 250/10 mcg) for 7–14 days<br><br>**If using 250/10 mcg:** Increase ICS dose (e.g. multiply ICS dose by 4) by adding a separate fluticasone propionate inhaler for 7–14 days § | Start short course prednisone (e.g. 37.5–50 mg each morning for 5–10 days) in addition to usual dose of fluticasone propionate/formoterol |
| | *Fluticasone propionate/salmeterol* (Seretide, Fluticasone and Salmeterol Cipla) | Increase ICS dose (e.g. multiply ICS dose by 4†) by adding a separate fluticasone propionate inhaler for 7–14 days §<br><br>Increase fluticasone propionate/salmeterol if necessary to achieve total daily dose of salmeterol 100 mcg | Start short course prednisone (e.g. 37.5–50 mg each morning for 5–10 days) in addition to usual dose of fluticasone propionate/salmeterol |

* Second-line options for clinicians to consider when writing instructions for patients. The individual's written asthma action plan should contain only one clear action for each situation.
† Increase only the fluticasone propionate dose (e.g. by prescribing a separate fluticasone propionate inhaler for 7–14 days in addition to the combination inhaler). The salmeterol dose should not be increased above 100 mcg/day.
§ This option may be preferred over oral corticosteroids for patients who experience significant mood effects or other significant side-effects (e.g. hyperglycaemia) with oral corticosteroids. It is unsuitable for patients who cannot tolerate increased risk of dysphonia (e.g. singers, actors, teachers) or who cannot afford an additional inhaler. For fluticasone furoate (*Arnuity*), the dose increase should take into account the fact that available formulations are medium and high doses, and that the inhaler must be discarded one month after opening.

**Notes**
The table provides options for adjustments the patient can make when asthma is getting worse (needing more reliever than usual, waking up with asthma, more symptoms than usual, asthma is interfering with usual activities, or when the use of

reliever is not achieving rapid relief from symptoms). After choosing the most suitable strategies for the individual, the clinician should translate these into clear, easy-to-follow instructions in the person's written asthma action plan.
For some preventer formulations, the suggested option may result in doses above those recommended in TGA-approved product information. If high doses are needed, they should be continued for only 7–14 days then reduced.
Templates for written asthma action plans (including templates designed for people using various preventer regimens) are available from the *National Asthma Council Australia*.

***Sources***
Canadian Thoracic Society. *Canadian respiratory guidelines. Recommendations for the diagnosis and management of asthma. Preschoolers, children and adults 2012 update ('Slim Jim' brochure)*. Ottawa: Canadian Thoracic Society; 2012. Available from: http://www.respiratoryguidelines.ca/toolkit
Reddel H, Barnes D. Pharmacological strategies for self-management of asthma exacerbations. *Eur Respir J* 2006; 28: 182–99. Available from: http://erj.ersjournals.com/content/28/1/182.long
Global Initiative for Asthma (GINA). *Global strategy for asthma management and prevention.* 2014. GINA; 2014. Available from: http://www.ginasthma.org/

Maintenance-and-reliever regimen

- The low-dose budesonide/formoterol combination can be used as both maintenance and reliever. Under this regimen, the combination is used for relief of asthma symptoms (instead of using a short-acting beta2 agonist reliever), in addition to its use as regular maintenance treatment.
- The combination of budesonide/formoterol can be used as maintenance-and-reliever treatment.

Poor recent asthma symptom control

- Review inhaler technique and adherence – correct if suboptimal
- Confirm that symptoms are likely to be due to asthma
- Consider increasing treatment until good asthma control is achieved, then step down again when possible

**Managing severe, high-risk and difficult-to-control asthma in adults**

Consider referral to a specialist respiratory physician with an interest in asthma for people with severe, high-risk or difficult-to-control asthma

Montelukast

Montelukast can be considered as an add-on option in patients with difficult-to-treat asthma who are already taking other preventers.

How this recommendatrion was developed Consensus
Based on clinical experience and expert opinion (informed by evidence, where available), with particular reference to the following source(s): - Ducharme, 20042
Montelukast for adults: efficacy

In adults and adolescents with asthma that is not controlled by low-dose inhaled corticosteroid, the addition of a leukotriene receptor antagonist is less effective than the addition of a long-acting beta2 agonist in reducing the rate of asthma flare-ups that require treatment with oral corticosteroids.2 The addition of a leukotriene receptor antagonist is also associated with lesser improvement in lung function and quality of life than the addition of a long-acting beta2 agonist.2

Montelukast taken 1 hour before exercise can be used to manage exercise-induced bronchoconstriction, but it is less effective than short-acting beta2 agonists.29

Retrospective analysis of clinical trial data suggests that some people with asthma who smoke,30 or are obese,31 may achieve better asthma control with montelukast than an inhaled corticosteroid. However, prospective studies would be needed to confirm this.

Post-marketing surveillance reports led to concerns about a possible association between leukotriene receptor antagonist use and suicide risk.32 A recent case-control study reported a statistically significant association between the use of leukotriene receptor antagonists and suicide attempts in people aged 19–24 years. However, this association was no longer statistically significant after adjusting for potential confounding factors, including previous exposure to other asthma medicines and previous exposure to other medicines associated with suicide.32

Tiotropium via mist inhaler

Tiotropium via mist inhaler can be considered as an add-on option in adults who have had a severe asthma flare-up within the previous year despite maintenance treatment with inhaled corticosteroid (equivalent to 800 mcg budesonide/day or higher) in combination with a long-acting beta2 agonist.

How this recommendation was developed
Based on clinical experience and expert opinion (informed by evidence, where available), with particular reference to the following source(s):

Anderson et al. 20153
Kew et al. 20164
Rodrigo et al. 20155

Omalizumab

Omalizumab treatment can be considered for adults and adolescents aged 12 years and over, with moderate-to-severe allergic asthma despite inhaled corticosteroid treatment, and raised IgE levels.

Note: For adults and adolescents with severe allergic asthma who may be eligible for PBS subsidy, whose asthma is not well-controlled despite optimal inhaled therapy, refer immediately for specialist assessment, because patients only become eligible for PBS subsidisation for omalizumab after at least 12 months' care by a specialist experienced in the management of severe asthma. After treatment is established, ongoing treatment with omalizumab may be administered by a GP, with 6-monthly review of ongoing eligibility at the specialist clinic.

How this recommendation was developed
Adapted from existing guidance
Based on reliable clinical practice guideline(s) or position statement(s):
Katelaris et al. 20097
Chung et al. 20141

When given in addition to inhaled corticosteroids in double-blind randomised placebo-controlled trials, omalizumab reduced rates of asthma flare-ups and hospitalisation in patients with moderate or severe allergic asthma.34 In non-blinded studies in patients with severe allergic asthma, omalizumab improved lung function and asthma control, reduced symptoms, severe flare-ups, work or school days lost due to severe flare-ups, and hospitalisations, and improved quality of life.35

Omalizumab treatment is generally well tolerated. The most common adverse events are injection site reactions and, in children aged 6-11 years, pyrexia, upper gastrointestinal pain and headache.33 Anaphylactoid reactions have been reported, including among Australian patients.36 Early reports suggested that omalizumab may be associated with an increased risk of malignancy. However, subsequent pooled results indicate that a causal relationship between omalizumab therapy and malignancy is unlikely.37, 33

Mepolizumab

Mepolizumab can be considered as an add-on treatment for patients aged 12 years and over with severe refractory eosinophilic asthma. Mepolizumab is given by subcutaneous injection every 4 weeks.

Note: For adults and adolescents with severe allergic asthma who may be eligible for PBS subsidy, whose asthma is not well-controlled despite optimal inhaled therapy, refer for specialist assessment, because patients only become eligible for PBS subsidisation for mepolizumab after 12 months of treatment by a specialist experienced in the management of severe asthma.

How this recommendation was developed Consensus

Based on clinical experience and expert opinion (informed by evidence, where available), with particular reference to the following source(s):
Menzella et al. 20168
Powell et al. 20159
In people with severe eosinophilic asthma, mepolizumab treatment has been shown to reduce the rate of asthma flare-ups, improve health-related quality of life, and reduce the need for systemic corticosteroids.9, 8, 39

Adverse effects include hypersensitivity reactions such as urticaria, angioedema, rash, bronchospasm, hypotension. These generally occur within hours of administration, but reactions up to days after administration have been recorded.38 No cases of anaphylaxis were recorded in a 52-week open-label study of subcutaneous mepolizumab, conducted among patients who had participated in two randomised controlled trials.40

*Anmerkung zu Empfehlungen: Stufenschema siehe Anhang*

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**SIGN, 2016 [19].**

*SIGN= Scottish Intercollegiate Guidelines Network in Kooperation mit British Thoracic Society*

British guideline on the management of asthma

**Leitlinienorganisation/Fragestellung**

The guideline considers asthma management in all patients with a diagnosis of asthma, although there is less evidence available for people at either age extreme.

**Methodik**

Grundlage der Leitlinie

This guideline was issued in 2014 and sections of the guideline will be updated on a biennial basis. The evidence base for this guideline was synthesised in accordance with SIGN methodology.

A systematic review of the literature was carried out u0000000000sing an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.

Update: Between 2004 and 2012 sections within the guideline were updated annually. Subsequently, updating moved to a biennial basis, beginning with the 2014 update. This edition of the guideline was issued in 2016. All updates were made available on both the BTS (www.brit-thoracic.org.uk) and SIGN (www.sign.ac.uk) websites. Any updates to the guideline in the period between scheduled updates will be noted on the SIGN and BTS websites.

The 2016 version includes a complete revision of the section on diagnosis, a major update to the section on pharmacological management of asthma, and updates to the sections on supported self-management, non-pharmacological management of asthma, acute asthma, difficult asthma, occupational asthma, and organisation and delivery of care.

Loe/GoE:

| KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS | |
|---|---|
| LEVELS OF EVIDENCE | |
| $1^{++}$ | High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias |
| $1^{+}$ | Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias |
| $1^{-}$ | Meta-analyses, systematic reviews, or RCTs with a high risk of bias |
| $2^{++}$ | High-quality systematic reviews of case-control or cohort studies<br>High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal |
| $2^{+}$ | Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal |
| $2^{-}$ | Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal |
| 3 | Non-analytic studies, eg case reports, case series |
| 4 | Expert opinion |
| GRADES OF RECOMMENDATION | |
| *Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.* | |
| A | At least one meta-analysis, systematic review, or RCT rated as $1^{++}$, and directly applicable to the target population; *or*<br>A body of evidence consisting principally of studies rated as $1^{+}$, directly applicable to the target population, and demonstrating overall consistency of results |
| B | A body of evidence including studies rated as $2^{++}$, directly applicable to the target population, and demonstrating overall consistency of results; *or*<br>Extrapolated evidence from studies rated as $1^{++}$ or $1^{+}$ |
| C | A body of evidence including studies rated as $2^{+}$, directly applicable to the target population and demonstrating overall consistency of results; *or*<br>Extrapolated evidence from studies rated as $2^{++}$ |
| D | Evidence level 3 or 4; *or*<br>Extrapolated evidence from studies rated as $2^{+}$ |
| GOOD PRACTICE POINTS | |
| ✓ | Recommended best practice based on the clinical experience of the guideline development group |

**Emfehlungen**

ADDITIONAL ADD-ON THERAPIES

If there is no improvement when a LABA is added, stop the LABA and try:

- an increased dose of ICS
- an LTRA
- a LAMA (LAMA are not licensed for this indication)

## An LTRA

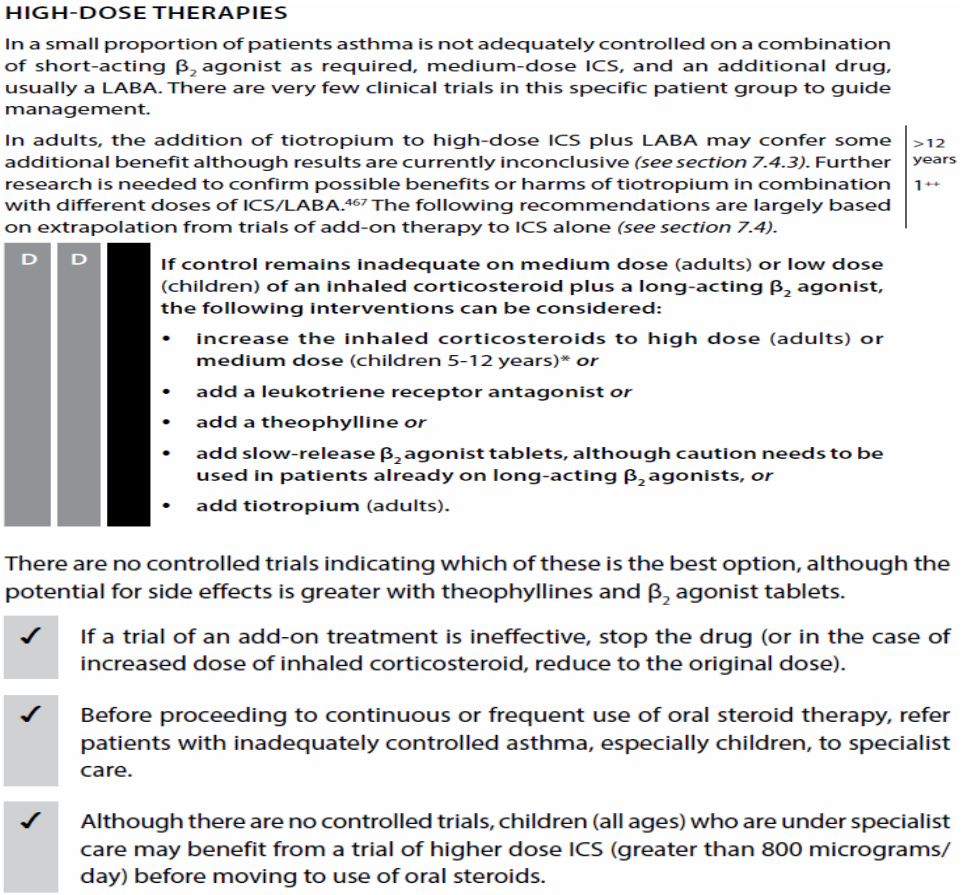
| | |
|---|---|
| Evidence to support the use of leukotriene receptor antagonists (LTRA) as an add-on therapy to ICS plus LABA is lacking and evidence for their use is largely based on extrapolation from trials of LTRA as add-on therapy to ICS alone. The addition of LTRA to ICS may provide improvement in lung function, a decrease in asthma attacks, and an improvement in symptoms in adults and children over five years of age, although reported benefits differ between studies and evidence is limited in children.[435,464,465] | >12 years<br>1++ |
| A systematic review of studies comparing the addition of LTRA to ICS with the addition of LABA to ICS showed that the addition of LABA to ICS was more effective at reducing asthma attacks (the primary outcome) and improving secondary outcomes including SABA use, symptoms and quality of life in adults, although differences were generally small. There was insufficient evidence on which to base conclusions regarding which add-on therapy is more effective in children.[453] | 1++ |
| In adults, the addition of LTRA to ICS is superior to ICS alone and has a similar effect on asthma control to high-dose ICS. High-dose ICS, however, appears superior to ICS-LTRA for some pulmonary function indices, although further studies to investigate this are required.[466] | 1+ |

## A LAMA

| | |
|---|---|
| A review of RCTs in adults taking tiotropium bromide, a long-acting muscarinic antagonist (LAMA), in addition to ICS plus LABA compared with ICS plus LABA, reported fewer asthma exacerbations (although results were inconclusive), improved lung function and some benefits relating to asthma control in those taking tiotropium, but no improvement in quality of life. Evidence relating to serious adverse effects was inconclusive but fewer non-serious adverse events were reported in those taking tiotropium. In two of the three trials included in the review patients were taking high-dose ICS, although it was not possible to draw conclusions about the effect of tiotropium in those taking different doses of ICS plus LABA.[467] | >12 years<br>1++ |
| There is insufficient evidence to suggest that addition of tiotropium to ICS in patients inadequately controlled on ICS alone has any benefit over addition of LABA to ICS.[468] The addition of LABA to ICS remains the first choice for add-on treatment in adults. In adults with asthma who do not respond to ICS plus LABA, the addition of tiotropium to ICS is a possible, although 'off-label' alternative.[469 470] | >12 years<br>1++<br>1+ |
| A review comparing the addition of tiotropium to ICS with increased dose of ICS in adults found only one study suitable for inclusion and insufficient evidence to say whether adding tiotropium to ICS ('off-label' use) is safer or more effective than increasing the dose of ICS.[471] | 1+ |

| | |
|---|---|
| OTHER APPROACHES | >12 years |
| Theophyllines may improve lung function and symptoms, but side effects occur more commonly.[444] | 1+ |
| Slow-release $\beta_2$ agonist tablets may also improve lung function and symptoms, but side effects occur more commonly.[443] | 1++ |
| Addition of short-acting anticholinergics is generally of no value.[445,472] Addition of nedocromil is of marginal benefit.[438,446] | 1+ |

✓ If control remains inadequate after stopping a LABA and increasing the dose of inhaled corticosteroid, consider sequential trials of add-on therapy, ie leukotriene receptor antagonists, theophyllines, slow-release $\beta_2$ agonist tablets (in adults only)



**HIGH-DOSE THERAPIES**

In a small proportion of patients asthma is not adequately controlled on a combination of short-acting $\beta_2$ agonist as required, medium-dose ICS, and an additional drug, usually a LABA. There are very few clinical trials in this specific patient group to guide management.

In adults, the addition of tiotropium to high-dose ICS plus LABA may confer some additional benefit although results are currently inconclusive *(see section 7.4.3)*. Further research is needed to confirm possible benefits or harms of tiotropium in combination with different doses of ICS/LABA.[467] The following recommendations are largely based on extrapolation from trials of add-on therapy to ICS alone *(see section 7.4)*.

>12 years
1++

D D

If control remains inadequate on medium dose (adults) or low dose (children) of an inhaled corticosteroid plus a long-acting $\beta_2$ agonist, the following interventions can be considered:

- increase the inhaled corticosteroids to high dose (adults) or medium dose (children 5-12 years)* *or*
- add a leukotriene receptor antagonist *or*
- add a theophylline *or*
- add slow-release $\beta_2$ agonist tablets, although caution needs to be used in patients already on long-acting $\beta_2$ agonists, *or*
- add tiotropium (adults).

There are no controlled trials indicating which of these is the best option, although the potential for side effects is greater with theophyllines and $\beta_2$ agonist tablets.

✓ If a trial of an add-on treatment is ineffective, stop the drug (or in the case of increased dose of inhaled corticosteroid, reduce to the original dose).

✓ Before proceeding to continuous or frequent use of oral steroid therapy, refer patients with inadequately controlled asthma, especially children, to specialist care.

✓ Although there are no controlled trials, children (all ages) who are under specialist care may benefit from a trial of higher dose ICS (greater than 800 micrograms/ day) before moving to use of oral steroids.

*Anmerkung zu Empfehlungen: Stufenschema siehe Anhang*

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**Chung KF et al., 2014 [4].**

*ERS/ATS*

International ERS/ATS Guidelines on Definition, Evaluation and Treatment of Severe Asthma

**Leitlinienorganisation/Fragestellung**

To review the definition and provide recommendations and guidelines on the evaluation and treatment of severe asthma in children and adults

**Methodik**

Grundlage der Leitlinie

- - repräsentatives Kommittee: Definition des Ziels, Erstellung von PICO Fragen, Diskussion von Evidenz und Erstellung von Empfehlungen
- - bei Vorliegen von Interessenkonflikte, keine Teilnahme an finaler Entscheidung über Empfehlung
- - systematische Literatursuche nach systematischen Reviews und wenn notwendig nach RCTs), wenn möglich Meta-Analyse der gefundenen Ergebnisse
- - develop recommendation based on the GRADE approach

- - Recommendations and their strength were decided by consensus and no recommendation required voting.

Recherche/Suchzeitraum:

- (Recherchezeitpunkt unterschiedlich für verschiedene Fragestellungen,
- für Anti-IgE monoclonal antibody November 2011

LoE

- Cochrane risk of bias
- Quality was categorized into 4 levels ranging from very low to high quality.

GoR

We labelled the recommendations as either “strong” or “conditional” according to the GRADE approach. We used the words “we recommend” for strong recommendations and “we suggest” for conditional recommendations.

**Empfehlungen**

Question 4. Should a monoclonal anti-IgE antibody be used in patients with severe allergic asthma?

Recommendation 4

In patients with severe allergic asthma we suggest a therapeutic trial of omalizumab both in adults (conditional recommendation, low quality evidence)

Summary of the evidence

2 Studien mit Kindern [271, 278]

The overall quality of evidence was low to very low mainly due to the risk of bias and indirectness of the evidence.

Undesirable consequences: Based on the case series of over 39,000 patients, postmarketing reports and data supplied by the manufacturer it has been estimated that use of omalizumab is associated with 0.09% risk of anaphylaxis [285, 286].

Values and preferences

This recommendation places higher value on the clinical benefits from omalizumab in some patients with severe allergic asthma and lower value on increased resource use.

Remarks

Adults and children (aged 6 and above) with severe asthma who are considered for a trial of omalizumab, should have confirmed IgE-dependent allergic asthma uncontrolled despite optimal pharmacological and non-pharmacological management and appropriate allergen avoidance, if their total serum IgE level is 30 to 700 IU/mL (in 3 studies the range was wider – 30 to 1300 IU/mL). Treatment response should be globally assessed by the treating physician taking into consideration any improvement in asthma control, reduction in exacerbations and unscheduled healthcare utilisation, and improvement in quality of life. If a patient does not respond within 4 months of initiating treatment, it is unlikely that further administration of omalizumab will be beneficial.

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# 4 Detaillierte Darstellung der Recherchestrategie

### Cochrane Library - Cochrane Database of Systematic Reviews (Issue 9 of 12) am 24.09.2018

| # | Suchfrage |
|---|---|
| 1 | [mh Asthma] |
| 2 | asthma*:ti |
| 3 | #1 or #2 |
| 4 | #3 with Cochrane Library publication date from Sep 2013 to Sep 2018, in Cochrane Reviews |

### Systematic Reviews in Medline (PubMed) am 24.09.2018

| # | **Suchfrage** |
|---|---|
| 1 | „asthma/therapy"[mh] |
| 2 | asthma*[ti] |
| 3 | (#2) AND (treatment*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR treating[tiab] OR treated[tiab] OR management[tiab] OR drug*[tiab]) |
| 4 | #1 OR #3 |
| 5 | (#4) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab])))) |
| 6 | (#5) AND ("2013/09/01"[PDAT] : "3000"[PDAT]) |

### Leitlinien in Medline (PubMed) am 24.09.2018

| # | **Suchfrage** |
|---|---|
| 1 | asthma[majr] |
| 2 | asthma*[ti] |
| 3 | #1 OR #2 |
| 4 | (#3) AND ((Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[ti] OR recommendation*[ti]) NOT (letter[ptyp] OR comment[ptyp]))) |
| 5 | (#5) AND ("2013/09/01"[PDAT] : "3000"[PDAT]) |

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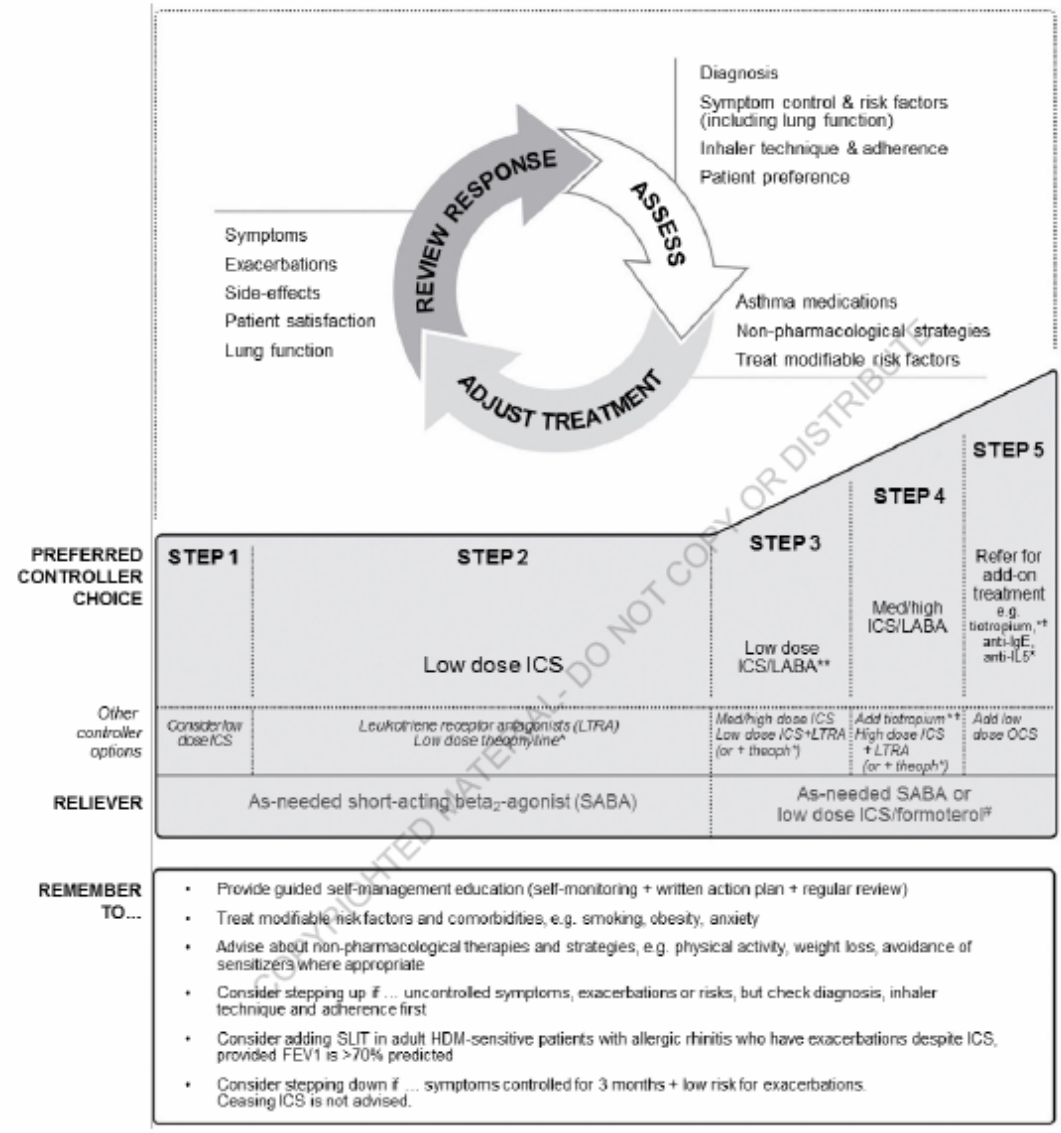
# Anhang

## Global Initiative for Asthma (GINA), 2017 [11]. Global strategy for asthma management and prevention; updated 2017

**Box 3-5. Stepwise approach to control symptoms and minimize future risk**






ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist; med: medium dose; OCS: oral corticosteroids; SLIT: sublingual immunotherapy. See Box 3-6 (p.44) for low, medium and high doses of ICS for adults, adolescents and children 6–11 years. See Chapter 3 Part D (p.66) for management of exercise-induced bronchoconstriction.

* Not for children <12 years.
** For children 6–11 years, the preferred Step 3 treatment is medium dose ICS.
# Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclometasone/formoterol maintenance and reliever therapy.
† Tiotropium by mist inhaler is an add-on treatment for patients with a history of exacerbations; it is not indicated in children <12 years.

**National Asthma Council Australia et al., 2017 [15]. Australian asthma handbook: australia's national guidelines for asthma management; Version 1.3**


ICS: inhaled corticosteroid; SABA: short-acting beta2 agonist; LABA: long-acting beta2 agonist

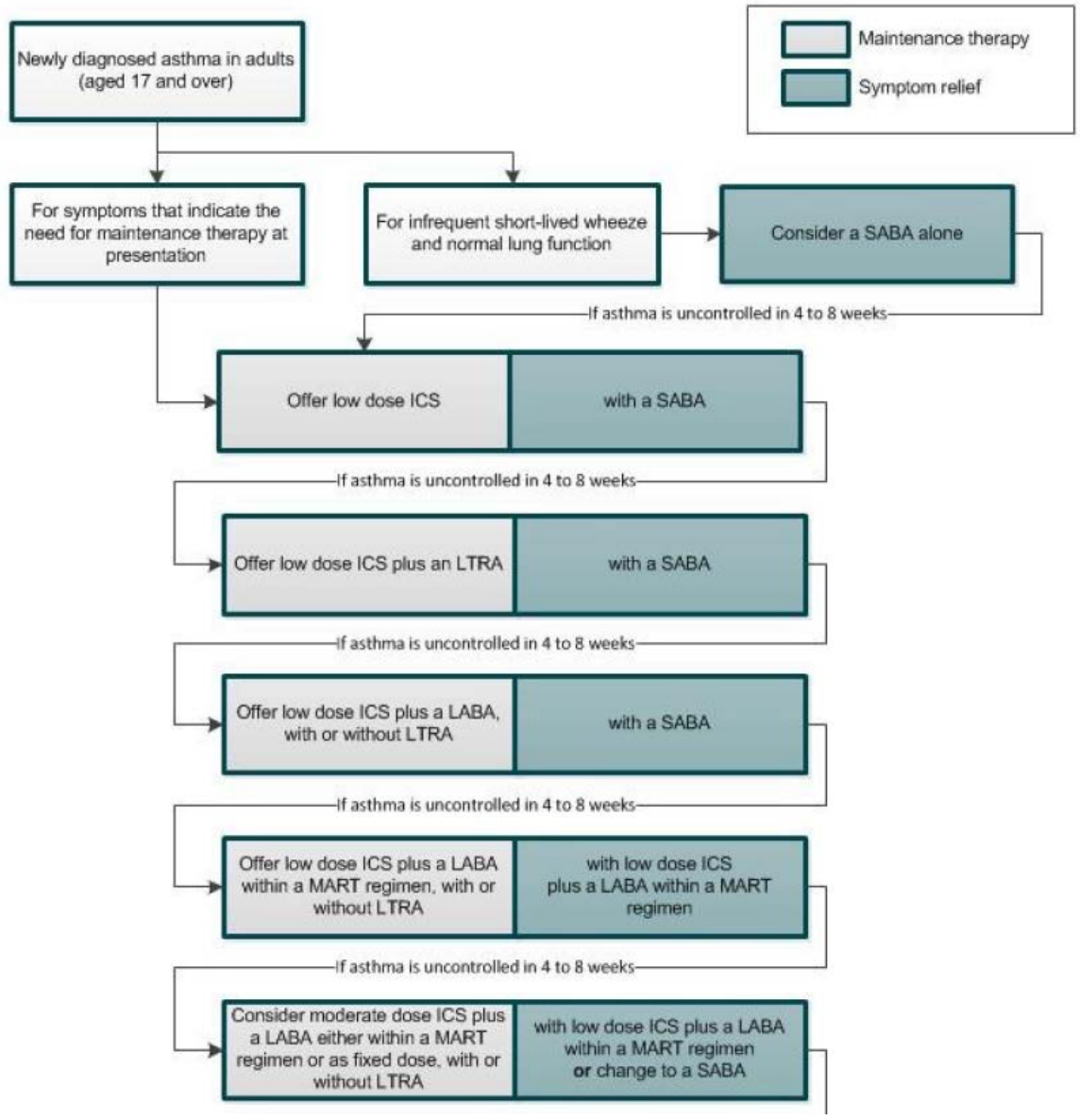
* Reliever means rapid-onset beta2 agonist and includes:

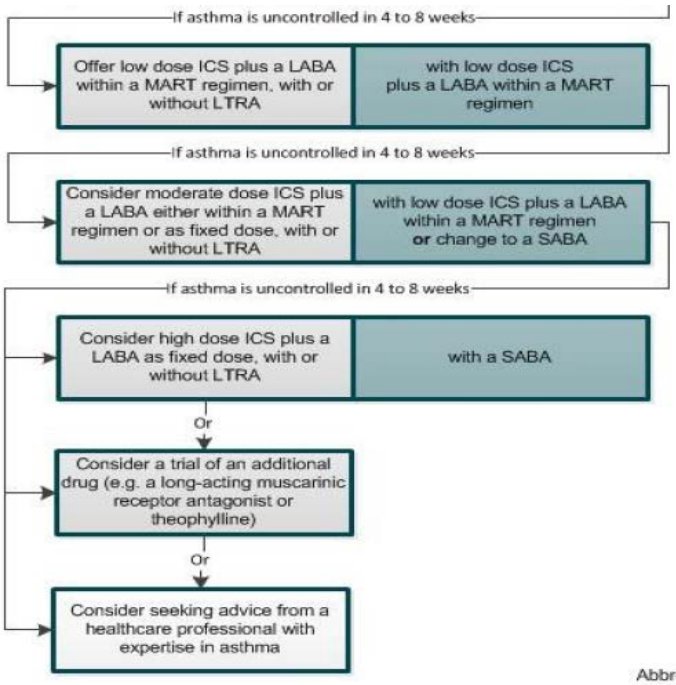
short-acting beta2 agonists
low-dose budesonide/formoterol combination – only applies to patients using this combination in a maintenance-and-reliever regimen. (This combination is not classed as a reliever when used in a maintenance-only regimen).

§ In addition, manage flare-ups with extra treatment when they occur, and manage exercise-related asthma symptoms as indicated.

**NICE, 2017 [16] Asthma: diagnosis, monitoring and chronic asthma management**

**Algorithm C: Pharmacological treatment of chronic asthma in adults aged 17 and over**






Abbreviations:
ICS, inhaled corticosteriod
LABA, long-acting beta agonist
LTRA, leukotriene receptor antagonist
MART, maintenance and reliever therapy
SABA, short-acting beta agonist

## SIGN, 2016 [19]. British guideline on the management of asthma (2016)