

## Desloratadine and depressed mood & depression

### Introduction

Desloratadine (Aerius®) is a histamine antagonist, selective for peripheral H1-receptors. It is indicated for *the relief of symptoms associated with allergic rhinitis and urticaria*. [1] Antihistamines can be divided into two generations, the first and second generation. Antihistamines of the first generation are lipophilic and easily cross the blood-brain barrier into the central nervous system, causing central nervous system effects like sedation. Desloratadine belongs to the second generation antihistamines. Drugs of this generation are more lipophobic than the antihistamines of the first generation. They cross the blood-brain barrier to a minimal extent and cause little if any sedation. [2] Desloratadine has been registered in the Netherlands since 2001 [1].

Depression is a common mental disorder with a life-time prevalence ranging from 20-25% in women and 7-12% in men [3]. It is defined as feelings of depressed mood or loss of interest present for at least two weeks, in combination with at least four of the following symptoms: appetite changes, difficulty sleeping, psychomotor agitation or retardation, fatigue or loss of energy, poor concentration, suicidal ideation and feelings of worthlessness or guilt [4]. At the Pharmacovigilance Centre Lareb, "depression" reported by a consumer is coded as "depression" when the patient uses antidepressants or it is mentioned the diagnosis is confirmed by a health professional. Otherwise, the reaction will be coded as "depressed mood".

Some drugs have been associated with inducing depression, including isotretinoin, beta blockers, calcium channel blockers, alpha interferons, corticosteroids and angiotensin converting enzyme (ACE) inhibitors. A causal relationship is often difficult to establish and good quality evidence of drug-induced depression is generally lacking [5].

### Reports

In the period from June 3<sup>rd</sup> 2004 until May 9<sup>th</sup> 2020, the Netherlands Pharmacovigilance Centre Lareb received 15 reports on depressed mood disorders associated with the use of desloratadine. Reports with the following PT's were included: depression (5 reports) and depressed mood (10 reports).

Table 1. Reports of depression and depressed mood associated with the use of desloratadine

Case	ID, sex, age, primary source	Drug	Dosage	Indication	Concomitant medication	Reported ADRs	Latency after start	Action taken	Outcome
1	NL-LRB-91176, female, 30-40 Years, Consumer or other non health professional	Desloratadine Tablet 5mg	5 mg / 1 Days	Hay fever	-	Depressed mood, Dyspepsia, Anxiety	5 Days 12 Hours 5 Days	Drug Withdrawn	Recovered Recovered Recovered
2	NL-LRB-100001, female, 30-40 Years, Consumer or other non health professional	Desloratadine Tablet 5mg	5 mg / 1 Days	Skin disorder	Lamotrigine Diclofenac Naproxen	Depressed mood	Unknown, the reaction occurred after withdrawal	-	Recovered
3	NL-LRB-127001, female, 30-40 Years, Pharmacist	Desloratadine Tablet 5Mg	5 mg / 1 Days	Dermatitis allergic	Desoximetasone	Somnolence, Fatigue, Depressed mood, Listlessness	1 Days 1 Days 1 Days 1 Days	Drug Withdrawn	Recovered Recovered Recovered Recovered
4	NL-LRB-188268, male, 2-4 Years, Consumer or other non health professional	Desloratadine 0,5mg/ml	1 dosage form / 1 Days	Asthma	Salmeterol/ Fluticasone	Agitation, Hyperactivity, Depressed mood	A few days	Drug Withdrawn	Recovering Recovering Recovering
5	NL-LRB-197503, female, 10-20 Years, Consumer	Desloratadine Tablet 5mg	5 mg / 1 Days	Hay fever	Hydroxychloroquine	Depressed mood	2 Days	Drug Withdrawn	Recovered

	or other non health professional				Ibuprofen Omeprazole Methylphenidate				
6	NL-LRB-206014, male, 40-50 Years, Consumer or other non health professional	Desloratadine Tablet 5mg	10 mg / 1 Days	Hay fever	-	Depressed mood	12 Hours	Drug Withdrawn	Recovered
7	NL-LRB-223791, male, 50-60 Years, Physician	Desloratadine Tablet 5mg	5 mg / 1 Days	Rhinitis	Budesonide	Depressed mood	3 Days	Drug Withdrawn	Recovered
8	NL-LRB-00283930, male, 10-20 Years, Physician	Desloratadine Tablet 5mg	5 mg / 1 Days	Hay fever	Beclometasone Salbutamol	Sleeplessness, Depressed mood	3 Days 3 Days	Drug Withdrawn	Recovered Recovered
9	NL-LRB-00348735, female, 30-40 Years, Consumer or other non health professional	Desloratadine Tablet 5mg	1 dosage form / 6 Hours	Urticaria	-	Depressed mood	4 Days	Dose Reduced	Not Recovered
10	NL-LRB-00394013, female, 40-50 Years, Consumer or other non health professional	Desloratadine Tablet 5mg	5 mg / 1 Days	Hay fever	Levothyroxine	Suicidal ideation, Depressed mood, Somnolence, Lethargy	Unknown	Drug Withdrawn	Recovered Recovered Recovered
11	NL-LRB-44472, female, 70 Years and older, Pharmacist	Desloratadine Tablet 5mg  Xylometazolin i Hcl	5 mg	Sinusitis	-	Agitation, Depressed state	A few hours	Drug Withdrawn,  Drug Withdrawn	Recovered Recovered
12	NL-LRB-57755, female, 40-50 Years, Pharmacist	Desloratadine Tablet 5Mg	5 mg / 1 Days	Hay fever	Loratadine Levocabastine	Depressed state	-	Drug Withdrawn	Recovered
13	NL-LRB-151276, female, 10-20 Years, Pharmacist	Desloratadine Tablet 5Mg	5 mg / 1 Days	Allergy	-	Depression, Fatigue, Headache	1 Years 1 Years 1 Years	Drug Withdrawn	Recovered Recovered Recovered
14	NL-LRB-212883, male, 70 Years and older, Consumer or other non health professional	Desloratadine Tablet 5Mg  Citalopram Tablet 20Mg	10 mg / 1 Days  20 mg / 1 Days	Pruritus Depression	-	Depression aggravated, Drug interaction	1 Days 1 Days 1 Days	Drug Withdrawn  Not Applicable	Recovered Recovered
15	NL-009507513-1910NLD010241, male, , Consumer or other non health professional	Montelukast 4mg  Mometason 50Mcg/Do 140Do  Desloratadine Tablet 5 mg  Salmeterol/ fluticason Diskus 50/500Mcg 60Do		Product used for unknown indication	-	Affective disorder, Depression, Sleepiness, Suicidal ideation	Unknown	Drug Withdrawn Unknown Unknown	Unknown Unknown Unknown

Additional information in the cases:

Case 1: The patient recovered a few days after withdrawal. A positive rechallenge was performed. The patient has no known medical history.

Case 2: The reporter mentioned the complaints started after the withdrawal of desloratadine. The patient has depression in his medical history.

Case 3: The patient has no known medical history. The reaction was not treated.

Case 4: The reaction started a few days after start. The patient was not treated for the depressed mood. The patient has no known medical history.

Case 5: The patient recovered one day after the withdrawal. The patient has no known medical history.

Case 6: A positive rechallenge was performed. The patient has no known medical history.

Case 7: The patient recovered a few days after the withdrawal. The patient has no known medical history.

Case 8: The patient mentioned the reaction starts every time she uses desloratadine for a few days. A few days after the withdrawal it gets better. Recovery time is a few days. The patient has no known medical history.

Case 9: The patient has no known medical history.

Case 10: In four days she started to feel depressed and got suicidal thoughts. The patient mentioned she did not experience these reactions before. She recovered 48 hours after the withdrawal.

Case 11: The reactions started a few hours after start and she recovered a few weeks after the withdrawal. The patient has no known medical history.

Case 12: The patient has no known medical history. The reaction was not treated.

Case 13: The patient went to a psychologist to treat the depression. After withdrawal, this treatment was not necessary anymore. The patient has no known medical history.

Case 14: The patient uses citalopram for a depression. The patient suspects an interaction between desloratadine and citalopram. His depression got worse after starting desloratadine.

Case 15: The patient contacted the suicide prevention phone line. It was mentioned that the patient had experience with depression in the past.

## Other sources of information

### *SmPC*

The Dutch summary of product characteristics (SmPC) of desloratadine mentions abnormal behavior as an adverse reaction. It does not specifically mention mood disorders [1]. The USA product label mentions that in clinical trials emotional lability was reported in 3.1% of the patients in the subgroup between 12 months and 23 months of age, compared with 0% in the placebo group [6].

Depression is mentioned in the Dutch SmPC of some of the other histamines of the second generation (levocetirizine, cetirizine and mizolastine) [7, 8, 9].

### *Literature*

A few studies have been conducted examining the safety of desloratadine. Layton et al. monitored the safety of desloratadine in 11,828 patients. Data were retrospectively collected by general practitioners via questionnaires. Sixteen patients reported experiencing depression in the first month of observation [10].

In 2013 a review of the published literature regarding the safety of desloratadine in the treatment of allergic rhinitis was performed. They concluded desloratadine does not cross the blood-brain barrier, thereby causing minimal sedation or other effects on the central nervous system [11].

In a study with eight healthy volunteers, the binding of desloratadine to H1-receptors in the brain was determined. The volunteers underwent PET imaging after a single dose of desloratadine, loratadine or placebo. The H1-receptor binding potential ratio of desloratadine did not significantly differ from placebo. They concluded that the amount of desloratadine penetrating the blood-brain barrier is too small to cause sedation and cognitive impairment [12].

In 2018 a drug safety signal was published based on a signal detection workshop with the Uppsala Monitoring Centre and the Netherlands Pharmacovigilance Centre Lareb. Forty-nine cases of depression or depressed mood related to desloratadine use were detected and analyzed from the WHO database. The median latency time was three days. Thirty patients were recovering or recovered after withdrawal of desloratadine. In five cases the reaction recurred after re-administration. Other possible causes for the depression were reported in some cases. Six patients reported at least one other suspect drug, twelve patients used concomitant medication with depression mentioned in the SmPC, one patient reported to have a history with depression and two with hypothyroidism, and five patients used an antidepressive drug. The concomitant medications were however not suspected by the reporters to have caused the depression. Suicidal ideation, thoughts of self-harm or suicide attempt were co-reported in six cases [13].

In the literature a possible relation between allergic disorders and depression has been suggested. However, some studies showed conflicting results. More research is necessary to confirm this association [14].

#### Other databases

Table 2. Reports of depression and depressed mood in the Lareb, Eudravigilance and WHO database [15, 16, 17]

Database	Drug	Preferred terms	Number of reports	ROR (95% CI)
Lareb	Desloratadine	Depression	5	1.2 [0.5-2.9]
	Desloratadine	Depressed mood	10	2.0 [1.1-3.7]
Eudravigilance	Desloratadine	Depression	37	1.0 [0.7-1.4]
	Desloratadine	Depressed mood	25	2.7 [1.8-4.0]
WHO Vigibase	Desloratadine	Depression	57	1.0 [0.8-1.3]
	Desloratadine	Depressed mood	28	2.5 [1.7-3.6]

#### Prescription data

Table 3. Number of patients using desloratadine in the Netherlands between 2015 and 2019 [18].

Drug	2015	2016	2017	2018	2019
R06AX27 Desloratadine	612,540	652,110	627,560	687,890	701,120

#### Mechanism

Although the exact mechanism of desloratadine-induced depression is unclear, it has been shown that histamine plays an important role in many physiological functions in the brain like regulation of sleep, appetite, memory, learning and emotions. It works as neurotransmitter acting on H<sub>1-4</sub> receptors. [19,20].

Kano et al. examined the cerebral histamine H<sub>1</sub> receptor binding in 10 patients with depression and 10 age-matched subjects. The study showed that decreased brain H<sub>1</sub> receptor binding correlates with severity of depression, suggesting an important role of the histaminergic neuron system in the pathophysiology of depression [20].

#### Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 15 reports of depression or depressed mood associated with the use of desloratadine. In two cases suicidal ideation was co-reported. A positive dechallenge was reported 11 times. In most of the cases the reaction started a few days after start, but varied between several hours to one year. Recovery time was in most of the cases a few days after withdrawal. A positive rechallenge was reported in two cases. Four patients reported depressed mood/depression in combination with suicidal thoughts or thoughts of self-harm. In three cases there was co-medication reported with depression mentioned in the Dutch SmPC. In two of these cases however, the time course of the reaction suggests an association with the use of desloratadine. Besides, these drugs were not suspected by the reporter to have caused the depression. In two reports a history with depression was reported. It is unknown if the depression reported in the cases reflects a depression according to the DSM-5 criteria.

The Dutch SmPC does not mention mood disturbances. In clinical trials emotional lability was reported in 3.1% of the cases in children between 12 months and 23 months of age. Emotional lability is mentioned as an adverse drug reaction in the USA product label [6].

The exact mechanism of desloratadine-induced depression is unclear but it has been shown that histamine plays an important role in the brain in regulating emotions. Although some studies showed it is unlikely that desloratadine does penetrate the central nervous system, effects like abnormal behaviour, hallucinations and aggression are listed in the Dutch SmPC of desloratadine. This indicates that it cannot be fully excluded that some extent of desloratadine passes the blood-brain barrier, leading to central nervous system effects like depression.

Desloratadine is a commonly used drug, used in all age categories, sometimes in high doses. Fifteen reports of depression or depressed mood in the past 16 years is relatively few. Some people are possibly more susceptible to experience depressive symptoms associated with the use of desloratadine than others. A possible relation between allergic rhinitis and depression has also been suggested in the literature and cannot be ruled out as possible cause. Because depression or depressed mood can have a great impact on the patient's daily life, attention for this association is warranted.

#### References

1. Dutch SmPC (Aerius®). [cited: 25-08-2020]. Available from: [https://www.ema.europa.eu/en/documents/product-information/aerius-epar-product-information\\_nl.pdf](https://www.ema.europa.eu/en/documents/product-information/aerius-epar-product-information_nl.pdf).
2. Simons FE, Simons KJ. H1 antihistamines: current status and future directions. World Allergy Organ J. 2008 Sep;1(9):145-55.
3. Wang J, Wu X, Lai W, Long E, Zhang X, et al. Prevalence of depression and depressive symptoms among outpatients: a systematic review and meta-analysis. BMJ Open. 2017 Aug 23;7(8):e017173.
4. Tolentino JC, Schmidt SL. DSM-5 Criteria and Depression Severity: Implications for Clinical Practice. Front Psychiatry. 2018 Oct 2;9:450.
5. Rogers D, et al. General medical with depression drugs associated. Psychiatry (Edgmont). 2008.
6. USA SmPC (Clarinet®). [cited: 25-08-2020]. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/021165s017,021300s014,021312s015,021563s003lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021165s017,021300s014,021312s015,021563s003lbl.pdf).
7. Dutch SmPC (Xyzal®). [cited: 07-09-2020]. Available from: [https://www.geneesmiddeleninformatiebank.nl/smpc/h26770\\_smpc.pdf](https://www.geneesmiddeleninformatiebank.nl/smpc/h26770_smpc.pdf).
8. Dutch SmPC (Zyrtec®). [cited: 07-09-2020]. Available from: [https://www.geneesmiddeleninformatiebank.nl/smpc/h13010\\_smpc.pdf](https://www.geneesmiddeleninformatiebank.nl/smpc/h13010_smpc.pdf).
9. Dutch SmPC (Mizollen®). [cited: 07-09-2020]. Available from: [https://www.geneesmiddeleninformatiebank.nl/smpc/h19982\\_smpc.pdf](https://www.geneesmiddeleninformatiebank.nl/smpc/h19982_smpc.pdf).
10. Layton D, Wilton L, Shakir SA. Examining the tolerability of the non-sedating antihistamine desloratadine: a prescription-event monitoring study in England. Drug Saf. 2009;32(2):169-79.
11. González-Núñez V, Valero A, Mullol J. Safety evaluation of desloratadine in allergic rhinitis. Expert Opin Drug Saf. 2013 May;12(3):445-53.
12. Nakamura T, Hiraoka K, Harada R, Matsuzawa T, Ishikawa Y, et al. Brain histamine H(1) receptor occupancy after oral administration of desloratadine and loratadine. Pharmacol Res Perspect. 2019 Jul 12;7(4):e00499.
13. Boer J, Ederveen E, Grundmark B. Desloratadine and depression, a drug safety signal based on worldwide spontaneous reporting of side effects. Ups J Med Sci. 2018 Sep;123(3):174-178.
14. Roxbury CR, Qiu M, Shargorodsky J, Woodard TD, Sindwani R, Lin SY. Association Between Rhinitis and Depression in United States Adults. J Allergy Clin Immunol Pract. 2019 Jul-Aug;7(6):2013-2020.
15. Netherlands Pharmacovigilance Centre Lareb Database [Internet]. [cited 25-08-2020].
16. Eudravigilance database [Internet]. European Medicines Agency. 2020 [cited 27-08-2020]. Available from: <http://bi.eudra.org> (access restricted).
17. WHO Global Individual Case Safety Reports database (Vigilyze) [Internet]. 2020 [cited 25-08-2020]. Available from: <https://tools.who-umc.org/webroot/> (access restricted).
18. GIPdatabase - Drug Information System of the Dutch Health Care Insurance Board [Internet]. 2019 [cited 1-9-2020]. Available from: <https://www.gipdatatabank.nl/>.
19. Haas H, Panula P. The role of histamine and the tuberomammillary nucleus in the nervous system. Nat Rev Neurosci. 2003 Feb;4(2):121-30.
20. Kano M, Fukudo S, Tashiro A, Utsumi A, Tamura D, et al. Decreased histamine H1 receptor binding in the brain of depressed patients. Eur J Neurosci. 2004 Aug;20(3):803-10.

*This signal has been raised on October 22, 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.cbq-meb.nl](http://www.cbq-meb.nl)*