

## Etanercept and headache

### Introduction

Etanercept is a Tumor Necrosis Factor alpha (TNF- $\alpha$ ) inhibitor and is indicated for *rheumatoid arthritis, juvenile idiopathic arthritis (JIA), psoriatic arthritis, axial spondyloarthritis* and *plaque psoriasis* [1]. TNF is a cytokine that naturally occurs in inflammatory processes. Etanercept inactivates TNF by binding to TNF. This inhibits binding of TNF to the TNF-receptor and prevents a TNF-mediated cellular response.

The innovator of etanercept (Enbrel®) was granted market authorization in the Netherlands in 2000. Three biosimilars were granted market authorization in the Netherlands: Benepali® in 2016, Erelzi® in 2017 and Lifmior® in 2017 [2-4].

Headache is a common complaint and can have many causes. The global prevalence of current headache disorder is 46% in the adult population and an estimated 25% to 75% of the adult population experiences a headache in one year [5-6]. Many subtypes of headache (e.g. migraine, tension headache, chronic headache, cluster headache) exist and headache can have many causes, including various underlying (neurologic) disorders, medication overuse and psychosocial factors [7].

### Reports

From 15 August 2000 to 1 November 2019 the Netherlands Pharmacovigilance Centre Lareb received 39 reports of headache (MedDRA HLT Headaches NEC) in association with the use of etanercept. Nine reports were received via the Dutch Biologic Monitor study, using Lareb Intensive Monitoring (LIM) [8] and thirty reports were spontaneous reports. A possible association with the moment of administration of etanercept was explicitly mentioned in 16 reports, including 7 LIM reports and 9 spontaneous reports. These reports are listed in table 1.

Table 1. Reports of headache associated with administration of etanercept

Patient, gender, age (years), source	Drug, dosage, indication	Concomitant medication	Comorbidities	Adverse drug reactions (Lower Level Term)	Latency after start, duration/course per administration, action taken with drug, outcome of adverse event
A: 053AC8C4-42E6-4C70-803A-B920BB697435, F, 60-70, consumer	Enbrel® and Benepali® (etanercept), dosage unknown, Rheumatoid arthritis	Methotrexate	Hypercholesterol emia Nervous system disorder	Headache Shoulder blade pain	- 32 months - Lasting 1 day after every administration, - Dose not changed, mentioned at specialist doctor and nurse - Not recovered
B: 1B4A9F23-D779-4CB1-B11B-A41390BC9899, F, 60-70, consumer	Enbrel® (etanercept), dosage unknown, Rheumatoid arthritis	Prednisone Sulfasalazine	Respiratory disorder	Headache Influenza like illness Sinusitis Gastrointestinal cramps	- 1.5 years - Lasting 1 - 3 days after every administration - Contact general practitioner and specialist doctor: Dose changed, treatment with fluticasone nasal spray, referral to ENT surgeon / own action: paracetamol and naproxen - Not recovered
C: 5343D280-6DC5-4F50-9121-E801E1FF3B77, M, 60-70, consumer	Enbrel® (etanercept), dosage unknown, Rheumatoid arthritis	Methotrexate	Cardiovascular disorder	Headache Injection site erythema	- 7 years - Lasting 1 day after every administration - Mentioned at general practitioner and specialist doctor / own action: paracetamol - Not recovered
D: 9C056A7E-71DA-4BB8-9633-89FBDDDB3CDA 4, F, 40-50, consumer	Enbrel® (etanercept), dosage unknown, Psoriatic arthritis and spondylitis peripheral	Prednisone		Headache Fatigue Burning leg	- Directly after start - Lasting several hours until 1 day after every administration - No contact HCP / no own action - Recovered
E: CF4B5A88-A3AF-468E-85D2-D3669CD606AD	Enbrel® (etanercept), dosage unknown, Rheumatoid arthritis		Hypercholesterol emia Psychiatric disorder	Headache Palpitations Sweating Shivering Stomach pain	- Directly after start - Lasting 2 days after administration

, F, 60-70, consumer				Diarrhea	- Mentioned at specialist doctor / own action: paracetamol - Not recovered
F: FBD0BC51-7951-4780-83C5-C8243815D299, F, 40-50, consumer	Enbrel® (etanercept), dosage unknown, Psoriatic arthritis			Headache	- 4 years - 2 – 3 times a month for several days - Contact general practitioner and chiropractor: treatment of neck by chiropractor / own action: paracetamol and naproxen - Aggravating
G: 9A813B29-6E0D-428E-B904-41ACD53F90A4, F, 60-70, consumer	Enbrel® (etanercept), dosage unknown, Rheumatoid arthritis	Prednisone Methotrexate	Thyroid disorder Chronic fatigue syndrome	Headache	- 4 months - Lasting 1 day after every administration - No contact HCP/ own action: paracetamol - Not recovered
H: NL-LRB-29126, F, 10-20, physician	Enbrel® (etanercept), 1 dosage form / 1 Weeks, Juvenile arthritis	Methotrexate Folic acid Nabumetone Omeprazole Lactulose Morphine		Headache	- 1 hour - Persisting and increasing after every administration - Dose reduced, methotrexate withdrawn, treatment with analgesics - Recovering
I: NL-PFIZER INC-2010180827, F, 50-60, physician via MAH	Enbrel® (etanercept), 50 milligram / 1 Weeks, Rheumatoid arthritis	Carbasalate calcium Atropine eyedrops Pantoprazole Omega-3-oil	Sjogren's syndrome	Headache Swelling of legs Injection site redness	- Directly after start - Occurred more than once - Dose not changed - Recovered
J: NL-PFIZER INC-2011028904, F, 60-70, physician via MAH	Enbrel® (etanercept), 50 milligram / 1 Weeks, indication unknown	Gabapentin Omeprazole Diclofenac/ Misoprostol Metoprolol Ursodeoxycholic acid		Headache Increased blood pressure	- 35 days - After second administration, occurred once - Dose not changed - Not recovered
K: NL-PFIZER INC-2011281372, F, 50-60, physician via MAH	Enbrel® (etanercept), 50 milligram / 1 Weeks, indication unknown	Diclofenac		Headache TIA Carotid artery stenosis Chest pressure Injection site reaction Nausea Tiredness	- 22 days - For 1 day after 4 <sup>th</sup> administration, lasted 2-5 days after following administrations - Drug withdrawn - Not recovered
L: NL-LRB-134677, M, 20-30, pharmacist	Enbrel® (etanercept), 100 milligram / 1 Weeks, Psoriasis			Headache Epistaxis	- 3 days - Started 2 hours after second administration - Action unknown, treatment with paracetamol - Recovered
M: NL-PFIZER INC-2013106668, F, 50-60, consumer via MAH	Enbrel® (etanercept), 50 milligram / 1 Weeks, Plaque psoriasis			Headache Erysipelas Elevated liver enzymes Bursitis Gingivitis Stomatitis	- Latency unknown - Flare up 1 day after administration - Dose not changed - Not recovered
N: NL-PFIZER INC-2013244670, F, 20-30, consumer via MAH	Enbrel® (etanercept), 50 milligram / 1 Weeks, indication unknown			Headache	- Latency unknown - Lasting several hours after administration - Dose not changed - Not recovered
O: NL-LRB-186567, M, 40-50, pharmacist	Enbrel® (etanercept), 50 milligram / 1 Weeks, Psoriatic arthritis	Duloxetine Spironolactone Omeprazole Metformin Isosorbide mononitrate Furosemide Ezetimibe Enalapril Alfuzosin Acetylsalicylic acid		Headache Injection site reaction Heavy feeling in arms & legs	- Latency unknown - Lasting 2 days after administration - Action unknown - Recovered

		Acetazolamide Beclometasone/Fo rmoterol Ciclesonide Liraglutide Naproxen Methotrexate Folic acid Betamethasone/C alciptriol Clobetasone Insulin glargine			
P: NL-PFIZER INC- 2018191690, M, 70 years and older, physician and consumer via MAH	Enbrel® (etanercept), 50 milligram / 1 Weeks, Rheumatoid arthritis	Venlafaxine Carvedilol Chlorthalidone Alprazolam		Headache recurrent Common cold Nose congestion Throat sore	- 1.5 years - Recurrent headaches - Dose not changed - Not recovered

Four cases involved males and twelve cases involved females. The age varied between 19 and 70 years old, with a mean age of 51 years and median of 54 years. Etanercept was used for rheumatoid arthritis in 7 cases, psoriatic arthritis in 2 cases, psoriasis in 2 cases, juvenile arthritis in 1 case, psoriatic arthritis and peripheral spondylitis in 1 case and the indication was unknown in 3 cases. The latency until the first episode of headache varied from directly after the first administration of etanercept until 7 years after start with etanercept. In 5 cases the first episode of headache occurred more than 1 year after start and in 3 cases the latency was unknown. In case A headache occurred during use of Enbrel® as well as biosimilar Benepali®. In 13 cases (A, B, C, D, E, G, H, J, K, L, M, N and O) headache occurred after at least one administration. In 8 cases (A, B, C, D, E, G, H, K) headache was recurrent and occurred after more than one administration. These patients recovered in between administrations in all cases except case H. Headache was persistent and aggravated after every administration in case H. Duration of headache was described in 13 cases (A, B, C, D, E, F, G, H, J, K, M, N, O) and lasted up to several days in all cases except case H. In cases F, I and P a recurrent headache was described without explicitly mentioning a relationship with administration. Paracetamol as treatment for headache was described in six cases (B, C, E, F, G and L), naproxen was mentioned in 2 cases (B and F) and analgesics were mentioned in case H. Treatment for tension headache by a chiropractor was described in case F. Methotrexate was mentioned as additional possible cause for headache in cases C and H. In case C methotrexate was usually administered at the same time as etanercept and in case H headache was reduced after withdrawal of methotrexate. In case B headache was first described as a recurrent headache that occurred for 2 days after every administration. The course of headache changed and later seemed related to sinusitis and influenza like illness, for which the patient was treated with fluticasone nasal spray. In 6 cases other reactions occurring at the same time as headache were described: nausea in case C, palpitations, hyperhidrosis and chills in case E, feeling hungover in case D, increased blood pressure in case J, transient ischaemic attacks and carotid artery stenosis in case K and common cold in case P. Comorbidities that could possibly be associated with headache were reported in case A, E, G and I.

The dose of etanercept was adjusted in case B (reduced frequency of administrations because of other reasons) and case H (dose reduced). Etanercept was withdrawn for other reasons in case G and temporarily discontinued in case K. No action with etanercept was taken in 10 cases (A, C, D, E, F, I, J, M, N and P) and the action was unknown in cases L and O. The patient recovered or was recovering from headache at the moment of reporting in 4 cases (D, I, L and O). The patient had not recovered from headache at the moment of reporting in 11 cases (A, B, C, E, F, G, J, K, M, N, P). Headache was aggravating in case F. The outcome is unknown in case H.

## Other sources of information

### SmPC

Headache is mentioned in the Dutch SmPCs of etanercept as a possible adverse drug reaction that occurred in clinical trials in pediatric patients with juvenile idiopathic arthritis but not with other indications [1-4]. Besides injection site reactions, no administration related reactions are mentioned.

Headache is a labelled adverse drug reaction in the Dutch SmPCs of the other TNF- $\alpha$  inhibitors: adalimumab, infliximab, golimumab and certolizumab pegol [9-12]. In the SmPC of infliximab, headache is also described as a symptom of a delayed hypersensitivity reaction which can occur up to 12 days after administration. Other symptoms of such a hypersensitivity reaction are myalgia, pyrexia, arthralgia and throat pain.

### Literature

There is little information about the occurrence of headache in relation to the use of etanercept. Headaches have been observed in clinical trials but not with higher incidence than in patients receiving placebo [13].

### Mechanism

Headache related to administration of etanercept could be part of an immediate reaction due to massive cytokine release of IL-1b, TNF- $\alpha$ , IFN- $\beta$ , IFN- $\gamma$ , IL-6 and IL-8. This could be a result of activation of various immune cells (including macrophages, monocytes, lymphocytes and natural killer cells) by receptor stimulation, antibody-dependent cell-mediated cytotoxicity, complement-mediated cytotoxicity or apoptosis. Common symptoms of these pro-inflammatory cytokine release reactions include headache, rash, fatigue, fever, myalgia, chills, nausea and diarrhoea. These reactions often occur after the first administration of biologics [14]. In some of the cases reported to Lareb, some of these other symptoms occurred at the same time as headache.

### Databases

Table 2. Reports of PT Headache associated with etanercept in the Lareb, WHO and Eudravigilance database [15-16].

Database	Drug	Number of reports	ROR (95% CI)
Lareb <sup>1</sup>	Etanercept	30	0.2 (0.17 – 0.35)
WHO	Etanercept	18,048	0.98 (0.96 – 0.99)
Eudravigilance	Etanercept	9,122	1.25 (1.22 – 1.27)

1. Lareb database of spontaneous reports, excluding Lareb intensive monitoring

### Prescription data

Table 3. Number of patients using etanercept in the Netherlands between 2014 and 2019 [17].

Drug	2014	2015	2016	2017	2018
Etanercept	14,265	14,695	15,469	16,035	16,573

### Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 39 cases (30 spontaneous and 9 via Lareb Intensive Monitoring) of headache in association with the use of etanercept and 16 cases indicate that headache was related to the moment of administration. Headache was recurrent in 3 cases and occurred after one or more administrations of etanercept in 13 cases. In 15 cases the patient recovered from headache within several days and in 1 case headache persisted and aggravated after every administration of etanercept. The association between headache and etanercept is disproportionately present in the Eudravigilance database, but not in the WHO and Lareb database.

Literature supporting headache related to etanercept is sparse. Headache is mentioned in the SmPC of etanercept in paediatric patients with juvenile idiopathic arthritis. However, the reports received by Lareb did not include paediatric patients and only one patient used etanercept for juvenile idiopathic arthritis. Headache is labelled in the SmPCs of all other TNF- $\alpha$  inhibitors and could be part of an immediate reaction due to massive cytokine release. However, headache or migraine can also be a manifestation of central nervous system involvement in systemic autoimmune diseases [18]. Additionally, other conditions such as comorbidities and other adverse events could contribute to the manifestation of headache.

Headache can have many causes and therefore, a relationship with etanercept can be easily overlooked. Despite a long latency after start in several cases, many reports received by Lareb indicate a correlation between headache and the moment of administration of etanercept, the association of headache and etanercept should be further investigated.

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*This signal has been raised on January 15, 2020. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB [www.cbg-meb.nl](http://www.cbg-meb.nl)*