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Pocket guide: biologics in upper and lower airways in adults

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Dear Editor:

The introduction of biologics for the treatment of severe upper and lower (type 2) airway inflammation has been a gamechanger in the management of these diseases. Biologics are injectable medications targeting different molecules relevant in (type 2) inflammation in patients with severe (type 2) airway diseases, like asthma, eosinophilic chronic obstructive pulmonary disease (COPD), chronic rhinosinusitis (CRS) and those who remain uncontrolled despite regular treatment [1-3]. After the phase 3 trials, showing significant impact on symptoms, quality of life and interventions like surgery (for the upper airways) and exacerbations needing hospitalisation (for the lower airways), biologics are now used in daily practice in many parts of the world [4, 5].
This pocket guide is aimed at all specialists treating adult patients with severe airway disease.

We now have to learn which patients are eligible for treatment with a biologic and which biologic is the best for a certain patient phenotype. Endotyping, although in its infancy, leads to the best option for a patient and tailored appropriate care. Patients with more severe airway disease often have a phenotype involving both the upper and lower airways. For these patients in particular biologics are an option. For optimal care intensive collaboration with the whole team of health care professionals is needed. But it is also important that all health care professionals treating patients with a biologic for airway diseases are fully aware of the diagnosis, management schemes and specific issues of the entire airway. So otorhinolaryngologist have to learn about the lower airways and pulmonologists/allergists about the upper airways. A health care professional/team that considers prescribing a biologic should re-evalute the diagnosis and if needed do additional investigations to confirm it. They must try to endotype the disease, define the severity and the level of control, evaluate the impact of the disease on quality of life, evaluate co-morbidities, consider earlier therapy, compliance, and treatable traits. Patients that are eligible for a biologic have severe/uncontrolled disease with usually proven type 2 inflammation, with a significant impact on quality of life and frequent need of oral corticsteroids/surgery [2, 6]. Patients need to be aware that biologics are injections that have to be (self)-adminitered regularly and presumably for a long period of time. In general, patients treated with biologics have excellent improvement in their quality of life and relevant signs and symptoms of their disease including improved sense of smell, reduced exacerbations and significantly reduced need for oral corticosteroids or rescue surgery. In this pocket guide one can also find advice on which biologic to choose as first choice in different pheno- and endotypes. A significant percentage of patients treated with a biologic achieve control and even clinical remission [7, 8]. It has been shown that increasing the interval between doses can be done in many patients, however data on inducing remission that is sustained after stopping the treatment are limited and much needed (9). Biologic therapy in airways disease is a rapidly evolving area. Currently there is a lack of information from head-to-head comparative studies and patient indications for a particular molecule are not yet certain. The advice in this guide is based on evidence from network meta-analyses and expert opinions in discussions between September and December 2024. We expect to update this pocket guide on a yearly base in the coming years. The development of biologic treatment for non-type 2 airway disease but also for other type 2 airway diseases is on the horizon. Finally, the EUFOREA pocket guide on biologics contains lists to help all health care professionals treating the airways with biologics and we hope that many of them will pin the summary of this pocket guide on the wall of their office.

Authorship contribution

This pocketguide and the letter were prepared by Peter Hellings, Vibeke Backer and Wytske Fokkens.
The content was discussed in a number of (online) meetings by all authors involved. The final version was approved by all authors.

Conflict of interest

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Roche, Sanofi, and Stallergenes Greer. JKH is research consultant for Sanofi, Regeneron, GlaxoSmithKline, and AstraZeneca. CH is an advisory board member of AstraZeneca, BioInspire Technologies, Dianosic, GlaxoSmithKline and Sanofi. GJ received consultation and/or speaker fees from AstraZeneca, Chiesi, GlaxoSmithKline and Sanofi. SL has received grants and received honoraria for advisory boards and lectures from ALK, Allergopharma, DBV-technologies, GSK, Sanofi-Aventis, Leti, Leo Pharma, Lilly, Viatris. SEL has received clinical trial funding and participated in advisory boards for AstraZeneca, Genentech, Eli Lilly, GSK, Optinose, Sanofi Regeneron, and holds equity in Diceros Therapeutics. JM is or has been a member of national and international scientific advisory boards, consulted, and received fees for lectures and grants for research projects or clinical trials from Almirall, AstraZeneca, GSK, LETI, Lilly, Menarini, MSD, NOUCOR/Uriach Group, OptiNose, Regeneron Pharmaceuticals, Sanofi Genzyme, UCB Pharma and Viatris/MEDA Pharma. ATP has received research grants from Sanofi/Regeneron and AstraZeneca. She has served as a consultant for GSK, Chiesi, Merck, Sanofi Regeneron, Eli Lilly and AstraZeneca. GKS Honoraria for articles, speaker and advisoryboards: ALK, Bayer, GlaxoSmithKline, Haleon, Noucor, Sanofi-Regeneron, and Viatris. Chair of BSACI rhinitis guidelines, Scientific Chief Editor, Rhinology Section of Frontiers in Allergy, Board member and AR lead for EUFOREA, and Chair/ member Data Monitoring Committees on SLIT for ALK. SS served as a speaker for Sanofi, GSK and Menarini Pharma; and is an advisory board member for Sanofi, GSK and AstraZeneca; and is an investigator for Sanofi, GSK, Novartis and AstraZeneca (grants paid to his institution). BS is consultant Lyra, Stryker, Neurent, Spirair, Smith and Nephew. IDP has received speaker's honoraria for speaking at sponsored meetings from Astra Zeneca, Aerocrine, Almirall, Sanofi/Regeneron, Menarini and GSK and payments for organising educational events from AZ, GSK and Sanofi/Regeneron. He has received honoraria for attending advisory panels with Sanofi/Regeneron, Astra Zeneca, GSK, Merck, Circassia, Chiesi, Upstream Bio and Areteia. He has received sponsorship to attend international scientific meetings from GSK, Astra Zeneca and Sanofi/Regeneron. SQ has been on advisory boards for and has received speaker's honoraria from Allergy Therapeutics, AstraZeneca, Chiesi, GlaxoSmithKline, Gebro, Novartis and Sanofi. MEW has received consulting, advisory, or speaking honoraria from the following: Allakos, Amgen, Areteia Therapeutics, Arrowhead Pharmaceutical, AstraZeneca, Avalo Therapeutics, Belenos Bio, Celldex, Connect Biopharma, Eli Lilly, Equillium, Glaxosmithkline, Incyte, Jasper Therapeutics, Kinaset, Kymera, Merck, MyBiometry, Pharming, Phylaxis, Pulmatrix, Rapt Therapeutics, recludix Pharma, Regeneron, Roche/Genentech, Sanofi/Genzyme, Sentien, Sound Biologics, Tetherex Pharmaceuticals, Uniquity Bio, Upstream Bio, Verona Pharma, Zurabio. PWH is recipient of consultancy/lecture fees or unrestrictedresearch grants from Sanofi/Regeneron, Novartis, GSK, Medtronicand Viatris.
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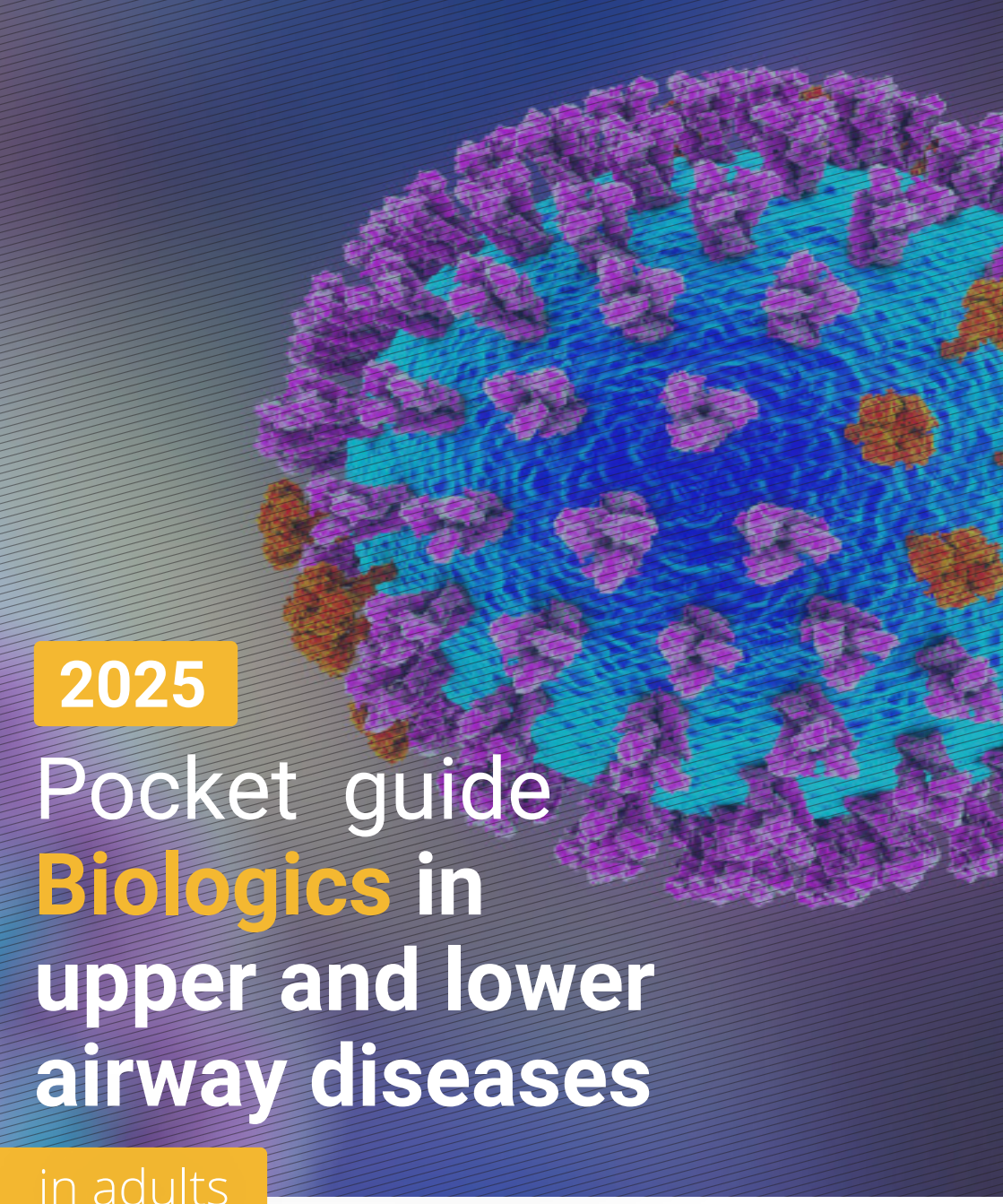


2025

Pocket guide Biologics in upper and lower airway diseases

in adults

DEVELOPED BY EUFOREA EXPERT TEAMS BASED ON INTERNATIONAL GUIDELINES

EUFOREA

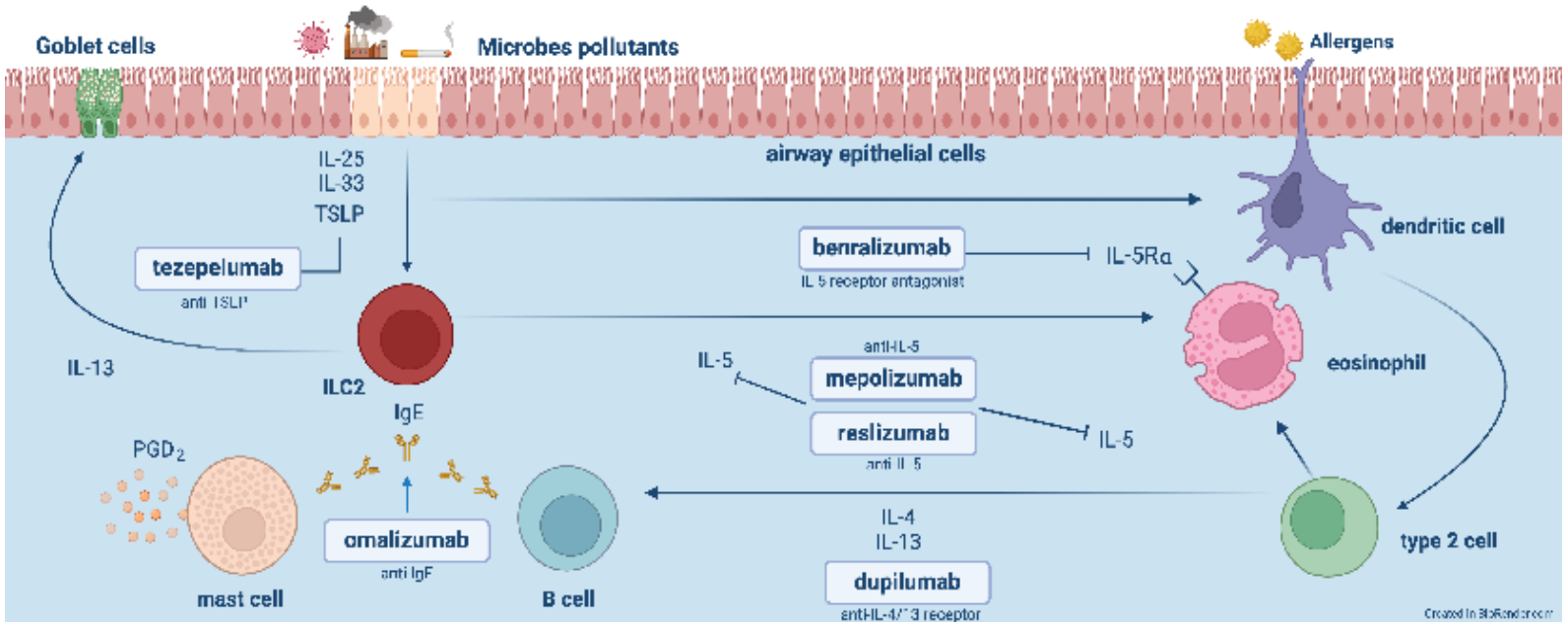
What are Biologics?

New injectable medications targeting different molecules relevant in (type 2) inflammation in patients with severe (type 2) airway diseases, like asthma, eosinophilic COPD, chronic rhinosinusitis (CRS) and who still have problems after regular treatment.

Biologics and their applications

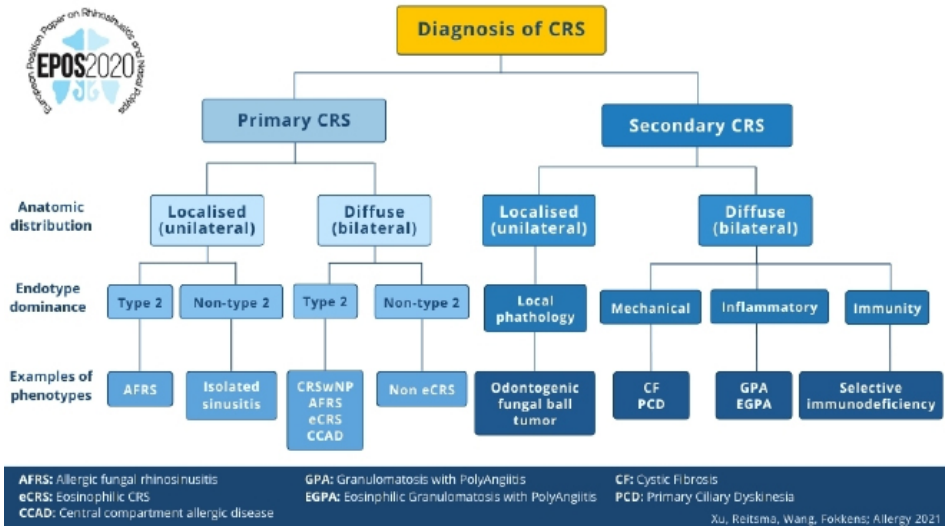
Molecules	Target	Dose	Indication
Benralizumab	IL-5Rα	30 mg - SC / 4 - 8 wk	Asthma
Dupilumab	IL-4Rα/ IL-13	300 mg- SC / 2 wk	Asthma CRSwNP eos COPD
Mepolizumab	IL-5	100 mg - SC / 4wk	Asthma CRSwNP
Omalizumab	IgE	Body weight and pre-treatment total IgE SC / 2-4wk	Asthma CRSwNP
Reslizumab	IL-5	3 mg/kg body weight i.v./4 wk	Asthma
Tezepelumab	TSLP	210 mg - SC / 4wk	Asthma

Working mechanism of biologics in type 2 inflammation



Definitions in Chronic Rhinosinusitis (CRS)

- Chronic Rhinosinusitis with nasal polyps: primary diffuse bilateral mostly type-2 form of chronic rhinosinusitis.



Key definitions in CRSwNP

Controlled CRSwNP	"Patient-reported control" with the absence of clinically relevant sinonasal symptoms of active disease (defined as overall symptom severity, nasal obstruction and smell)". CONTROL can be with or without ongoing / past treatment.
Uncontrolled CRSwNP	"Patient-reported lack of control" and the presence of clinically relevant sinonasal symptoms of active disease (defined as overall symptom severity, nasal obstruction and smell)".
Remission in CRSwNP	REMISSION in CRSwNP is defined as sustained CONTROL (as defined earlier) for ≥ 12 months combined with the absence of signs of active disease evaluated by nasal endoscopy. REMISSION can be reached with or without treatment (not including systemic steroids and sinonasal surgery in the last 12 months).
CRSwNP Cure	Sustained remission without treatment for at least 5 years.

Definitions in Asthma

- **Allergic asthma:** asthma in patients with sensitisation to allergens that trigger asthma symptoms.
- **Eosinophilic asthma:** Adult-onset asthma with high blood eosinophils (≥150 cells/μL) and frequent exacerbations.
- **Type 2 asthma:** asthma characterized by type 2 airway inflammation, as evidenced by high blood eosinophils and/or high FeNO.
- **Non-type 2 asthma:** asthma characterised by the absence of high blood eosinophils and high FeNO after ruling out other chronic obstructive airway diseases.

Key definitions in asthma

Controlled asthma (or well-controlled asthma):	Current control of asthma symptoms (i.e. no or few asthma symptoms, no sleep disturbance due to asthma, and unimpaired physical activity) PLUS reduced risk of future adverse outcomes (e.g. no exacerbations in the previous year).
Uncontrolled asthma	Persistent asthma symptoms (e.g. frequent asthma symptoms, sleep disturbance due to asthma, or impaired physical activity) OR an increased risk of future adverse outcomes (e.g. history of exacerbation(s) in the previous year).
Clinical asthma remission (on treatment):	Long-term well-controlled asthma (on treatment), without exacerbations, without use of (maintenance or burst) systemic corticosteroids, AND with normal or stable personal best lung function.
Biological asthma remission (on or off treatment):	Resolution of asthma-related inflammation and negative direct bronchial hyperresponsiveness (on or off treatment).
Complete asthma remission (on or off treatment):	Clinical and biological remission of asthma (on or off treatment)
Asthma cure	Long-term complete remission of asthma, off treatment.

Diagnosis of Chronic Rhinosinusitis (CRS)

- **Two or more symptoms suggestive of CRS for ≥ 3 months**
  - Nasal congestion / obstruction
  - Nasal secretions (rhinorrhoea and/or post-nasal drip)
  - Smell dysfunction (hyposmia or anosmia)
  - Facial pain / headache
- **Abnormalities at:**
  - Nasal endoscopy (polyps, purulence, mucosal swelling)
  - OR CT scan of paranasal sinuses
- **Markers of inflammation:**
  - Allergy tests
  - Blood/tissue eosinophils

Click here for CRS Pocket Guide OR scan above QR code

Diagnosis of Asthma

- **History of:**
  - Cough
  - Chest tightness
  - Shortness of breath
  - Wheezing
- **Lung-function abnormality: variable expiratory airflow limitation:**
  - FEV1 or FVC reversibility (to SABA)
  - Increased reactivity to direct or indirect stimuli (methacholine; mannitol, Eucapinic hyperventilation, hypertonic saline, exercise)
  - PEF variability
  - Allergy tests
- **Markers of inflammation:**
  - Blood/sputum eosinophils
  - FeNO

Click here for Asthma Pocket Guide OR scan above QR code

Treatment of Chronic Rhinosinusitis (CRS)

- **Step 1: Basic treatment**
  - Saline rinses and/or
  - Nasal corticosteroid spray or drops
- **Step 2**
  - + oral corticosteroids and/or antibiotics
  - If no improvement Endoscopic Sinus Surgery (ESS)
- **Step 3: Endo-typing by nasal endoscopy, blood tests and/or histology**
  - Non-type 2: long-term antibiotics, xylitol, steroid eluting implants, revision surgery
  - Type 2: Aspirin treatment after desensitisation (ATAD), biologics, steroid eluting implants, revision surgery

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Treatment of Asthma

- **Step 1: Basic treatment:**
  - Standard of care
  - Identify treatable traits
- **Step 2:**
  - Re-identify treatable traits
  - Adjust pharmacological treatment (increase ICS, add LABA/LAMA, LTRA, ATAD, immunotherapy, long term antibiotics)
- **Step 3: Choose biologics based on phenotype/endotype**
  - Allergic asthma (anti-IgE)
  - Eosinophilic asthma (anti-IL5/IL5R, anti-TSLP)
  - Type 2 asthma (anti-IL4R, anti-TSLP)
  - Non-type 2 asthma after ruling out other chronic obstructive airway diseases (anti-TSLP)

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Indications for Biologics*

CRSwNP

≥ 3 out of 5 of the criteria below in patients that had at least one sinus surgery (or cannot be operated)

Evidence of type 2 inflammation (blood eosinophil ≥ 150 cells/µL or tissue eosinophilia ≥ 10/hpf)

Need for systemic corticosteroids or contraindication to systemic corticosteroids

Significant impaired quality of life

Significant loss of smell

Diagnosis of comorbid asthma

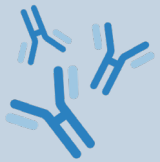
ASTHMA / COPD

Uncontrolled severe asthma/ COPD with type 2 inflammation (except Tezepelumab)

Blood eosinophil ≥ 150 cells/µL (for COPD > 300) (all but omalizumab and tezepelumab)

Need for systemic corticosteroids or contraindication to systemic corticsoteroids

Sensitization to inhaled perennial allergens (omalizumab)



***Today there are no indications for biologics for patients with non-type 2 CRS or allergic rhinitis but they are expected in the coming years. Re-imbursement depending on local situation.**

Click here for CRS Pocket Guide OR scan above QR code

Click here for Asthma Pocket Guide OR scan above QR code

What should the physician do when considering a biologic?

- ☐ Re-evaluate diagnosis
- ☐ Define the severity of disease
- ☐ Define the level of control
- ☐ Evaluate the impact on quality of life
- ☐ Evaluate earlier therapy, compliance and treatable traits
- ☐ Endotype the disease (blood, tissue)
- ☐ Ask about history of allergies, (type 2) comorbidities
- ☐ Confirm suspicion by additional investigations (nasal endoscopy, lung function tests including FeNO and provocation tests, blood, skin prick testing, smell testing, CT scan paranasal sinuses)

What to discuss with the patient?

- ✓ Treatment is a regular injection (for dosing, see figure 1 in this pocket guide)
- ✓ First 2 injection(s) in the hospital, then self injection is possible
- ✓ Start of effect can be in weeks - months
- ✓ Potential side effects
- ✓ When to warn the health care professional
- ✓ Treatment has to be taken for a long time but sometimes interval between injections can be prolonged (1 year especially in patients with CRSwNP)

Which biologic to choose based on network meta-analysis and/or expert opinion*?

- Females planning pregnancy in the near future: omalizumab
- CRSwNP: dupilumab
- CRSwNP with highly eosinophilic asthma: mepolizumab
- Allergy-driven asthma: omalizumab
- Eosinophilic asthma: mepolizumab, reslizumab, benralizumab
- Type 2 asthma: dupilumab, tezepelumab
- Non type 2 asthma: tezepelumab
- Eosinophilic COPD: dupilumab

*Biologic therapy in airways disease is a rapidly evolving area. Currently there is a lack of information from head-to-head comparative studies and patient indications for a particular molecule are not yet certain. The advice in this guide is based on evidence from cluster meta-analyses and expert opinions in discussions between September and December 2024.

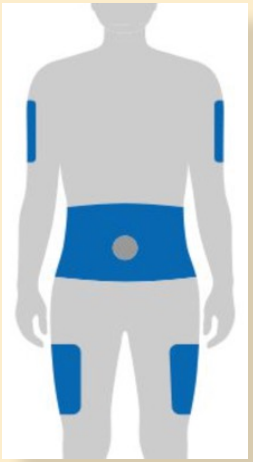
This pocket guide will be revised when further evidence becomes available.

The first injection(s)

- Most biologics come with an auto-injector
- First 2 injection(s) in hospital because of training and minimal risk of side effects (anaphylaxis)

How to train the patient?

- ☐ **Prepare the medication**
- ☐ **Wash your hands thoroughly and use an alcohol wipe to clean the injection site**
- ☐ **Inject under skin in abdomen, thigh, or upper arm with auto-injector or with pre-filled syringe**



Sites of subcutaneous injection

Biologics in airway diseases

	Chronic Rhinosinusitis with nasal polyps (CRSwNP)	Asthma	CRSwNP & Asthma
	Educate patient about chronicity and severity of disease, need for optimal adherence and avoidance of infectious, occupational, and environmental triggers e.g. by wearing a mask		
	For all diseases give basic maintenance therapy		
Indication for biologic	**Patients with CRSwNP and a history of sinus surgery, with ≥ 3 of 5 criteria:** • Evidence of type 2 inflammation • Need for systemic corticosteroids or contraindication to systemic corticosteroids • Significantly impaired quality of life • Significant loss of smell • Co-morbid asthma	**Patients with poor asthma control** • Asthma symptoms despite ICS/LABA • Interference with daily activity and/or sleep • Chronic OCS use • At least 2 exacerbations in prior year	**Patients with CRSwNP & asthma** • Most patients with CRSwNP and asthma have type 2 disease • Indication based on CRSwNP and/or asthma
Choice of biologics Based on network meta-analysis and/or expert opinion	• Dupilumab: first choice in CRSwNP patients • Omalizumab: first choice in female patients planning pregnancy • Mepolizumab: consider in patients with co-morbid highly eosinophilic asthma	• Allergy-driven asthma: omalizumab, consider dupilumab and tezepelumab • Eosinophilic asthma: mepolizumab, reslizumab, or benralizumab • Type 2 asthma: dupilumab • Type 2/non-type 2 asthma: tezepelumab • Female patients planning pregnancy: omalizumab	• Type 2 disease: dupilumab • Eosinophilic disease (≥ 150 cells/µL): mepolizumab • Female patients planning pregnancy: omalizumab
Real life experience	• Excellent effect on QOL and relevant signs and symptoms • Rescue OCS or surgery seldom needed • Significant percentage achieve control	• Excellent effect on QOL and relevant signs and symptoms including exacerbations, variable effect on lung-function • Significantly reduced OCS need • Significant percentage achieves control and clinical remission	• Excellent effect on QOL and relevant signs and symptoms including exacerbations, lung-function • Rescue OCS or surgery seldom needed • Similar effect on upper and lower airways in most patients
Comorbidities	**Consider evaluating (type-2) comorbidities such as allergies/ eosinophilic otitis media/N-ERD, atopic dermatitis /eosinophilic oesophagitis/eosinophilic COPD**		

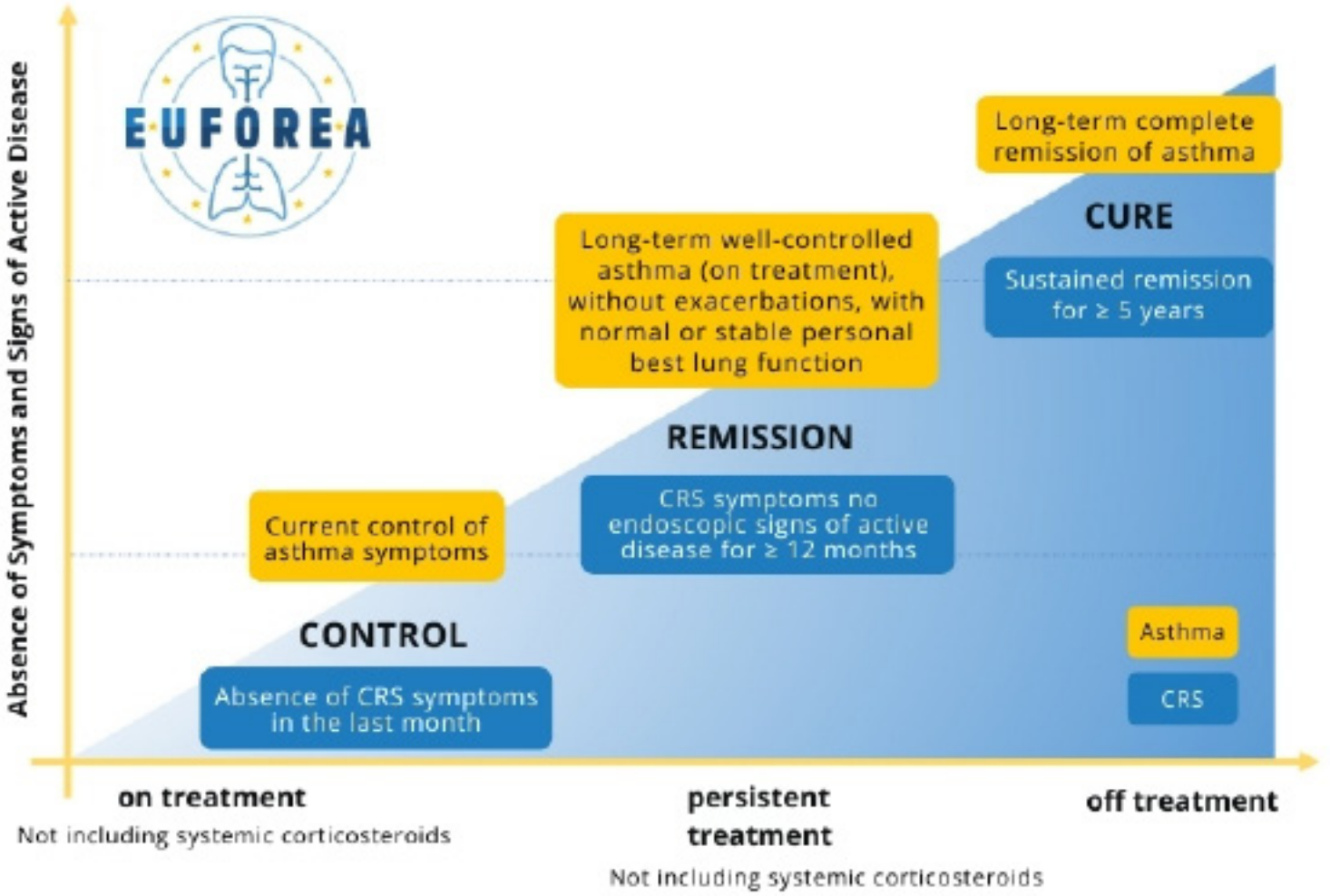
PATIENT PARTICIPATION IN TREATMENT PLAN

Goals of Care

Future airway indications for biologics

- New type 2 and non-type 2 indications, such as allergic rhinitis will arise in the near future
- In the future other indications such as non-type 2 diffuse CRS and other forms of lower airways diseases will follow

Figure 1.



Additional Resources:

SNOT 22 & EPOS 2020 Criteria of Control

EUFOREA instructional videos for patients

Biologics: How to inject a pre-filled pen?

Biologics: How to inject a pre-filled syringe?

Abbreviations

AD: Atopic dermatitis

AIT: Allergen immunotherapy

ATAD: Aspirin treatment after desensitisation (ATAD)

COPD: Chronic obstructive pulmonary disease

CRS: Chronic rhinosinusitis

CRSwNP: Chronic rhinosinusitis with nasal polyps

CT: Computed tomography scan

EGPA: Eosinophilic Granulomatosis with PolyAngiitis

EPOS: European Position Paper on Rhinosinusitis and Nasal Polyps

FeNO: Fraction of exhaled nitric oxid

FEV1: Forced expiratory volume in one second

FVC: Forced vital capacity

GPA: Granulomatosis with PolyAngiitis

HES: HyperEosinophilic Syndrome

HPF: High power field

LTRA: Leucotriene Antagonists

N-ERD: NSAID-exacerbated respiratory disease

NE: Nasal endoscopy

NP: Nasal polyps

NSAID: Non-steroidal anti-inflammatory drugs

PEF: Peak expiratory flow

PFT: Pulmonary function test

SNOT-22: Sinonasal outcome test

The nature of pocket guides by reason of their brevity, should not be considered completely inclusive or exclusive. Further information can be sought in the appropriate guidelines/statements.

Vision

EUFOREA is an international non-profit organization forming an alliance of all stakeholders dedicated to reducing the prevalence and burden of chronic respiratory diseases through the implementation of optimal patient care via education, research and advocacy.

Mission

Based on its medical and scientific core competency, EUFOREA offers a platform to introduce innovation and education in healthcare leading to optimal patient care.

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