ATIVAN®
(LORAZEPAM)

1. NAME OF THE MEDICINAL PRODUCT

ATIVAN®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablet contains 1.0 mg or 2.0 mg of lorazepam.

3. PHARMACEUTICAL FORM

Oral Tablets

DESCRIPTION

Active ingredients, active moieties

Lorazepam (INN)

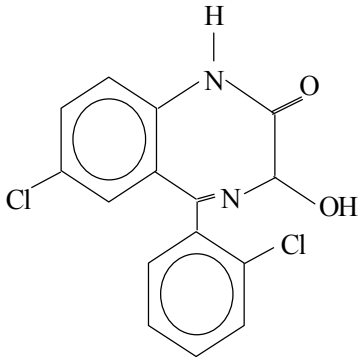
Lorazepam is a white or almost white, almost odorless crystalline powder.

Practically insoluble in water; sparingly soluble in alcohol; slightly soluble in chloroform; sparingly or slightly soluble in dichloromethane.

Chemical name

7-chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one.

Structure



Molecular formula

$C_{15}H_{10}Cl_2N_20_2$

Molecular weight

321.2

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

- Short-term management of anxiety disorders, including the following:
  - Short-term relief of symptoms of anxiety
  - Generalized anxiety disorders
  - Anxiety in psychotic states
  - Anxiety associated with somatic symptoms
  - Anxiety associated with depression or depressive symptoms
  - Reactive anxiety
- Insomnia associated with anxiety
- Alcohol withdrawal
- Prevention of delirium tremens
- Surgical premedication
- Adjunctive therapy to standard antiemetic drugs for the prophylactic and symptomatic treatment of nausea and vomiting associated with cancer chemotherapy

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Dosage and duration of therapy should be individualized. The lowest effective dose should be prescribed for the shortest duration possible. The risk of withdrawal and rebound phenomena is greater after abrupt discontinuation; therefore, the drug should be discontinued gradually (See section **4.4. Special warnings and precautions for use**).

Extension of the treatment period should not take place without re-evaluation of the need for continued therapy.

The recommended dosage range is 2 to 6 mg/day, but the daily dosage may vary from 1 to 10 mg/day.

Increases in the dosage of lorazepam should be made gradually to help avoid adverse effects. The evening dose should be increased before the daytime doses.

Short-term management of anxiety disorders

The initial recommended dose is 2 to 3 mg/day, in divided doses 2 or 3 times daily.

Insomnia associated with anxiety

The recommended dose is 0.5 mg to 4 mg/day, at bedtime.

Alcohol withdrawal

The initial recommended dose is 2 to 3 mg/day, in divided doses 2 or 3 times daily.

Prevention of delirium tremens

The initial recommended dose is 2 to 3 mg/day, in divided doses 2 or 3 times daily.

Surgical premedication

The recommended dosage is 2 to 4 mg the night before a procedure and/or 1 - 2 hours pre-procedure.

Adjunctive therapy to standard antiemetic drugs for the prophylactic and symptomatic treatment of nausea and vomiting associated with cancer chemotherapy

The recommended dosage is 1 mg at bedtime the night before chemotherapy and/or 1 mg given 60 minutes prior to chemotherapy, and repeated 6 hours and 12 hours after chemotherapy, if needed.

Elderly and debilitated patients

For elderly and debilitated patients, reduce the initial dose by approximately 50% and adjust the dosage as needed and tolerated.

Use in patients with hepatic impairment

Dosage for patients with severe hepatic insufficiency should be adjusted carefully according to patient's response. Lower doses may be sufficient in such patients. See section **4.4. Special warnings and precautions for use.**

Use in patients with renal impairment

No specific dosage recommendations. See section **5.2. Pharmacokinetic properties.**

Use in pediatric patients

Information not available

4.3. CONTRAINDICATIONS

Hypersensitivity to benzodiazepines or to any components of the formulation.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use of benzodiazepines, including lorazepam, may lead to potentially fatal respiratory depression.

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required.[93]

The use of benzodiazepines, including lorazepam, may lead to physical and psychological dependence (See section **4.10. Abuse and dependence**).

Severe anaphylactic/anaphylactoid reactions have been reported with the use of benzodiazepines. Cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of benzodiazepines. Some patients taking benzodiazepines have had additional symptoms such as dyspnea, throat closing, or nausea and vomiting. Some patients have required medical therapy in the emergency department. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with a benzodiazepine should not be rechallenged with the drug.[1]

Ativan® (lorazepam) should be used with caution in patients with compromised respiratory function (e.g., COPD, sleep apnea syndrome).[2]

Pre-existing depression may emerge or worsen during use of benzodiazepines, including lorazepam.

The use of benzodiazepines may unmask suicidal tendencies in depressed patients and should not be used without adequate antidepressant therapy.

Elderly or debilitated patients may be more susceptible to the effects of lorazepam; therefore, these patients should be monitored frequently and have their dosage adjusted carefully according to patient response (See section **4.2. Posology and method of administration**).

Paradoxical reactions have been occasionally reported during benzodiazepine use (See section **4.8. Adverse reactions**).[3]

Such reactions may be more likely to occur in children and the elderly. Should these occur, use of the drug should be discontinued.

Use in patients with hepatic impairment

As with all benzodiazepines, the use of lorazepam may worsen hepatic encephalopathy; therefore, lorazepam should be used with caution in patients with severe hepatic insufficiency and/or encephalopathy.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The benzodiazepines, including lorazepam, produce additive central nervous system (CNS) depressant effects, including respiratory depression, when co-administered with other CNS depressants such as opioids, alcohol, barbiturates, antipsychotics, sedative/hypnotics, anxiolytics, antidepressants, narcotic analgesics, sedative antihistamines, anticonvulsants, and anesthetics (See section **4.4. Special warnings and precautions for use**).[93]

Concomitant use of clozapine and lorazepam may produce marked sedation, excessive salivation, and ataxia.[10,11]

Concurrent administration of lorazepam with valproate may result in increased plasma concentrations and reduced clearance of lorazepam.[12,13] Lorazepam dosage should be reduced to approximately 50% when co-administered with valproate.

Concurrent administration of lorazepam with probenecid may result in a more rapid onset or prolonged effect of lorazepam due to increased half-life and decreased total clearance.[14] Lorazepam dosage needs to be reduced by approximately 50% when co-administered with probenecid.

Administration of theophylline or aminophylline may reduce the sedative effects of benzodiazepines, including lorazepam.[15,16,17]

4.6. FERTILITY, PREGNANCY AND LACTATION

Ativan® (lorazepam) should not be used during pregnancy.

An increased risk of congenital malformations associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested in several studies.[4] In humans, umbilical cord blood samples indicate placental transfer of benzodiazepines and their glucuronide metabolites.[5] Infants of mothers who ingested benzodiazepines for several weeks or more preceding delivery have been reported to have withdrawal symptoms during the postnatal period. Symptoms such as hypoactivity, hypotonia, hypothermia, respiratory depression, apnea, feeding problems, and impaired metabolic response to cold

stress have been reported in neonates born of mothers who have received benzodiazepines during the late phase of pregnancy or at delivery.[6]

Lorazepam has been detected in human breast milk[Error! Bookmark not defined.6,7]; therefore, it should not be administered to breast-feeding women, unless the expected benefit to the woman outweighs the potential risk to the infant.[8]

Sedation and inability to suckle have occurred in neonates of lactating mothers taking benzodiazepines.[9] Infants of lactating mothers should be observed for pharmacological effects (including sedation and irritability).

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

As with all patients on CNS-acting drugs, patients should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from lorazepam.

4.8. UNDESIRABLE EFFECTS

Adverse Drug Reaction Table

System Organ Class	Adverse Drug Reactions
Blood and lymphatic system disorders	Agranulocytosis,[43] pancytopenia,[44] thrombocytopenia[42]
Immune system disorders	Anaphylactic/oid reactions,[34] hypersensitivity reactions[33]
Endocrine disorders	SIADH[35]
Metabolism and nutrition disorders	Hyponatremia[36]
Psychiatric disorders	Suicidal ideation/attempt,[53] euphoria,[51] paradoxical reactions, including anxiety,[45,56] agitation,[57] excitation,[58] hostility,[59] aggression,[60] rage,[60] disinhibition,[50] confusion,[66] depression, unmasking of depression, change in libido,[61] decreased orgasm,[68] sleep disturbances/insomnia, sexual arousal,[61] hallucinations[62]
Nervous system disorders±	Coma,[52] convulsions/seizures,[49] sedation,[63] drowsiness,[63] ataxia,[65] dizziness, extrapyramidal symptoms,[45] tremor,[46] dysarthria/slurred speech,[48] headache, amnesia, impaired attention/concentration,[54] balance disorder[55]
Eye disorders	Visual disturbances (including diplopia and blurred vision)
Ear and labyrinth disorders	Vertigo[47]
Vascular disorders	Hypotension,[38] lowering in blood pressure[38]
Respiratory, thoracic and mediastinal disorders	Apnea,[70] respiratory depression,[β,69] worsening of obstructive pulmonary disease,[71] worsening of sleep apnea[2]
Gastrointestinal disorders	Nausea, constipation[39]
Hepatobiliary disorders	Jaundice[40]
Skin and subcutaneous tissue disorders	Angioedema,[1] allergic skin reactions, alopecia[72]
Musculoskeletal and connective tissue disorders	Muscle weakness
Reproductive system and breast disorders	Impotence[67]
General disorders and administration site conditions	Hypothermia,[37] fatigue,[64] asthenia
Investigations	Increase in bilirubin,[40] increase in liver transaminases,[41] increase in alkaline phosphatase[41]

± Benzodiazepine effects on the CNS are dose-dependent, with more severe CNS depression occurring with high doses.
β The extent of respiratory depression with benzodiazepines is dose-dependent, with more severe depression occurring with high doses.

4.9. OVERDOSE

In post-marketing experience, overdose with lorazepam has occurred predominantly in combination with alcohol and/or other drugs.[73]

Symptoms

Symptoms can range in severity and include drowsiness, mental confusion, lethargy, dysarthria, ataxia, paradoxical reactions, CNS depression, hypotonia, hypotension, respiratory depression, cardiovascular depression, coma, and death.Error! Bookmark not defined.[73,74]

Treatment

General supportive and symptomatic measures are recommended; vital signs must be monitored.

When there is a risk of aspiration, induction of emesis is not recommended.

Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Administration of activated charcoal may also limit drug absorption.

Lorazepam is poorly dialyzable.[75] Lorazepam glucuronide, the inactive metabolite, may be highly dialyzable.

The benzodiazepine antagonist, flumazenil, may be used in hospitalized patients as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose.[76,77] The physician should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.[78]

4.10. ABUSE AND DEPENDENCE

The use of benzodiazepines may lead to physical and psychological dependence.[18,19] The risk of dependence increases with higher doses and longer term use and is further increased in patients with a history of alcoholism or drug abuse or in patients with significant personality disorders. The dependence potential is reduced when lorazepam is used at the appropriate dose for short-term treatment.[Error! Bookmark not defined.18,20,21,22]

In general, benzodiazepines should be prescribed for short periods only (e.g., 2 - 4 weeks). Continuous long-term use of lorazepam is not recommended.

Withdrawal symptoms (e.g., rebound insomnia) can appear following cessation of recommended doses after as little as one week of therapy. Abrupt discontinuation of lorazepam should be avoided and a gradual dosage-tapering schedule followed after extended therapy.Error! Bookmark not defined.[18,Error! Bookmark not defined.20,23,24,25]

Abrupt termination of treatment may be accompanied by withdrawal symptoms. Symptoms reported following discontinuation of benzodiazepines include headache, anxiety, tension, depression, insomnia, restlessness, confusion, irritability, sweating, rebound phenomena, dysphoria, dizziness, derealization, depersonalization, hyperacusis, numbness/tingling of extremities, hypersensitivity to light, noise, and physical contact/perceptual changes, involuntary movements, nausea, vomiting, diarrhea, loss of appetite, hallucinations/delirium, convulsions/seizures, tremor, abdominal cramps, myalgia, agitation, palpitations, tachycardia, panic attacks, vertigo, hyperreflexia, short-term memory loss, and hyperthermia.[Error! Bookmark not defined.18,Error! Bookmark not defined.19,Error! Bookmark not defined.20,Error! Bookmark not defined.23,Error! Bookmark not defined.24,Error! Bookmark not defined.25] Convulsions/seizures may be more common in patients with pre-existing

seizure disorders or who are taking other drugs that lower the convulsive threshold, such as antidepressants.[Error! Bookmark not defined.20,Error! Bookmark not defined.24,26,27]

There is evidence that tolerance develops to the sedative effects of benzodiazepines.[28]

Ativan® (lorazepam) may have abuse potential, especially in patients with a history of drug and/or alcohol abuse.[29,30,31]

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacological class, therapeutic class

Benzodiazepine
Anxiolytic
ATC code: NO5BA06

Ativan® (lorazepam) is a benzodiazepine that interacts with the γ-aminobutyric acid (GABA)-benzodiazepine receptor complex and enhances the affinity of GABA.[79]

PHARMACODYNAMICS, CLINICAL EFFICACY

The pharmacodynamic consequences of benzodiazepine agonist actions include antianxiety effects, sedation, and reduction of seizure activity.[80,81]

The intensity of action is directly related to the degree of benzodiazepine receptor occupancy.

5.2. PHARMACOKINETIC PROPERTIES

Absorption

Absolute bioavailability is greater than 90% following oral and sublingual administration to healthy subjects.[82,83]

Peak plasma concentration occurs in approximately 2 hours following oral administration to healthy subjects.[**Error! Bookmark not defined.**81,**Error! Bookmark not defined.**82]

Distribution

The volume of distribution is approximately 1.3 L/kg.[**Error! Bookmark not defined.**82] Unbound lorazepam penetrates the blood/brain barrier freely by passive diffusion. Lorazepam is approximately 92% bound to human plasma proteins at lorazepam concentration of 160 ng/mL.[84]

Metabolism

Lorazepam is rapidly conjugated at its 3-hydroxy group into lorazepam glucuronide, an inactive metabolite.[85]

Elimination

The elimination half-life of unconjugated lorazepam in human plasma is approximately 12 to 16 hours.[**Error! Bookmark not defined.**81,**Error! Bookmark not defined.**84]

Following a single 2 mg oral dose of ^{14}C-lorazepam to 8 healthy subjects, approximately 88% of the administered dose was recovered in urine and 7% was recovered in feces.[Error! Bookmark not defined.84] Approximately 74% of lorazepam glucuronide was recovered in the urine.[Error! Bookmark not defined.84]

Elderly

Elderly patients typically respond to lower benzodiazepine doses than younger patients.[86]

Renal insufficiency

Single-dose pharmacokinetic studies in patients with degrees of renal insufficiency ranging from mild impairment to renal failure have reported no significant changes in absorption, clearance, or excretion of lorazepam. Hemodialysis did not have any significant effect on the pharmacokinetics of intact lorazepam, but substantially removed the inactive glucuronide from the plasma.[Error! Bookmark not defined.75]

Hepatic insufficiency

No change in the clearance of lorazepam was reported in patients with mild to moderate hepatic impairment (i.e., hepatitis, alcoholic cirrhosis).[87]

Concentration-effect relationship

The plasma levels of lorazepam are proportional to the dose given.[Error! Bookmark not defined.81]

There is no evidence of accumulation of lorazepam after oral administration for up to six months.[88]

5.3. PRECLINICAL SAFETY DATA

Lorazepam glucuronide, the major metabolite of lorazepam, has no demonstrable CNS activity in animals.

Carcinogenicity

No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam.[89,90]

Mutagenicity

A study of the mutagenic activity of lorazepam on *Drosophila melanogaster* indicated that this agent was mutationally inactive.[91]

Impairment of fertility

A pre-implantation study in rats was performed with oral lorazepam at a 20 mg/kg dose that showed no impairment of fertility.[92]

Effect of anesthetic and sedative drugs

Nonclinical research has shown that administration of anesthetic and sedation drugs that block N-methyl-D-aspartate (NMDA) receptors and/or potentiate gamma-aminobutyric acid (GABA) activity can increase neuronal cell death in the brain and result in long term deficits in cognition and behavior of juvenile animals when administered during the period of peak brain development. Based on comparisons across nonclinical species, the window of vulnerability of the brain to these effects is believed to correlate with human exposures in the third trimester of pregnancy through the first year of life, but may extend to approximately 3 years of age. While there is limited information of this effect with lorazepam, since the

mechanism of action includes potentiation of GABA activity, a similar effect may occur. The relevance of these nonclinical findings to human use is unknown.[94]

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Excipients for Ativan 1 mg

MICROCRYSTALLINE CELLULOSE
POLACRILIN POTASSIUM
MAGNESIUM STEARATE USP
LACTOSE EP-NF SPRAY DRIED

Excipients for Ativan 2 mg

MICROCRYSTALLINE CELLULOSE
POLACRILIN POTASSIUM
MAGNESIUM STEARATE USP
LACTOSE EP-NF SPRAY DRIED
FD&C YELLOW # 5 LAKE

6.2. INCOMPATIBILITIES

Information not available

6.3. SHELF LIFE

36 Months

6.5. NATURE AND CONTENTS OF CONTAINER

Primary container consist of printed aluminum foil and rigid PVC.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Kindly follow procedure EHS/II/042 “Collection & Disposal of waste” for safe disposal of product and refer to the SDS of lorazepam for handling and personal protection.

Ativan/LPD/PK-04
According to CDS V 6.0 dated: 02 August, 2018; Supersedes CDS V 5.0 dated: 02 June, 2017

Manufactured by:
Pfizer Pakistan limited.
B-2, S.I.T.E. Karachi.

7. REFERENCES

1. Justification for a Safety Labeling Decision: Lorazepam, Lormetazepam, Oxazepam, Temazepam: Angioedema, dated 09 October 2007.

2. Guilleminault C. Benzodiazepines, breathing, and sleep. *American Journal of Medicine*. 1990;88(supp3A):25S-28S.

3. Hall RCW, Zisook S. Paradoxical reactions to benzodiazepines. *Br J Clin Pharmacol*. 1981;11:99S-104S.

4. Safra MJ, Godfrey PJ. Association between cleft lip with or without cleft palate and prenatal exposure to diazepam. *Lancet*. 1975;2:478-480.

5. Kanto J, Aaltonen L, Liukko P, *et al*. Transfer of lorazepam and its conjugate across the human placenta. *Acta Pharmacol et Toxicol*. 1980;47:130-134.

6. Whitelaw AG, Cummings AJ, McFadyen IR. Effect of maternal lorazepam on the neonate. *Br Med J*. 1981;282(6270):1106-1108.

7. Summerfield RJ, Nielsen MS. Excretion of lorazepam into breast milk. *Br J Anaesth*. 1985;57(10):1042-1043.

8. Anonymous: American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. *Pediatrics*. 1994;93(1):137-150.

9. McElhatton PR. The effects of benzodiazepine use during pregnancy and lactation. *Reprod Toxicol*. 1994;8(6):461-475.

10. Cobb CD, Anderson CB, Seidel DR. Possible interaction between clozapine and lorazepam. *Am J Psychiatry*. 1991;148(11):1606-1607.

11. Jackson CW, Marlowitz JS, Brewerton TD. Delirium associated with clozapine and benzodiazepine combinations. *Ann Clin Psychiatry*. 1995;7(3):139-141.

12. Samara EE, Granneman RG, Galen FW, *et al*. Effect of valproate on the pharmacokinetics and pharmacodynamics of lorazepam. *J Clin Pharmacol*. 1997;37:442-450.

13. Anderson GD, Gidal BE, Kantor ED, *et al*. Lorazepam-valproate interaction: studies in normal subjects and isolated perfused rat liver. *Epilepsia*. 1994;35(1):221-225.

14. Abernethy DR, Greenblatt DJ, Ameer B, *et al*. Probenecid impairment of acetaminophen and lorazepam clearance: direct inhibition of ether glucuronide formation. *J Pharmacol Exp Ther*. 1985;234(2):345-349.

15. Kleindienst G, Usinger P. Diazepam sedation is not antagonised completely by aminophylline. *Lancet*. 1984;i:113.

16. Niemand D, *et al*. Aminophylline inhibition of diazepam sedation: is adenosine blockade of GABA receptors the mechanism? *Lancet*. 1984;i: 463-464.

17. Henauer SA, *et al*. Theophylline antagonises diazepam-induced psychomotor impairment. *Eur J Clin Pharmacol*. 1983; 25: 743-747.

18. Ashton H Benzodiazepine withdrawal: an unfinished story. *BMJ*. 1984;288:1135-1140.

19. Busto U, Sellers E, Naranjo C, *et al*. Withdrawal reaction after long-term therapeutic use of benzodiazepines. *N Engl J Med*. 1986;315(14):854:859.

20. Soni SD, Smith ED, Shah A, *et al*. Lorazepam withdrawal seizures: Role of predisposition and multi-drug therapies. *Int Clin Psychopharmacol*. 1986;1:165-169.

21. Clare AW. Diazepam, alcohol, and barbiturate abuse. *BMJ*. 1971;4:340.

22. Busto UE, Romach MK, Sellers EM. Multiple drug use and psychiatric comorbidity in patients admitted to the hospital with severe benzodiazepine dependence. *J Clin Psychopharmacol*. 1996;16(1):51-57.

23. Petursson H, Lader MH. Withdrawal from long-term benzodiazepine treatment. *BMJ*. 1981;283:643-645.

24. Martinez-Cano H, Vela-Bueno A, de Iceta M, *et al*. Benzodiazepine withdrawal syndrome seizures. *Pharmacopsychiat*. 1995;28:257-262.

25. Mandos LA, Rickels K, Cutler N. Placebo-controlled comparison of the clinical effects of rapid discontinuation of ipsapirone and lorazepam after 8 weeks of treatment for generalized anxiety disorder. *Int Clin Pyschopharmacol*. 1995;10:251-256.

26. Fialip J, Aumaitre O, Eschalier A. Benzodiazepine withdrawal seizures: Analysis of 48 case reports. *Clin Neuropharmacol*. 1987;10(6):538-44.

27. De La Fuente JR, Rosenbaum A, Martin HR. Lorazepam-related withdrawal seizures. *Mayo Clin Proc*. 1980;55:190-192.

28. Van Steveninck AL, Wallnofer AE, Schoemaker RC, *et al*. A study of the effects of long-term use on individual sensitivity to temazepam and lorazepam in a clinical study. *Br J Clin Pharmacol*. 1997;44:267-275.

29. Griffiths RR, Wolf B. Relative abuse liability of different benzodiazepines in drug abusers. *J Clin Psychopharmacol*. 1990;10(4):237-243.

30. Preston KL, Wolf B, Guarino JJ, *et al*. Subjective and behavioral effects of diphenhydramine, lorazepam and methocarbamol: evaluation of abuse liability. *J Pharmacol Exp Ther*. 1992;262(2):707-720.

31. Orzack MH, Friedman L, Dessain E, *et al*. Comparative study of the abuse liability of alprazolam, lorazepam, diazepam, methaqualone, and placebo. *Int J Addictions*. 1988;23(5):449-467.

32. Fontaine L: Justification document: Frequency estimates for lorazepam adverse reactions, 10 September 2001.

33. Warner L: Justification Document: Hypersensitivity, 27 July 2001.

34. Warner L: Justification Document: Anaphylaxis/anaphylactoid reaction, 23 July 2001.

35. Warner L: Justification Document: Syndrome of inapproriate ADH secretion, 27 July 2001.

36. Warner L: Justification Document: Hyponatremia, 30 July 2001.

37. Warner L: Justification Document: Hypothermia, 26 July 2001.

38. Warner L: Justification Document: Hypotension, 30 July 2001.

39. Warner L: Justification Document: Constipation, 27 July 2001.

40. Warner L: Justification Document: Increased bilirubin/jaundice, 23 July 2001.

41. Warner L: Justification Document: Increased liver function tests and increased alkaline phosphatase, 23 July 2001.

42. Warner L: Justification Document: Thrombocytopenia, 28 August 2001.

43. Warner L: Justification Document: Agranulocytosis, 28 August 2001.

44. Warner L: Justification Document: Pancytopenia, 28 August 2001.

45. Warner L: Justification Document: Extrapyramidal symptoms, 31 July 2001.

46. Warner L: Justification Document: Tremor, 27 July 2001.

47. Warner L: Justification Document: Vertigo, 30 July 2001.

48. Warner L: Justification Document: Dysarthria/slurred speech, 24 July 2001.

49. Warner L: Justification Document: Seizure/convulsion, 28 August 2001.

50. Warner L: Justification Document: Disinhibition, 25 July 2001.

51. Warner L: Justification Document: Euphoria, 23 July 2001.

52. Warner L: Justification Document: Coma, 24 July 2001.

53. Warner L: Justification Document: Suicidal ideation and suicide attempt, 31 July 2001.

54. Justification for a safety labeling decision: Lorazepam, Lormetazepam, Oxazepam and Temazepam: Impaired attention/concentration, dated 14-May-2008.

55. Justification for a safety labeling decision: Lorazepam, Lormetazepam, Oxazepam and Temazepam: Balance disorder, dated 22-May-2008.

56. Warner L: Justification Document: Anxiety, 31 July 2001.

57. Warner L: Justification Document: Agitation, 25 July 2001.

58. Warner L: Justification Document: Excitability, 25 July 2001.

59. Warner L: Justification Document: Hostility, 26 July 2001.

60. Warner L: Justification Document: Rage and aggression, 25 July 2001.

61. Warner L: Justification Document: Change in libido and sexual arousal, 25 July 2001.

62. Warner L: Justification Document: Hallucinations, 27 July 2001.

63. Warner L: Justification Document: Drowsiness/sedation, 30 July 2001.

64. Warner L: Justification Document: Fatigue, 26 July 2001.

65. Warner L: Justification Document: Ataxia, 20 July 2001

66. Warner L: Justification Document: Confusion, 24 July 2001.

67. Warner L: Justification Document: Impotence, 24 July 2001

68. Warner L: Justification Document: Anorgasmia, 25 July 2001.

69. Warner L: Justification Document: Respiratory depression, 31 July 2001.

70. Warner L: Justification Document: Apnea, 28 August 2001.

71. Warner L: Justification Document: Worsening of obstructive pulmonary diseases, 28 August 2001.

72. Warner L: Justification Document: Alopecia, 25 July 2001.

73. Serfaty M, Masterton G. Fatal poisonings attributed to benzodiazepines in Britain during the 1980s. *Br J Psychiatry*. 1993;163:386-393.

74. Vlachos P, Kentarchou P, Poulos L, *et al*. Lorazepam poisoning. *Toxicol Lett*. 1978;2:109-110.

75. Morrison G, Chiang ST, Koepke HH. Effect of renal impairment and hemodialysis on lorazepam kinetics. *Clin Pharmacol Ther*. 1984;35(5):646-652.

76. Hojer J, Baehrendtz S. The effect of flumazenil (Ro 15-1788) in the management of self-induced benzodiazepine poisoning. *Acta Med Scand*. 1988;224:357-365.

77. O'Sullivan GF, Wade DN. Flumazenil in the management of acute drug overdosage with benzodiazepines and other agents. *Clin Phamacol Ther*. 1987;42:254-259.

78. Spivey WH. Flumazenil and seizures: analysis of 43 cases. Clin Ther. 1992;14(2):292-305.

79. Goodchild CS. Gaba receptors and benzodiazepines. Br J Anaesth. 1993;71:127-33.

80. Paul SM, Syapin PJ, Paugh BA, *et al*. Correlation between benzodiazepine receptor occupation and anticonvulsant effects of diazepam. *Nature*. 1979;281:688-689.

81. Facklam M, Schoch P, Bonetti E, *et al*. Relationship between benzodiazepine receptor occupancy and functional effects in vivo of four ligands of differing intrinsic efficacies. *J Pharmacol Exp Ther*. 1992;261(3);1113-1121.

82. Greenblatt DJ, Shader RI, Franke K, *et al*. Pharmacokinetics and bioavailability of intravenous intramuscular, and oral lorazepam in humans. *J Pharm Sci*. 1979;68(1):57-63.

83. Greenblatt DJ, Divoll M, Harmatz J, *et al*. Pharmacokinetic comparison of sublingual lorazepam with intravenous, intramuscular, and oral lorazepam. *J Pharm Sci*. 1982;71(2):248-252.

84. Fluck ER. The binding of lorazepam (Wy-4036) to the proteins of human plasma. Wyeth-Ayerst Laboratories GTR 8011, 1980.

85. Greenblatt DJ, Schillings RT, Kyriakopoulos AA, *et al*. Clinical pharmacokinetics of lorazepam. I. Absorption and disposition of oral 14C-lorazepam. *Clin Pharmacol Ther*. 1976;20(3):329-341.

86. Greenblatt DJ, Harmatz JS, Shader RI. Clinical Pharmacokinetcs of anxiolytics and hypnotics in the elderly: Therapeutic considerations (Part I). *Clin Pharmacokinet*. 1991;21:165-177.

87. Wilkinson GR. The effects of liver disease and aging on the disposition of diazepam, chlorodiazepoxide, oxazepam, and lorazepam in man. *Acta Psychiatrica Scandinavica*. 1978;274:56-74.

88. Greenblatt DJ, Knowles JA, Comer WH, *et al*. Clinical pharmacokinetics of lorazepam. IV. Long-term oral administration. *J Clin Pharmacol*. 1977;17:495-500.

89. Hudyma GM. WY-04036 80-week carcinogenic study in mice drug diet. Wyeth-Ayerst Laboratories GTR 05764, 1976.

90. Tucker WE. Histopathology report chronic drug safety study 78-weeks WY-04036 rats. Wyeth-Ayerst Laboratories GTR 04440, 1973.

91. Filippova LM, Rapoport IA, Shapiro YL, *et al*. Mutagenic activity of psychotropic preparations. *Genetica*. 1975;11(6):77-82.

92. Owen G. WY-04036 reproductive study in rats. Wyeth-Ayerst Laboratories GTR 00930, 1967.

93. 2.5 Clinical Overview to Support Updates to Sections 4.4 and 4.5 of the Core Data Sheet, May 2017.

94. 2.4 NON CLINICAL OVERVIEW to Support LORAZEPAM CDS update FOR NEURONAL DEATH, JUNE 2018.