Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2017-B-279 Lanadelumab

Stand: Januar 2018

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

Lanadelumab
Langzeitprophylaxe von Patienten mit hereditärem Angioödem

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 Tabelle „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	*Es liegen keine Beschlüsse vor.*
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Lanadelumab	*Geplantes Anwendungsgebiet lt. Beratungsanforderung:* Langzeitprophylaxe von über 12-jährigen Patienten mit hereditärem Angioödem (Injektion s.c.)
C1-Esterase-Inhibitor B06AC01 Cinryze®	Behandlung und vor einem medizinisch indizierten Eingriff durchgeführte Prophylaxe von Angioödem-Attacken bei Erwachsenen, Jugendlichen und Kindern (2 Jahre und älter) mit hereditärem Angioödem (HAE). Routineprophylaxe gegen Angioödem-Attacken bei Erwachsenen, Jugendlichen und Kindern (6 Jahre und älter) mit schweren und wiederkehrenden Attacken eines hereditären Angioödems (HAE), bei denen orale prophylaktische Behandlungen nicht vertragen werden oder keinen ausreichenden Schutz bieten, oder bei Patienten, die sich mit wiederholten Akutbehandlungen nur unzureichend therapieren lassen.
Tranexamsäure B02AA02 Cyklokapron® Filmtabletten	Zur Vorbeugung des Auftretens von Ödemen bei hereditärem Angioödem (Schwelllungsneigung im Unterhautgewebe an verschiedenen Körperstellen sowie Schleimhäuten, einschließlich Kehlkopf und Rachen).

Quellen: AMIS-Datenbank, Fachinformationen

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *Angioödem* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 29.11.2017 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, 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 134 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 3 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Langzeitprophylaxe von über 12-jährigen Patienten mit hereditärem Angioödem

Abkürzungen:

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
C1-INH	C1 esterase inhibitor
DAHTA	DAHTA-Datenbank
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
HAE	Hereditäres Angioödem
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LTP	Long-term Prophylaxis
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG Berichte/G-BA Beschlüsse

Es wurden keine relevanten Quellen identifiziert.

Cochrane Reviews

Es wurden keine relevanten Quellen identifiziert.

Systematische Reviews

Canadian Agency for Drugs and Technologies in Health (CADTH), 2015 [2].	1. Fragestellung 1. What is the clinical effectiveness of C1 esterase inhibitor as prophylaxis against hereditary angioedema attacks? (2. What is the cost-effectiveness of C1 esterase inhibitor as prophylaxis against hereditary angioedema attacks?) (3. What are the evidence-based guidelines for the prophylactic use of C1 esterase inhibitor in hereditary angioedema?)
C1 Esterase Inhibitor for Prophylaxis against Hereditary Angioedema Attacks: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines	2. Methodik Population: Patients with hereditary angioedema (HAE) Intervention: prophylactic C1 esterase inhibitor Komparator: Active comparators (e.g., on-demand C1 esterase inhibitor, Firazyr [icatibant], Kalbitor [ecallantide], Ruconest [C1 esterase inhibitor –recombinant], attenuated androgens [e.g., danazol, oxandrolone], tranexamic acid); Placebo; No treatment; No comparator Endpunkt: - Clinical effectiveness (e.g., symptom reduction/management, time to symptom relief) - Safety (e.g., anaphylaxis, headache, GI symptoms, thromboembolic events, increased pain associated with HAE attacks) Recherche: A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD), and ECRI databases, Canadian and major international health technology agencies, as well as a focused Internet search. The search was also limited to English language documents published between January 1, 2010 and March 24, 2015. Anzahl eingeschlossene Studien/Patienten (Gesamt): 12 publications (one systematic review[8], one crossover randomized controlled trial (RCT),[9] and nine non-randomized studies[10-18])

	Qualitätsbewertung der Studien: - systematic reviews: Assessment of Multiple Systematic Reviews (AMSTAR) tool, - randomized and non-randomized studies: Downs and Black checklist (Downs et al. J Epidemiol Community Health. 1998 Jun;52(6):377-84.) - guidelines: AGREE II instrument
	3. Ergebnisdarstellung Qualität der Studien: Overall, the included studies had major limitations, including small patient populations and lack of comparator data. Findings from the included studies must be interpreted with caution. (Details siehe Anhang) High quality systematic reviews and randomized controlled trials were lacking. <u>Findings from the Systematic Review[8]:</u> Meta-analysis was not possible. For long-term prophylaxis use, a reduction in symptom intensity was reported by one prospective cohort study, where 14 patients received C1-INH as LTP for an average of nine years (93.3% of attacks were considered severe without the use of prophylaxis, compared to 3.8% with prophylaxis). A decrease in attack frequency was reported by another prospective cohort study, where 15 out of 30 patients who before treatment had previously experienced one or two attacks per week did not report any HAE attacks while on LTP (C1-INH two to three times per week). A retrospective study reported no episodes of HAE for two pregnant patients (500 U of pdC1-INH administered intravenously, once per week). An additional five cases studies reported adequately controlled HAE with the use of LTP C1-INH. Based on the limited evidence, the study authors concluded that C1-INH was effective at reducing the severity and number of HAE attacks. <u>Findings from the Randomized Study[9]</u> - 24 patients, 22 completed (11 C1 inhibitor, 11 placebo) - normalized average number of attacks during 12 week period: 6.26 for C1 inhibitor, and 12.73 for placebo treatment. - mean severity of attacks: C1 inhibitor compared to placebo. 1.3 ± 0.85 vs. 1.9 ± 0.36, P < 0.001; on a three point scale with 1 indicating a mild attack, and 3 indicating a severe attack - duration of attacks: C1 inhibitor compared to placebo :2.1 ± 1.13

	vs. 3.4 ± 1.39 days, P = 0.002 - days of swelling C1 inhibitor compared to placebo: 10.1 ± 10.73 vs. 29.6 ± 16.9, respectively, P < 0.001 - rescue therapy for acute attacks: 11 patients on C1 inhibitor prophylaxis required an average of 4.7 injections compared to an average of 15.4 injections for 22 patients on placebo (P < 0.001) - Safety: 3 AEs were thought to be related to the study drug (lightheadedness, fever, and pruritus and rash) Summary on safety: Safety was also an outcome of interest for all studies, with one study[18] reporting adverse events (AEs) with an unknown relationship to C1-INH use, and one study[9] reporting AEs thought to be related to C1-INH use.[9] Major depression and musculoskeletal chest pain were reported AEs with an unknown relationship to the C1-INH use; lightheadedness, fever, and pruritus and rash were AEs thought to be related to C1-INH use.[9] A retrospective, post-hoc analysis of the RCT data for pediatric patients, reported two children with three AEs related to C1-INH use; these included nausea and headache, and infusion-site erythema.[15] Zuraw and Kalfus[18] reported serious AEs related to thromboembolic events, though there was no reported association with C1-INH use. Additionally, Busse et al.[10] reported two patients with thromboembolic events. References: 8. Bork K, Steffensen I, Machnig T. Treatment with C1-esterase inhibitor concentrate in type I or II hereditary angioedema: a systematic literature review. Allergy Asthma Proc. 2013 Jul;34(4):312-27. 9. Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. N Engl J Med. 2010 Aug 5;363(6):513-22. 10. Busse P, Bygum A, Edelman J, Lumry W, Machnig T, Martinez-Saguer I, et al. Safety of c1-esterase inhibitor in acute and prophylactic therapy of hereditary angioedema: findings from the ongoing international Berinert patient registry. J Allergy Clin Immunol Pract. 2015 Mar;3(2):213-9. 15. Lumry W, Manning ME, Hurewitz DS, Davis-Lorton M, Fitts D, Kalfus IN, et al. Nanofiltered C1-esterase inhibitor for the acute management and prevention of hereditary angioedema attacks due to C1-inhibitor deficiency in children. J Pediatr. 2013 May;162(5):1017-22. 18. Zuraw BL, Kalfus I. Safety and efficacy of prophylactic nanofiltered C1-inhibitor in hereditary angioedema. Am J Med. 2012 Sep;125(9):938-7.
	4. Anmerkungen/Fazit der Autoren According to the identified studies and guideline, the use of C1-INH for the prophylaxis of HAE attacks is clinically effective and relatively safe. This includes its use as a short-term prophylactic before surgical or invasive procedures, or as a long-term prophylaxis agent. This was found for patients of all ages, including vulnerable patient populations such as pregnant women. However, due to the lack of high quality data, and lack of comparator or control data, there are many limitations and the findings should be interpreted with caution. The prophylactic use of C1-INH in clinical practice may depend on a patient's disease history, including responses to other therapies, attack severity, attack frequency, and exposure to known HAE attack

	triggers (i.e., surgical procedures).

Leitlinien

Betschel, S. et al., 2014 [1]. Canadian hereditary angioedema guideline	Fragestellung/Zielsetzung: The objective of this guideline is to provide graded recommendations for the management of patients in Canada with HAE-1, HAE-2 and HAE-nC1INH. This includes the treatment of attacks, short-term prophylaxis, long-term prophylaxis, and recommendations for self-administration, individualized therapy, QoL, and comprehensive care.
	Methodik Grundlage der Leitlinie • Canadian Hereditary Angioedema Guideline Committee (national and international experts, patient representatives), Conflict of interests published • systematic search of Ovid MEDLINE (1946-October week 1, 2013): 11 relevant randomized control trials and 34 lower-quality comparative studies without blinding or randomization were identified and included • evidence tables for each intervention • development of draft recommendations, draft approval by Committee Members, • formal consensus process at Consensus Conference for wording of recommendations, LoE and GoR LoE /GoR • Each identified RCT was assessed by two reviewers for quality using the Cochrane Risk of Bias Tool • Non-randomized, non-blinded trials were considered to be Low quality evidence. • Levels of Evidence and Strength of Recommendation were adapted from the GRADE system
	Empfehlungen **Recommendation 14: Long-term prophylaxis may be appropriate for some patients to reduce frequency, duration and severity of attacks.** **Level of Evidence: High (100% Agree)** **Strength of Recommendation: Strong (100%)** **Recommendation 15: Attenuated androgens are effective for long-term prophylaxis in some patients.** **Level of Evidence: Moderate (92% Agree, 4% Disagree, 4% Abstain)** **Strength of Recommendation: Strong (90% Agree, 6%**

	Disagree, 4% Abstain) ***Clinical considerations*** Controlled trials (none was randomized) and observational studies have demonstrated that treatment with 17-alpha-alkylated anabolic androgens, such as danazol, reduces the frequency and severity of HAE attacks [55-60]. Androgens can affect serum lipid levels, can be hepatotoxic resulting in hepatitis and have been associated with hepatocellular adenoma and, in very rare cases, carcinoma [58,61,62]. Virilising effects of androgen therapy can occur and include menstrual irregularities, masculinization, irreversible voice alteration, and hirsutism. Psychological side effects include emotional irritability and lability, aggressive behaviour and depression. Androgens are associated with interactions with several medications. They are contraindicated in pregnancy and during lactation, before puberty, and in patients with androgen-dependent malignancy and hepatitis [61,62]. **Recommendation 16: Plasma-derived C1-INH is effective for long-term prophylaxis in some patients.** **Level of Evidence: High (100% Agree)** **Strength of Recommendation: Strong (100% Agree)** ***Clinical considerations*** Controlled clinical trials have demonstrated that pdC1-INH used for prophylaxis in HAE-1 and HAE-2 reduces the number, duration and severity of attacks of angioedema [27,29]. Side effects reported in trials with pdC1-INH are minimal and include pruritus and rash, light-headedness, fever and severe thrombosis (10 cases in three years (2008-2011) in FDA registry of drug related adverse events [63]. **Recommendation 17: Anti-fibrinolytics are effective for long-term prophylaxis in some patients.** **Level of Evidence: Moderate (96% Agree, 4% Disagree)** **Strength of Recommendation: Strong (86% Agree, 14% Disagree)** ***Clinical considerations*** The benefit of the anti-fibrinolytic agent tranexamic acid was demonstrated in a randomized placebo controlled trial with 18 subjects aged 12 years and over taking 1 g of tranexamic acid three times a day [65], and a double-blind crossover study of epsilonamino-caproic acid in 9 patients aged 7 to 40 years resulting in these agents

	being given a moderate level of evidence [66]. These data suggested that anti-fibrinolytic agents could be useful for LTP for HAE-1 and HAE-2. The role in current long-term prophylaxis was felt to be justified only in some patient groups due to the lack of efficacy and the potential side effects at the dosage studied. Although not specifically studied in paediatric patients, it was felt, due to the concern of using attenuated androgens in this patient demographic, that anti-fibrinolytic agents could be considered. **Recommendation 18: It is not necessary to fail other long-term prophylaxis therapies before use of pdC1-INH for long-term prophylaxis is considered.** **Level of Evidence: Expert Opinion (100% Agree)** **Strength of Recommendation: Strong (100% Agree)** ***Clinical considerations*** There is no recommended order or hierarchy for which therapies should be chosen for long-term prophylaxis. This should be based on the efficacy of the therapy, its side effects and safety, and the patient's preference. The participants were unanimous in their recommendation that should a patient require long-term prophylaxis they can be started on prophylactic pdC1-INH without need to be tried on other prophylactic therapies first. **Recommendation 19: There is insufficient evidence to make a recommendation for or against long-term prophylaxis for patients with HAE with normal C1-INH.** **Level of Evidence: Very Low (100% Agree)** **Strength of Recommendation: Insufficient Evidence (N/A)** There is some evidence that progesterone, anti-fibrinolytics and attenuated androgens may be efficacious in patients with HAE-nC1INH [12]. However, the data were of low quality and uniform recommendations could not be made regarding their use. References: 12. Bork K: Hereditary angioedema with normal C1 inhibitor. Immunol Allergy Clin N Am 2013, 33:457–470. 27. Waytes AT, Rosen FS, Frank MM: Treatment of hereditary angioedema with a vapor-heated C1-INH concentrate. N Engl J Med 1996, 334:1630–1634. 29. Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J: NanofilteredC1-INH concentrate for treatment of hereditary angioedema. N Engl J Med 2010, 363:513–522. 55. Gelfand JA, Sherins RJ, Alling DW, Frank MM: Treatment of hereditary angioedema with danazol.Reversal of clinical and biochemical abnormalities. N Engl J Med 1976, 23(295):1444–1448. 56. Hosea SW, Santaella ML, Brown EJ, Berger M, Katusha K, Frank MM: Long-term therapy of hereditary angioedema with danazol. Ann Intern Med 1980, 93:809–812. 57. Sheffer AL, Fearon DT, Austen KF: Clinical and biochemical effects of stanozolol therapy for hereditary angioedema. J Allergy Clin Immunol 1981, 68:181–187. 58. Cicardi M, Bergamaschini L, Cugno M, Hack E, Agostoni G, Agostoni A: Long-term treatment of hereditary angioedema with attenuated androgens: a survey of a 13-year experience. J Allergy Clin Immunol 1991, 87:768–773.

	59. Bork K, Bygum A, Hardt J: Benefits and risks of danazol in hereditary angioedema: a long-term survey of 118 patients. Ann Allergy Asthma Immunol 2008, 100:153–161. 60. Fust G, Farkas H, Csuka D, Varga L, Bork K: Long-term efficacy of danazol treatment in hereditary angioedema. Eur J Clin Invest 2011, 41:256–262. 61. Cicardi M, Castelli R, Zingale LC, Agostoni A: Side effects of long-term prophylaxis with attenuated androgens in hereditary angioedema: comparison of treated and untreated patients. J Allergy Clin Immunol 1997, 99:194–196. 62. Farkas H, Czaller I, Csuka D, Vas A, Valentin S, Varga L: The effect of long-term danazol prophylaxis on liver function in hereditary angioedema-a longitudinal study. Eur J Clin Pharmacol 2010, 66:419–426. 63. Gandhi PK, Gentry WM, Bottorff MB: Thrombotic events associated with C1 esterase inhibitor products in patients with hereditary angioedema: investigation from the United States Food and Drug Administration adverse event reporting system database. Pharmacotherapy 2012, 32:902–909. 65. Sheffer AL, Austen KF, Rosen FS: Tranexamic acid therapy in hereditary angioneurotic edema. N Engl J Med 1972, 287:452–454. 66. Gwynn CM: Therapy in hereditary angioneurotico edema. Arch Dis Child 1974, 49:636–640.
Craig T et al., 2012 [3]. **World Allergy Organization** WAO Guideline for the Management of Hereditary Angioedema	Fragestellung/Zielsetzung: The goal of this guideline is to provide clinicians and their patients with guidance for rational decisions in the management of HAE types 1 and 2 (HAE-1/2).
	Methodik Grundlage der Leitlinie - systematic searches of the MEDLINE and COCHRANE databases (January 1985 through September 2010) - Consensus Conference: expert group developed recommendations and agreed on the strength of these recommendations - International experts in HAE reviewed the Guidelines and provide feedback, suggestions and areas of dispute with the authors. - The guidelines were then reviewed by the official body of the WAO composed of the regional allergy societies. LoE A, Randomized, double-blind, clinical trial of high quality (eg, sample size calculation, flow chart of patient inclusion, intention-to-treat analysis, sufficient sample size); B, Randomized clinical trial of lesser quality (eg, only single blind and limited sample size: at least 15 patients per study arm); C, Comparative trial with severe methodological limitations (eg, not blinded, very small sample size, and no randomization) or large retrospective observational studies; D, Adapted from existing consensus document or statement based on expert opinion voting during consensus conference. GoR - strength of a recommendation followed the GRADE definition Sonstige methodische Hinweise

	A WAO/EAACI update of the Guideline is currently in development.
	Empfehlungen - Long-term prophylaxis of HAE refers to the use of regular medication to prevent episodes of angioedema in patients with confirmed HAE-1/2. Long-term prophylaxis should be considered in all severely symptomatic HAE-1/2 patients taking into consideration the severity of disease, frequency of attacks, patient's quality of life, availability of resources, and failure to achieve adequate control by appropriate on-demand therapy. - C1-INH concentrate or androgens can be used for long-term prophylaxis and the decision to use one over the other should depend upon contraindications, adverse events, risk factors for adverse effects, tolerance, response to intervention, and dose required to control attacks. None of the current prophylactic modalities are capable of preventing upper airway edema with certainty.[39,42,43,46,76] - Long-term prophylaxis with androgen derivatives is effective but must be regarded critically, especially on account of their androgenic and anabolic effects. ***Recommendation 11*** Before the initiation of long-term prophylaxis with androgens, measurements of complete blood count, urine analysis, liver function tests, lipid profile, assessment of cardiac risk factors, and liver ultrasound should be performed. While using androgens for long-term prophylaxis and for 6 months after stopping therapy, complete blood count, urine analysis, lipid panel, liver function tests, and blood pressure should be monitored every 6 months and an ultrasound of the liver should be done yearly to assess for adverse events associated with androgens and contraindications to androgens. Evidence grade: C, strength of recommendation: strong. - Antifibrinolytics are not recommended for long-term prophylaxis because data supporting their efficacy are lacking. Nevertheless, they are widely used especially when androgens are contraindicated and may anecdotally have some benefit in a minority of patients. Side effects are usually minor. They include gastrointestinal upsets (can be reduced by taking the drug with food), myalgia/creatine kinase elevation, and a theoretical risk of thrombosis. Contraindications/ precautions include presence of thrombophilia or increased thrombotic risk or acute thrombosis. References: 39. Bowen T, Cicardi M, Farkas H, Bork K, Kreuz W, et al. Canadian 2003 International Consensus Algorithm For the Diagnosis, Therapy, and Management of Hereditary Angioedema. J Allergy Clin Immunol. 2004;114:629–637. 42. Gompels MM, Lock RJ, Abinun M, Bethune CA, Davies G, et al. C1 inhibitor deficiency: consensus document. Clin Exp Immunol. 2005;139:379–394. 43. Bowen T, Cicardi M, Bork K, Zuraw B, Frank M, et al. Hereditary angiodema: a current state-of-the-art review, VII: Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. Ann Allergy Asthma Immunol.

	2008;100(suppl 2):S30–S40. 46. Bowen T, Cicardi M, Farkas H, Bork K, Longhurst HJ, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy Asthma Clin Immunol. 2010;6:24. 76. Caballero T, Baeza ML, Cabañas R, Campos A, Cimbollek S, et al. Consensus statement on the diagnosis, management, and treatment of angioedema mediated by bradykinin. Part II. Treatment, follow-up, and special situations. J Investig Allergol Clin Immunol. 2011;21:422–441; quiz 442–423.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 29.11.2017

#	Suchfrage
#1	MeSH descriptor: [Angioedema] explode all trees
#2	(angioedema* or angio next edema* or angiooedema* or angio next oedema* or Angioneurotic next Edema* or Angioneurotic next oedema* or giant next urticaria* or "HAE"):ti,ab,kw or (quincke* next edema* or quincke* next oedema):ti,ab,kw or (c1 and inhibitor* and deficienc*):ti,ab,kw (Word variations have been searched)
#3	#1 or #2
#4	#3 Publication Year from 2012 to 2017

SR, HTAs in Medline (PubMed) am 29.11.2017

#	Suchfrage
1	angioedema[MeSH Terms]
2	(((angioedema*[Title/Abstract] OR angio edema*[Title/Abstract] OR angiooedema*[Title/Abstract] OR angio oedema*[Title/Abstract] OR Angioneurotic Edema*[Title/Abstract] OR Angioneurotic oedema*[Title/Abstract] OR giant urticaria*[Title/Abstract] OR "HAE"[Title/Abstract])) OR (quincke*[Title/Abstract] AND edema*[Title/Abstract])) OR (quincke*[Title/Abstract] AND oedema*[Title/Abstract])
3	(C1[Title/Abstract] AND Inhibitor*[Title/Abstract] AND Deficienc*[Title/Abstract])
4	(#1 OR #2 OR #3)
5	(#4) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
6	(#4) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
7	#5 OR #6
8	(#7) AND ("2012/11/01"[PDAT] : "2017/11/29"[PDAT])
9	(#8) NOT "The Cochrane database of systematic reviews"[Journal]

Leitlinien in Medline (PubMed) am 29.11.2017

#	**Suchfrage**
1	angioedema[MeSH Terms]
2	(((angioedema*[Title/Abstract] OR angio edema*[Title/Abstract] OR angiooedema*[Title/Abstract] OR angio oedema*[Title/Abstract] OR Angioneurotic Edema*[Title/Abstract] OR Angioneurotic oedema*[Title/Abstract] OR giant urticaria*[Title/Abstract] OR "HAE"[Title/Abstract])) OR (quincke*[Title/Abstract] AND edema*[Title/Abstract])) OR (quincke*[Title/Abstract] AND oedema*[Title/Abstract])
3	(C1[Title/Abstract] AND Inhibitor*[Title/Abstract] AND Deficienc*[Title/Abstract])
4	(#1 OR #2 OR #3)
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title])
6	(#5) AND ("2012/11/01"[PDAT] : "2017/11/29"[PDAT])

Literatur

1. **Betschel S, Badiou J, Binkley K, Hebert J, Kanani A, Keith P, et al.** Canadian hereditary angioedema guideline. Allergy Asthma Clin Immunol 2014;10(1):50.

2. **Canadian Agency for Drugs and Technologies in Health (CADTH).** C1 esterase inhibitor for prophylaxis against hereditary angioedema attacks: a review of the clinical effectiveness, cost-effectiveness, and guidelines [online]. Ottawa (CAN): CADTH; 2015. [Zugriff: 29.11.2017]. (Rapid response report). URL: https://www.cadth.ca/sites/default/files/pdf/htis/apr-2015/RC0650%20Prophylactic%20C1%20Esterase%20Inhibitor%20Final.pdf.

3. **Craig T, Aygoren-Pursun E, Bork K, Bowen T, Boysen H, Farkas H, et al.** WAO guideline for the management of hereditary angioedema. World Allergy Organ J 2012;5(12):182-199.

Anhang

Canadian Agency for Drugs and Technologies in Health (CADTH), 2015 [2]: C1 Esterase Inhibitor for Prophylaxis against Hereditary Angioedema Attacks: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines

Table A4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[6]

Strengths	Limitations
Bork[8]	
• Clearly stated objectives and key research questions • Duplicate study selection and data extraction	• No meta-analysis was performed • No appraisal of included studies was provided • Uncertain generalizability to C1-INH products other than Berinert (CSL Behring, Marburg, Germany) • Unclear search strategy (no MESH terms provided) • There was no exploration into publication bias

C1-INH = C1 esterase inhibitor

Table A5: Strengths and Limitations of Randomized Controlled Trials using Downs and Black[5]

Strengths	Limitations
Zuraw[9]	
• Randomized, placebo-controlled trial, which allowed for comparison of C1-INH to a control group • Clearly stated objective, and primary outcomes	• Patients participating in the trial may not be representative of the source population, as inclusion criteria was a high frequency of HAE attacks • Findings may not be generalizable to the greater HAE population, as characteristics of patients participating in RCTs may differ from the other HAE patients • Possible confounding effect of baseline androgen therapy in 3/22 patients, with no further exploration in the main results • Uncertain blinding of patients and investigators

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; RCT = randomized-controlled trial

Table A6: Strengths and Limitations of Clinical Studies using Downs and Black[6]

Strengths	Limitations
Busse[10]	
• Clearly stated objective and main findings • Multicentre, multinational patient registry • Use of C1-INH by patients in the registry is likely reflective of clinical practice	• Non-comparative, non-randomized study • External validity may be limited as the patient population was not ethnically diverse • Included data collected retrospectively, and subject to biases (e.g., recall or reporting bias) • Patients participating in the registry may not be representative of the greater HAE population, and as such, the registry may be subject to selection bias

Table A6: Strengths and Limitations of Clinical Studies using Downs and Black[6]	
Strengths	**Limitations**
Nanda[11]	
• Clearly stated objectives and patient characteristics • Large survey of HAE patients	• Non-comparative, non-randomized study • HAE was self-reported and only the first 250 survey responses were included, this may subject the study to selection bias • Recall bias may interfere with responders answers • Definition of short term prophylactic failure is vague and questions regarding failure may be misinterpreted by responders
Gavigan[12]	
• Clearly stated objectives and primary outcomes • Clearly stated study intervention, including dosing of C1-INH	• Non-comparative, non-randomized study • Small number of patients • Retrospective design may include biases • Long duration of study, and variable doses, may not be representative of current practice and have limited generalizability • Possible confounding from a few patients with concomitant attenuated androgen use was not explored
Bernstein[13]	
• Clearly stated objective, primary outcomes, main findings, and adverse events • Patients were followed for the same length of time, and reasons for discontinuation of study participants was clearly reported	• Not powered to determine drug efficacy • Open-label, non-randomized study • Uncertain external validity as circumstances for drug administration (e.g. setting and dose) may not reflect clinical practice
Baker[14]	
• Clearly stated objectives and primary outcomes • Provided adequate justification for lack of control or comparator (e.g., unethical considering vulnerable patient population)	• Open-label, non-randomized study • Small number of patients • Lack of control group prevented any statistical analysis, descriptive statistics reported • Uncertain external validity for other pregnant patients, as these patients were part of studies with other primary objectives (not related to pregnancy)
Lumry[15]	
• Clearly stated objective, primary outcomes, and main findings • Provided adequate justification for lack of control or comparator (e.g., unethical considering vulnerable patient population)	• Post hoc analysis of previous clinical trial data, including open-label, non-randomized data • No comparison to placebo or other drugs • Uncertain external validity for other pediatric patients, as these patients were part of studies with other objectives (not related to pediatrics)

Table A6: Strengths and Limitations of Clinical Studies using Downs and Black[6]	
Strengths	**Limitations**
Farkas[16]	
• Clearly stated objective, and interventions • Comparison of intervention to other drugs	• Non-randomized • Uncertain patient recruitment, which may result in selection bias and limited generalizability to other HAE patients
Grant[17]	
• Clearly stated objectives and study outcomes	• Post hoc analysis of previous clinical trial data, including open-label, non-randomized data • No comparison to placebo or other drugs • Possible recall bias, as case report forms were filled out post hoc by physicians
Zuraw[18]	
• Large number of patients • Clearly stated objective, and primary outcomes	• Open-label, non-randomized study • No comparison to placebo or other drugs • Uncertain patient recruitment, which may result in selection bias and limited generalizability to other HAE patients

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema