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The American Academy of Pedodontics
Volume 4, Special Issue 1


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Alphaprodine HCl: characteristics

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Alphaprodine is a narcotic analgesic that is pharmacologically similar to morphine and meperidine, with the exception that it has a rapid onset and short duration of action. Alphaprodine acts primarily on the CNS and on smooth muscle. After intravenous administration, analgesia occurs in one to two minutes and lasts for 30 to 90 minutes. Following subcutaneous administration, analgesia usually occurs within 10 minutes and lasts for one to more than two hours.

The half-life of alphaprodine is approximately two hours. It is metabolized in the liver and probably is detoxified there as well. As with other narcotic analgesics, alphaprodine is excreted (in unchanged and metabolized forms) primarily in the urine. A small portion of a dose is excreted in the feces.

Alphaprodine was first marketed by Hoffmann-LaRoche in 1949 as an injectable narcotic analgesic for use in labor and delivery, urologic procedures and surgical procedures. A new usage outside the package insert recommendations became apparent after there were sporadic reports of adverse reactions involving pediatric dentistry. These adverse reactions usually occurred with high doses of alphaprodine, administered either submucosally or intramuscularly (the intramuscular route was contraindicated in the package insert). The reports of adverse reactions received between the years 1970-1980 are presented in Table 1.

Table 1. Adverse reactions — pediatric dentistry.

Weight *Year*	*Nisentil® Dose*	*Other Drugs*	*Outcome*
12 kg 1970	12 mg 6 mg	5 mg Phenergan® 5 cc 2% Xylocaine®	death
unknown 1976	16 mg	5 mg p.o. Phenergan® 1.25 mg Phenergan®	cerebral damage
unknown 1978	9 mg 9 mg	75 mg Lidocaine® 25 mg Phenergan®	death
25 lb 1980	20 mg (IM)	35 mg IM Phenergan®	cerebral damage

As far as we can determine from the sometimes sketchy details of the reports supplied to us, doses given to children were not calculated on a milligram per kilogram basis. Fixed doses were given. Ages of the children ranged from 28 months to 4 years. In all cases concomitant medications were given. Promethazine (Phenergan) p.o. or IM was a common denominator in the medication regimen of these children. The final outcome of these cases was either death or severe cerebral damage due to anoxia.

Because of these serious adverse reactions which occurred as a result of pediatric dentistry, Roche decided to withdraw alphaprodine from the market. There was an overwhelming response from pediatric dentists, obstetricians and other specialists who for years had used the drug safely and with no sequelae. Because of the thousands of calls and letters we received, we decided to reassess the situation and look in a systematic fashion at the safety and efficacy of alphaprodine in pediatric dentistry. Our factory sales data did not reflect the extent of alphaprodine use by the pediatric dentist, since purchases from Roche were through wholesalers, and dentists using the 60-mg/cc vial could conceivably use one vial for as many as 100 cases.

What we did undertake was a retrospective study of pediatric dental usage from 12 different dentists. Table 2 lists the names of the various dentists who submitted over 7000 case reports to us. Obviously the data are strongly weighted towards the information from Drs. Doan and Ryan, since they submitted over 4600 case reports to us.

Patients' ages ranged from 24 months to 12 years. The majority of patients were in the range of 2 to 8 years, with an average of 5.7 years for males and 5.8 years for females. Average weights were 18.2 and 18.1 kg, respectively. The average alphaprodine dose used was about 10 mg for males, 9.8 mg for females (Table 3).

Doses ranged from 5 to 15 mg in over 80% of the cases submitted, with approximately 60% in the 5-10 mg range (Table 4). Data were tabulated on the diagnosis for which these children were treated and given alphaprodine. Dental caries was the diagnosis listed in 90% of the cases (Table 5).

Table 2. Dentists submitting case reports.

Center	Participant	Cases/ Submitted
1	Doan/Ryan	4614
2	Mueller	87
3	Schuyler	466
4	Pyron	481
5	Creedon	75
6	Duperon	78
7	Mack	708
8	Morgan	26
9	Reznik	25
10	Hoffmann	214
11	Troutman	105
12	Matsuishi	493
	Total:	7372

Table 3. Averages for alphaprodine use.

	Male	Female
Average age	5.7 yrs	5.8 yrs
Average weight	18.2 kg	18.1 kg
Average Nisentil® dose	10.0 mg	9.8 mg

Table 4. Range of dosage.

Nisentil® Dosage	No.	%
Less than 5 mg	88	1
5-10 mg	4425	60
10-15 mg	1911	26
15-20 mg	694	9
20 mg or greater	254	3
Total:	7372	100%

Table 5. Diagnosis for which children were given alphaprodine.

Diagnosis	No. Patients	%
Dental caries	6146	90
Bottle mouth syndrome	170	2
Trauma	52	1
Other	499	7
Total:	6867	100%

Table 6. Procedures performed on patients.

Procedure	No. Patients	%
Restorative	5439	79
Extraction	1349	20
Other	79	1
Total:	6867	100%

Table 7. Overall efficacy of alphaprodine.*

Center:	1	2	3	4	5	6	7	8	9	10	11	12
Male	2.8	3.0	2.8	2.8	NA	2.5	2.9	2.8	NA	2.8	NA	NA
Female	2.8	3.0	2.8	2.8	NA	2.5	2.9	2.9	NA	2.9	NA	NA

*1 = poorly effectively; 3 = very effective; NA = not available.

Restorative procedures were done in 79% of the patients, while extractions were done in 20% (Table 6). Overall efficacy was rated on a 3-point scale, a rating of 1 being poorly effective, 3 being very effective. Average efficacy in the various centers are listed in Table 7.

The incidence of side effects is reported in Table 8. The side effect "sleep" is heavily weighted to the Doan/Ryan data comprising approximately 4600 cases, with 2331 of the 2381 mentions of "sleep." Drs. Doan and Ryan routinely followed-up all patients with a call to inquire about the child's status after they arrived at home. Parents were asked if the child slept upon arrival at home: if the answer was affirmative, this was listed as a side effect possibly related to alphaprodine or promethazine. In many cases the child's sleep may have occurred with his/her daily nap time, so an interpretation of this particular side effect is not really possible.

Serious adverse reactions such as respiratory depression, unresponsiveness, or seizures were mentioned a total of 8 times out of the 7372 case reports. However, more than one of these serious adverse reactions may have occurred in a given patient. When the individual investigator tabulations were examined, these 8 cases occurred in anywhere from 5-8 separate patients. In 3 of the individual patients, alphaprodine had been used in conjunction with promethazine.

We looked further at adverse reactions by age and weight when alphaprodine was administered in combination or alone (Tables 9 and 10, respectively). These numbers do not necessarily correlate with Table 8; Table 8 records all side effects reported. Tables 9 and 10 list a side effect only if age or weight were also reported.

Table 8. Incidence of adverse reactions associated with alphaprodine.

	Patient Frequency With			
Side Effect	*Nisentil®*	*Nisentil®/ Phenergan®*	*Nisentil®/ Home Brew*	*Incidences*
Nausea	209	67	1	277
Vomiting	9	1	—	10
Sleep	16	2364	1	2381
Swelling	11	—	—	11
Hypertension	—	5	—	5
Respiratory Depression	4	1	—	5
Unresponsive	1	1	—	2
Dizziness	1	1	—	2
Seizure/ Convulsions	—	1	—	1
Pain	—	4	—	4
Disoriented	—	1	—	1
Local Skin Reaction	9	—	—	9
Other	—	2	1	3

Table 9. Alphaprodine/promethazine adverse reactions by ag

Age (yr):	<2	2-4	4-6	6-8	8-10	10-12	>12
Nausea	2	10	20	14	16	3	2
Vomiting	0	0	0	0	1	0	0
Sleep	35	463	727	555	358	161	65
Respiratory depression	0	0	0	0	0	0	0
Unresponsiveness	0	0	1	0	0	0	0
Dizziness	0	0	1	0	0	0	0
Swelling	0	0	0	0	0	0	0
Seizures/ convulsions	0	0	0	1	0	0	0
Pain	0	0	2	2	0	0	0
Disoriented	0	0	1	0	0	0	0
Local skin reaction	0	0	0	0	0	0	0
Bleeding	0	0	0	0	0	0	0
Hypotension	0	3	2	0	0	0	0
Other	0	0	0	0	0	0	0

The dose of alphaprodine was cross-tabulated with the weight of the child (Table 9). An average range of 0.3-0.6 mg/kg (.66-1.2 mg/lb) of alphaprodine was used in the majority of patients.

As a result of this data, package insert changes were made. Dosage guidelines on submucosal administration for pediatric dentistry have been incorporated. Routine reversal with naloxone HCL (Narcan®) is also recommended. The package insert is reproduced in its entirety below:

A.H.F.S. Category 28:08 **CII**

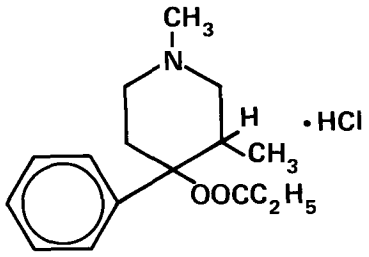
NISENTIL® (alphaprodine HCl/Roche)Injectable

WARNINGS

- **Nisentil should be used with great caution and in reduced dosage in patients who are receiving other narcotic analgesics, general anesthetics, tranquilizers (including phenothiazines), sedative-hypnotics (including barbiturates), tricyclic antidepressants, MAO inhibitors and other CNS depressants, including alcohol. The depressant effects of Nisentil are potentiated in the presence of such drugs. *Fatalities, severe cerebral damage, respiratory depression, hypotension, and profound sedation or coma may result.***
- The **Dosage and Administration** section should be strictly adhered to and careful attention should be given to the **Overdosage** section, particularly for treatment of respiratory depression.
- *Nisentil should be used only when resuscitative equipment and personnel trained in such use are immediately available.*
- Narcan (naloxone hydrochloride) should be immediately available when Nisentil use is contemplated. Routine narcotic reversal with Narcan should be performed following each pediatric dental procedure when Nisentil has been administered.
- *Nisentil should be administered by intravenous, subcutaneous or submucosal routes only.* (See **Dosage and Administration** section.) Nisentil should never be administered intramuscularly because absorption is too unpredictable.

Description: Nisentil (alphaprodine hydrochloride/Roche), a synthetic narcotic analgesic, is a sterile aqueous solution for intravenous, subcutaneous or submucosal administration.

Alphaprodine hydrochloride, a white powder which is freely soluble in water, has a calculated molecular weight of 297.82. Chemically, alphaprodine hydrochloride, a piperidine derivative, is (±)-1, 3-dimethyl-4-phenyl-4-piperidinol propionate (ester) hydrochloride. The structural formula is as follows:



Clinical Pharmacology: Nisentil is a rapid-acting narcotic analgesic with a short duration of action. Except for its more rapid onset and shorter duration of analgesic action, the pharmacologic properties of Nisentil are similar to those of morphine or meperidine. Also, Nisentil is more potent than meperidine. Nisentil acts principally on the central nervous system and on organs composed of smooth muscle. Nisentil is metabolized and probably detoxified by the liver. There is evidence that Nisentil enters the fetal circulation.

In man, the half-life of Nisentil has been reported to be 131 minutes following intravenous administration.

The onset of action following intravenous administration is 1 to 2 minutes; the duration of analgesic action is 30 to 90 minutes. Subcutaneous administration provides analgesic effects usually within 10 minutes (ranging from 2 to 30 minutes). The duration of action following subcutaneous administration of Nisentil lasts from 1 hour to over 2 hours, depending upon the dosage administered, as compared to the duration of action of meperidine, which is 2 to 4 hours.

Indications and Usage: Nisentil is indicated for obstetric analgesia; for urologic examinations and procedures — particularly cystoscopy; preoperatively in major surgery; in minor surgery where rapid analgesia of brief duration is desirable — particularly in children requiring analgesia during dental procedures. Nisentil is indicated in children only for analgesia during dental procedures.

Contraindications: Nisentil is contraindicated in patients with a known hypersensitivity to this drug or to other opiates.

Warnings: (See **Warnings** box.) *Drug Dependence. Nisentil may be habit forming.* Nisentil can produce drug dependence of the morphine type and has the potential for being abused. Psychological and physical dependence and tolerance may develop upon repeated administration of Nisentil; it should be prescribed and administered with the same degree of caution appropriate to the use of morphine.

Intravenous Use: When Nisentil is given intravenously, special attention should be given to the possibility of respiratory depression. Such depression is especially likely in patients with pulmonary disease and in the elderly or debilitated. The patient should be lying down when the drug is administered, and Narcan (naloxone hydrochloride), a narcotic antagonist, and facilities for assisted or controlled respiration should be immediately available.

Hypotensive Effects: The administration of Nisentil may result in severe hypotension in the postoperative patient or in any individual whose ability to maintain blood pressure has been compromised by a depleted blood volume or by the administration of drugs, such as the phenothiazines or certain anesthetics. Narcotics may produce orthostatic hypotension in ambulatory patients.

Head Injury: The respiratory depressant effects of Nisentil may be markedly exaggerated in the presence of head injury or other intracranial lesions. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries. In such patients, Nisentil must be markedly exaggerated in the presence of head injury or other intracranial lesions. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries. In such patients, Nisentil must be used with extreme caution and only if its use is deemed essential.

Asthma and Other Respiratory Conditions: Nisentil should be used with extreme caution in patients with bronchial asthma, chronic obstructive pulmonary disease or *cor pulmonale.* Similarly, it should be used with extreme caution in patients having a decreased respiratory reserve or with pre-existing respiratory depression, hypoxia or hypercapnia. In such patients, usual therapeutic doses of narcotics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

Chronic Pain: Nisentil should not be used for relief of chronic pain because its short duration of action would require more frequent administration and might increase the possibility of physical dependence.

PRECAUTIONS: *General:* The administration of Nisentil or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Nisentil should be administered with caution and the initial dose should be reduced in patients who are elderly or debilitated,

Table 10. Alphaprodine adverse reactions by weight.

Weight (Gm):	©10	10-15	15-20	20-25	25-30	□30
Nausea	85	14	27	38	22	24
Vomiting	0	2	2	2	1	0
Sleep	0	3	7	1	1	5
Repiratory depression	0	2	0	0	1	1
Unresponsiveness	0	0	0	0	0	1
Dizziness	0	0	0	1	0	0
Swelling	0	3	7	0	0	1
Seizures/ convulsions	0	0	0	0	0	0
Pain	0	0	0	0	0	0
Disoriented	0	0	0	0	0	0
Local skin reaction	0	0	7	2	0	0
Bleeding	0	0	0	0	0	0
Hypotension	0	0	0	0	0	0
Other	0	0	0	0	0	0

and in those patients with acute alcoholism, severe CNS depression, delirium tremens, severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, toxic psychosis, and prostatic hypertrophy or urethral stricture.

Nisentil should be used with caution in patients with atrial flutter and other supraventricular tachycardias because of possible vagolytic action which may produce a significant increase in the ventricular response rate.

Nisentil may aggravate preexisting convulsions in patients with convulsive disorders. If dosage is escalated substantially above recommended levels because of tolerance development, convulsions may occur in individuals without a history of convulsive disorders.

Information for Patients: When Nisentil is administered to ambulatory patients, they should be cautioned against engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving a motor vehicle following drug administration.

Drug Interactions: (See **Warnings** box).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There have been no studies performed with Nisentil to permit an evaluation of its carcinogenic or mutagenic potential. Studies have not been performed to determine the effect of Nisentil on fertility or reproduction.

Pregnancy: Teratogenic Effects: Pregnancy Category C. There are no adequate or well-controlled studies of Nisentil in either laboratory animals or in pregnant women. While the safety and efficacy of Nisentil as an analgesic agent in obstetrics have been established, it is not known whether the drug can cause fetal harm when administered earlier in pregnancy. Nisentil should be used prior to the labor period only if it is clearly needed.

Nonteratogenic Effects: Animal studies have demonstrated that Nisentil depresses fetal respiratory movement and maternal respiratory rate in the rabbit and that it depresses both fetal and maternal cerebral oxygen availability in the guinea pig. (Also see *Labor and Delivery* section).

Labor and Delivery: When used as an obstetric analgesic, Nisentil passes into the fetal circulation, which may produce depression of respiration and physiologic functions in the newborn. Narcan Neonatal should be used to reverse respiratory depression in the newborn. Resuscitation may be required. (See **Overdosage** section). It has been reported that Nisentil may shorten the duration of labor; however, other studies have reported that Nisentil does not decrease the duration of labor. One study showed that in 9.6% of patients, Nisentil interfered with the mechanism of labor by decreasing the frequency and duration of uterine contractions. A possible explanation of this occurrence is that the drug was administered too early in labor. There are no long-term follow-up studies available on the growth, development and functional maturation of the child.

Nursing Mothers: It has been reported that trace amounts of alphaprodine are excreted in human milk. If Nisentil is administered to a nursing mother, the infant should not be breastfed for a period of 24 hours following drug administration to the mother because of the potential for serious adverse reactions from Nisentil in nursing infants.

Pediatric Use: Use of Nisentil in children for indications other than pediatric dentistry cannot be recommended because safety and effectiveness have not been established.

Adverse Reactions: *Note:* Included in this listing are adverse reactions which have not been reported with this specific drug; however, the pharmacologic similarities among the narcotics require that each of the reactions be considered with Nisentil administration.

Deaths and cerebral damage have been reported, especially when Nisentil has been given concomitantly with other CNS depressants. (See Warnings box.)

The major hazard of Nisentil administration, as with other narcotic analgesics, is respiratory depression which has led to respiratory arrest. This has also been reported following the administration of Nisentil preoperatively and during labor. The severity of respiratory depression may warrant active measures, particularly in neonatal situations. It is recommended that Narcan (naloxone hydrochloride) be administered in such cases. (See **Overdosage** section.) Circulatory depression, shock and cardiac arrest have also been reported following the administration of narcotic analgesics.

Other adverse reactions include:

Neurologic: Pinpoint pupils, visual disturbances, coma, sedation, dizziness, lightheadedness, headache, tremors, uncoordinated muscle movements.

Psychiatric: Euphoria, dysphoria, weakness, agitation, disorientation, confusion, hallucinations.

Cardiovascular: Hypotension, collapse, tachycardia, bradycardia, palpitation, syncope, phlebitis.

Dermatologic: Rash, urticaria (both local and generalized), pruritis, wheal and flare over the vein with intravenous injection.

Gastrointestinal: Nausea, emesis, constipation, dry mouth, biliary tract spasm.

Genitourinary: Urinary retention.

Miscellaneous: Diaphoresis, flushing, pain at the site of injection, allergic and anaphylactoid reactions, local tissue irritation and induration following subcutaneous injection.

Drug Abuse and Dependence: *Nisentil is subject to* Schedule II control under the Federal Controlled Substances Act of 1970. A narcotic order is required. This drug can produce drug dependence of the morphine type, and therefore has the potential for being abused. Psychological and physical dependence and tolerance may develop upon repeated administration of Nisentil, and consequently the same precautions should be taken in administering the drug as with morphine.

Overdosage: Serious overdosage with Nisentil is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe

overdosage, apnea, circulatory collapse, cardiac arrest and death may occur. The triad of coma, pinpoint pupils, and depressed respiration strongly suggests opioid poisoning.

Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and through the institution of assisted or controlled ventilation. The narcotic antagonist Narcan (naloxone hydrochloride) is a specific antidote against respiratory depression resulting from narcotic overdosage or unusual sensitivity to narcotics. An appropriate dose of this antagonist should be administered simultaneously, preferably by the intravenous route, with efforts at respiratory resuscitation.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed if needed.

Management of Respiratory Depression in Neonates: As in the case of adults, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and through the institution of assisted or controlled ventilation. Administer Narcan (naloxone hydrochloride) at an initial dose of 0.01 mg/kg body weight by I.M., I.V., or S.C. routes. This dose may be repeated at 2- to 3-minute intervals, if necessary, until adequate narcotic reversal is accomplished. Oxygen, intravenous fluids, vasopressors, or other supportive measures should be employed.

NOTE: The administration of the usual dose of a narcotic antagonist will precipitate an acute withdrawal syndrome in patients physically dependent on narcotics. The severity of this syndrome will depend on the degree of physical dependence and the dose of the antagonist administered.

The use of narcotic antagonists in such patients should be avoided if possible. If a narcotic antagonist must be used in physically-dependent patients to treat serious respiratory depression, the antagonist should be administered with extreme care using only 1/5 to 1/10 the usual initial dose.

Death, cerebral damage, and respiratory arrest have been reported when Nisentil has been administered within recommended dosages but concomitantly with other CNS depressants, or administered intramuscularly. (See **Warnings** box.) Death and cerebral damage have been reported in children administered 2½ to 7½ times the recommended dosage of Nisentil.

The acute toxicity of Nisentil is as follows:

Species	*Route*	*LD_{50} (mg/kg)*
Mouse	I.V.	51.5 ± 4.0
Rat	I.V.	25.0 ± 6.8
	S.C.	50.0 ± 17.7
	P.O.	90.0 ± 18.7
Rabbit	I.V.	22.0 ± 2.9
Dog	I.V.	36.2 ± 18.3

Dosage and Administration: The dosages suggested are the usual amounts employed in adults; however, as with any other narcotic analgesic, good medical practice dictates the use of the minimal effective dose. If dosage is escalated substantially above recommended levels because of tolerance development, convulsions may occur. *The usual dosage is in the range of 0.4 to 0.6 mg/kg intravenously or 0.4 to 1.2 mg/kg subcutaneously.* Intitially, the lower dosage range is recommended in order to evaluate the patient's response. Thus, *the initial intravenous dose should not exceed 30 mg, nor should the initial subcutaneous dose exceed 60 mg.* The total dose administered by any route should not be more than 240 mg in 24 hours. Whenever this drug is given intravenously, a narcotic antagonist and facilities for resusciation should be available.

Subcutaneous administration provides analgesic effects usually within 10 minutes, lasting from 1 to over 2 hours. If required, an additional ¼ dose may be given 30 minutes after the initial dose. The *intravenous* route is recommended when more rapid onset (1 to 2 minutes) and shorter duration ½ to 1½ hours) of action are desired. An additional amount of ¼ the initial dose may be injected after 15 minutes, if required.

Obstetrics: Initially, 40 to 60 mg subcutaneously after cervical dilation has begun, repeated as required at two-hour intervals. Nisentil may be combined with scopolamine or atropine, and may be used in conjunction with nerve block or inhalation anesthesia as required. (See **Warnings** box on use with CNS depressants.)

Urologic Procedures, e.g., Cystoscopy: Initially, 20 to 30 mg intravenously.

Preoperatively in Major Surgery: Initially, 20 to 40 mg subcutaneously or 10 to 20 mg intravenously.

Minor Surgery: Initially, 40 mg subcutaneously or 20 mg intravenously.

Pediatric Dentistry: The usual recommended dose is 0.3 to 0.6 mg/kg by submucosal route only. Routine narcotic reversal with Narcan (naloxone hydrochloride) should be performed following each procedure when Nisentil has been administered. **Nisentil should be used with great caution and in reduced dosage in pedatric dental patients who are receiving other narcotic analgesics, general anesthetics, tranquilizers (including phenothiazines), sedative-hypnotics (including barbiturates), tricyclic antidepressants, MAO inhibitors and other CNS depressants. The depressant effects of Nisentil are potentiated in the presence of such drugs. Fatalities, severe cerebral damage, respiratory depression, hypotension and profound sedation or coma may result.** *Use of Nisentil in children for indications other than pediatric dentistry cannot be recommended due to limited experience.*

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever possible.

How Supplied: Nisentil is supplied in:

1-ml ampuls — each ml contains 40 mg/ml alphaprodine hydrochloride compounded with 0.0875% citric acid and sodium citrate to adjust pH to approximately 4.6 — boxes of 10 (NDC 0004-1915-06).

10-ml vials — each ml contains 60 mg/ml alphaprodine hydrochloride compounded with 0.45% phenol as preservative, 0.0875% citric acid and sodium citrate to adjust pH to approximately 4.6 (NDC 0004-1917-06).

Narcotic order required.

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