CYCLOPAK- cyclobenzaprine hydrochloride tablet , lidocaine and prilocaine, PureTek Corporation

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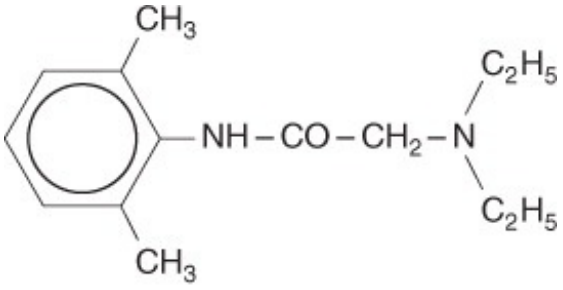
Cyclopak

(Cyclobenzaprine HCl 5mg, Lidocaine 2.5% and Prilocaine 2.5% Cream USP 30gm and Pill Swallowing Spray, 2 fl oz)

DESCRIPTION

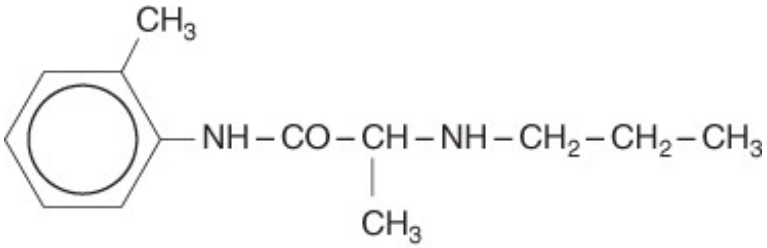
Lidocaine 2.5% and Prilocaine 2.5% Cream, USP is an emulsion in which the oil phase is a eutectic mixture of lidocaine and prilocaine cream in a ratio of 1:1 by weight. This eutectic mixture has a melting point below room temperature and therefore both local anesthetics exist as a liquid oil rather than as crystals. It is packaged in 5 gram and 30 gram tubes.

Lidocaine is chemically designated as acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl), has an octanol: water partition ratio of 43 at pH 7.4, and has the following structure:



$C_{14}H_{22}N_2O$ M.W. 234.3

Prilocaine is chemically designated as propanamide, N-(2-methylphenyl)-2-(propylamino), has an octanol: water partition ratio of 25 at pH 7.4, and has the following structure:



$C_{13}H_{20}N_2O$ M.W. 220.3

Each gram of lidocaine and prilocaine cream contains lidocaine 25 mg, prilocaine 25 mg, polyoxyethylene fatty acid esters (as emulsifiers), carboxypolymethylene (as a thickening agent), sodium hydroxide to adjust to a pH approximating 9, and purified

water to 1 gram. Lidocaine and prilocaine cream contains no preservative, however it passes the USP antimicrobial effectiveness test due to the pH. The specific gravity of lidocaine and prilocaine cream is 1.00.

CLINICAL PHARMACOLOGY

Mechanism of Action: Lidocaine and prilocaine cream applied to intact skin under occlusive dressing, provides dermal analgesia by the release of lidocaine and prilocaine from the cream into the epidermal and dermal layers of the skin and by the accumulation of lidocaine and prilocaine in the vicinity of dermal pain receptors and nerve endings. Lidocaine and prilocaine are amide-type local anesthetic agents. Both lidocaine and prilocaine stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic action.

The onset, depth and duration of dermal analgesia on intact skin provided by lidocaine and prilocaine cream depend primarily on the duration of application. To provide sufficient analgesia for clinical procedures such as intravenous catheter placement and venipuncture, lidocaine and prilocaine cream should be applied under an occlusive dressing for at least 1 hour. To provide dermal analgesia for clinical procedures such as split skin graft harvesting, lidocaine and prilocaine cream should be applied under occlusive dressing for at least 2 hours. Satisfactory dermal analgesia is achieved 1 hour after application, reaches maximum at 2 to 3 hours, and persists for 1 to 2 hours after removal. Absorption from the genital mucosa is more rapid and onset time is shorter (5 to 10 minutes) than after application to intact skin. After a 5 to 10 minute application of lidocaine and prilocaine cream to female genital mucosa, the average duration of effective analgesia to an argon laser stimulus (which produced a sharp, pricking pain) was 15 to 20 minutes (individual variations in the range of 5 to 45 minutes).

Dermal application of lidocaine and prilocaine cream may cause a transient, local blanching followed by a transient, local redness or erythema.

Pharmacokinetics: Lidocaine and prilocaine cream is a eutectic mixture of lidocaine 2.5% and prilocaine 2.5% formulated as an oil in water emulsion. In this eutectic mixture, both anesthetics are liquid at room temperature (see DESCRIPTION) and the penetration and subsequent systemic absorption of both prilocaine and lidocaine are enhanced over that which would be seen if each component in crystalline form was applied separately as a 2.5% topical cream.

Absorption: The amount of lidocaine and prilocaine systemically absorbed from lidocaine and prilocaine cream is directly related to both the duration of application and to the area over which it is applied. In two pharmacokinetic studies, 60 g of lidocaine and prilocaine cream (1.5 g lidocaine and 1.5 g prilocaine) was applied to 400 cm^2 of intact skin on the lateral thigh and then covered by an occlusive dressing. The subjects were then randomized such that one-half of the subjects had the occlusive dressing and residual cream removed after 3 hours, while the remainder left the dressing in place for 24 hours. The results from these studies are summarized below.

TABLE 1 Absorption of Lidocaine and Prilocaine from Lidocaine and Prilocaine Cream: Normal Volunteers (N=16)

Lidocaine and Prilocaine Cream (g)	Area (cm^2)	Time on (hrs)	Drug Content (mg)	Absorbed (mg)	C_{max} (µg/mL)	T_{max} (hr)
60	400	3	lidocaine 1500	54	0.12	4
			prilocaine 1500	92	0.07	4
60	400	24*	lidocaine 1500	243	0.28	10
			prilocaine 1500	503	0.14	10

*Maximum recommended duration of exposure is 4 hours.

When 60 g of lidocaine and prilocaine cream was applied over 400 cm^2 for 24 hours, peak blood levels of lidocaine are approximately 1/20 the systemic toxic level. Likewise, the maximum prilocaine level is about 1/36 the toxic level. In a pharmacokinetic study, lidocaine and prilocaine cream was applied to penile skin in 20 adult male patients in doses ranging from 0.5 g to 3.3 g for 15 minutes. Plasma concentrations of lidocaine and prilocaine following lidocaine and prilocaine cream application in this study were consistently low (2.5 to 16 ng/mL for lidocaine and 2.5 to 7 ng/mL for prilocaine). The application of lidocaine and prilocaine cream to broken or inflamed skin, or to 2,000 cm^2 or more of skin where more of both anesthetics are absorbed, could result in higher plasma levels that could, in susceptible individuals, produce a systemic pharmacologic response.

The absorption of lidocaine and prilocaine cream applied to genital mucous membranes was studied in two open-label clinical trials. Twenty-nine patients received 10 g of lidocaine and prilocaine cream applied for 10 to 60 minutes in the vaginal fornices. Plasma concentrations of lidocaine and prilocaine following lidocaine and prilocaine cream application in these studies ranged from 148 to 641 ng/mL for lidocaine and 40 to 346 ng/mL for prilocaine and time to reach maximum concentration (t_{max}) ranged from 21 to 125 minutes for lidocaine and from 21 to 95 minutes for prilocaine. These levels are well below the concentrations anticipated to give rise to systemic toxicity (approximately 5000 ng/mL for lidocaine and prilocaine).

Distribution: When each drug is administered intravenously, the steady-state volume of distribution is 1.1 to 2.1 L/kg (mean 1.5, ±0.3 SD, n=13) for lidocaine and is 0.7 to 4.4 L/kg (mean 2.6, ±1.3 SD, n=13) for prilocaine. The larger distribution volume for prilocaine produces the lower plasma concentrations of prilocaine observed when equal amounts of prilocaine and lidocaine are administered. At concentrations produced by application of lidocaine and prilocaine cream, lidocaine is approximately 70% bound to plasma proteins, primarily alpha-1-acid glycoprotein. At much higher plasma concentrations (1 to 4 µg/mL of free base) the plasma protein binding of lidocaine is concentration dependent. Prilocaine is 55% bound to plasma proteins. Both lidocaine and prilocaine cross the placental and blood brain barrier, presumably by passive diffusion.

Metabolism: It is not known if lidocaine or prilocaine are metabolized in the skin. Lidocaine is metabolized rapidly by the liver to a number of metabolites including monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which have pharmacologic activity similar to, but less potent than that of lidocaine. The metabolite, 2,6-xylidine, has unknown pharmacologic activity. Following intravenous administration, MEGX and GX concentrations in serum range from 11 to 36% and from 5 to 11% of

lidocaine concentrations, respectively. Prilocaine is metabolized in both the liver and kidneys by amidases to various metabolites including *ortho*-toluidine and N-n-propylalanine. It is not metabolized by plasma esterases. The *ortho*-toluidine metabolite has been shown to be carcinogenic in several animal models (see Carcinogenesis subsection of PRECAUTIONS). In addition, *ortho*-toluidine can produce methemoglobinemia following systemic doses of prilocaine approximating 8 mg/kg (see ADVERSE REACTIONS). Very young patients, patients with glucose-6-phosphate dehydro- genase deficiencies and patients taking oxidizing drugs such as antimalarials and sulfonamides are more susceptible to methemoglobinemia (see Methemoglobinemia subsection of WARNINGS).

Elimination: The terminal elimination half-life of lidocaine from the plasma following IV administration is approximately 65 to 150 minutes (mean 110, ±24 SD, n=13). More than 98% of an absorbed dose of lidocaine can be recovered in the urine as metabolites or parent drug. The systemic clearance is 10 to 20 mL/min/kg (mean 13, ±3 SD, n=13). The elimination half-life of prilocaine is approximately 10 to 150 minutes (mean 70, ±48 SD, n=13). The systemic clearance is 18 to 64 mL/min/kg (mean 38, ±15 SD, n=13). During intravenous studies, the elimination half-life of lidocaine was statistically significantly longer in elderly patients (2.5 hours) than in younger patients (1.5 hours). No studies are available on the intravenous pharmacokinetics of prilocaine in elderly patients.

Pediatrics: Some pharmacokinetic (PK) data are available in infants (1 month to <2 years old) and children (2 to <12 years old). One PK study was conducted in 9 full-term neonates (mean age: 7 days and mean gestational age: 38.8 weeks). The study results show that neonates had comparable plasma lidocaine and prilocaine concentrations and blood methemoglobin concentrations as those found in previous pediatric PK studies and clinical trials. There was a tendency towards an increase in methemoglobin formation. However, due to assay limitations and very little amount of blood that could be collected from neonates, large variations in the above reported concentrations were found.

Special Populations: No specific PK studies were conducted. The half-life may be increased in cardiac or hepatic dysfunction. Prilocaine's half-life also may be increased in hepatic or renal dysfunction since both of these organs are involved in prilocaine metabolism.

CLINICAL STUDIES

Lidocaine and prilocaine cream application in adults prior to IV cannulation or venipuncture was studied in 200 patients in four clinical studies in Europe. Application for at least 1 hour provided significantly more dermal analgesia than placebo cream or ethyl chloride. Lidocaine and prilocaine cream was comparable to subcutaneous lidocaine, but was less efficacious than intradermal lidocaine. Most patients found lidocaine and prilocaine cream treatment preferable to lidocaine infiltration or ethyl chloride spray.

Lidocaine and prilocaine cream was compared with 0.5% lidocaine infiltration prior to skin graft harvesting in one open label study in 80 adult patients in England. Application of lidocaine and prilocaine cream for 2 to 5 hours provided dermal analgesia comparable to lidocaine infiltration.

Lidocaine and prilocaine cream application in children was studied in seven non-US studies (320 patients) and one US study (100 patients). In controlled studies, application of lidocaine and prilocaine cream for at least 1 hour with or without presurgical medication prior to needle insertion provided significantly more pain reduction than placebo. In children under the age of seven years, lidocaine and prilocaine cream was less effective than in older children or adults.

Lidocaine and prilocaine cream was compared with placebo in the laser treatment of facial port-wine stains in 72 pediatric patients (ages 5 to 16). Lidocaine and prilocaine cream was effective in providing pain relief during laser treatment.

Lidocaine and prilocaine cream alone was compared with lidocaine and prilocaine cream followed by lidocaine infiltration and lidocaine infiltration alone prior to cryotherapy for the removal of male genital warts. The data from 121 patients demonstrated that lidocaine and prilocaine cream was not effective as a sole anesthetic agent in managing the pain from the surgical procedure. The administration of lidocaine and prilocaine cream prior to lidocaine infiltration provided significant relief of discomfort associated with local anesthetic infiltration and thus was effective in the overall reduction of pain from the procedure only when used in conjunction with local anesthetic infiltration of lidocaine.

Lidocaine and prilocaine cream was studied in 105 full term neonates (gestational age: 37 weeks) for blood drawing and circumcision procedures. When considering the use of lidocaine and prilocaine cream in neonates, the primary concerns are the systemic absorption of the active ingredients and the subsequent formation of methemoglobin. In clinical studies performed in neonates, the plasma levels of lidocaine, prilocaine, and methemoglobin were not reported in a range expected to cause clinical symptoms.

Local dermal effects associated with lidocaine and prilocaine cream application in these studies on intact skin included paleness, redness and edema and were transient in nature (see ADVERSE REACTIONS).

The application of lidocaine and prilocaine cream on genital mucous membranes for minor, superficial surgical procedures (eg, removal of condylomata acuminata) was studied in 80 patients in a placebo-controlled clinical trial (60 patients received lidocaine and prilocaine cream and 20 patients received placebo). Lidocaine and prilocaine cream (5 to 10 g) applied between 1 and 75 minutes before surgery, with a median time of 15 minutes, provided effective local anesthesia for minor superficial surgical procedures. The greatest extent of analgesia, as measured by VAS scores, was attained after 5 to 15 minutes' application. The application of lidocaine and prilocaine cream to genital mucous membranes as pretreatment for local anesthetic infiltration was studied in a double-blind, placebo-controlled study in 44 female patients (21 patients received lidocaine and prilocaine cream and 23 patients received placebo) scheduled for infiltration prior to a surgical procedure of the external vulva or genital mucosa. Lidocaine and prilocaine cream applied to the genital mucous membranes for 5 to 10 minutes resulted in adequate topical anesthesia for local anesthetic injection.

Individualization of Dose: The dose of lidocaine and prilocaine cream that provides effective analgesia depends on the duration of the application over the treated area.

All pharmacokinetic and clinical studies employed a thick layer of lidocaine and prilocaine cream (1 to 2 g/10 cm^2). The duration of application prior to venipuncture was 1 hour. The duration of application prior to taking split thickness skin grafts was 2 hours. A

thinner application has not been studied and may result in less complete analgesia or a shorter duration of adequate analgesia.

The systemic absorption of lidocaine and prilocaine is a side effect of the desired local effect. The amount of drug absorbed depends on surface area and duration of application. The systemic blood levels depend on the amount absorbed and patient size (weight) and the rate of systemic drug elimination. Long duration of application, large treatment area, small patients, or impaired elimination may result in high blood levels. The systemic blood levels are typically a small fraction (1/20 to 1/36) of the blood levels that produce toxicity. Table 2 below gives maximum recommended doses, application areas and application times for infants and children.

TABLE 2 LIDOCAINE AND PRILOCAINE CREAM MAXIMUM RECOMMENDED DOSE, APPLICATION AREA, AND APPLICATION TIME BY AGE AND WEIGHT* For Infants and Children Based on Application to Intact Skin

Age and Body Weight Requirements	Maximum Total Dose of Lidocaine and Prilocaine cream	Maximum Application Area**	Maximum Application Time
0 up to 3 months or < 5 kg	1 g	10 cm^2	1 hour
3 up to 12 months and > 5 kg	2 g	20 cm^2	4 hours
1 to 6 years and > 10 kg	10 g	100 cm^2	4 hours
7 to 12 years and > 20 kg	20 g	200 cm^2	4 hours

Please note: If a patient greater than 3 months old does not meet the minimum weight requirement, the maximum total dose of lidocaine and prilocaine cream should be restricted to that which corresponds to the patient's **weight.**

* These are broad guidelines for avoiding systemic toxicity in applying lidocaine and prilocaine cream to patients with normal intact skin and with normal renal and hepatic function.

** For more individualized calculation of how much lidocaine and prilocaine may be absorbed, physicians can use the following estimates of lidocaine and prilocaine absorption for children and adults:

The estimated mean (±SD) absorption of lidocaine is 0.045 (±0.016) mg/cm^2/hr.

The estimated mean (±SD) absorption of prilocaine is 0.077 (±0.036) mg/cm^2/hr.

An I.V. antiarrhythmic dose of lidocaine is 1 mg/kg (70 mg/70 kg) and gives a blood level of about 1 µg/mL. Toxicity would be expected at blood levels above 5 µg/mL. Smaller areas of treatment are recommended in a debilitated patient, a small child or a patient with impaired elimination. Decreasing the duration of application is likely to decrease the analgesic effect.

INDICATIONS AND USAGE

Lidocaine and prilocaine cream (a eutectic mixture of lidocaine 2.5% and prilocaine 2.5%) is indicated as a topical anesthetic for use on:

- **normal intact skin** for local analgesia.

- **genital mucous membranes** for superficial minor surgery and as pretreatment for infiltration anesthesia.

Lidocaine and prilocaine cream is not recommended in any clinical situation when penetration or migration beyond the tympanic membrane into the middle ear is possible because of the ototoxic effects observed in animal studies (see WARNINGS).

CONTRAINDICATIONS

Lidocaine and prilocaine cream (lidocaine 2.5% and prilocaine 2.5%) is contraindicated in patients with a known history of sensitivity to local anesthetics of the amide type or to any other component of the product.

WARNINGS

Application of lidocaine and prilocaine cream to larger areas or for longer times than those recommended could result in sufficient absorption of lidocaine and prilocaine resulting in serious adverse effects (see Individualization of Dose).

Patients treated with class III anti-arrhythmic drugs (e.g., amiodarone, bretylium, sotalol, dofetilide) should be under close surveillance and ECG monitoring considered, because cardiac effects may be additive.

Studies in laboratory animals (guinea pigs) have shown that lidocaine and prilocaine cream has an ototoxic effect when instilled into the middle ear. In these same studies, animals exposed to lidocaine and prilocaine cream only in the external auditory canal, showed no abnormality. Lidocaine and prilocaine cream should not be used in any clinical situation when its penetration or migration beyond the tympanic membrane into the middle ear is possible.

Methemoglobinemia: Lidocaine and prilocaine cream should not be used in those rare patients with congenital or idiopathic methemoglobinemia and in infants under the age of twelve months who are receiving treatment with methemoglobin-inducing agents.

Very young patients or patients with glucose-6-phosphate dehydrogenase deficiencies are more susceptible to methemoglobinemia.

Patients taking drugs associated with drug-induced methemoglobinemia such as sulfonamides, acetaminophen, acetanilid, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, quinine, are also at greater risk for developing methemoglobinemia.

There have been reports of significant methemoglobinemia (20 to 30%) in infants and children following excessive applications of lidocaine and prilocaine cream. These cases involved the use of large doses, larger than recommended areas of application, or infants under the age of 3 months who did not have fully mature enzyme systems. In addition, a few of these cases involved the concomitant administration of methemoglobin-inducing agents. Most patients recovered spontaneously after removal of the cream. Treatment with IV methylene blue may be effective if required.

Physicians are cautioned to make sure that parents orother caregivers understand the need for careful application of lidocaine and prilocaine cream, to ensure that the doses and areas of application recommended in Table 2 are not exceeded (especially in children under the age of 3 months) and to limit the period of application to the minimum required to achieve the desired anesthesia.

Neonates and infants up to 3 months of age should be monitored for Met-Hb levels before, during, and after the application of lidocaine and prilocaine cream, provided the test results can be obtained quickly.

PRECAUTIONS

General: Repeated doses of lidocaine and prilocaine cream may increase blood levels of lidocaine and prilocaine. Lidocaine and prilocaine cream should be used with caution in patients who may be more sensitive to the systemic effects of lidocaine and prilocaine including acutely ill, debilitated, or elderly patients.

Lidocaine and prilocaine cream should not be applied to open wounds.

Care should be taken not to allow lidocaine and prilocaine cream to come in contact with the eye because animal studies have demonstrated severe eye irritation. Also the loss of protective reflexes can permit corneal irritation and potential abrasion. Absorption of lidocaine and prilocaine cream in conjunctival tissues has not been determined. If eye contact occurs, immediately wash out the eye with water or saline and protect the eye until sensation returns.

Patients allergic to paraaminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine and/or prilocaine, however, lidocaine and prilocaine cream should be used with caution in patients with a history of drug sensitivities, especially if the etiologic agent is uncertain.

Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations of lidocaine and prilocaine.

Lidocaine and prilocaine have been shown to inhibit viral and bacterial growth. The effect of lidocaine and prilocaine cream on intradermal injections of live vaccines has not been determined.

Information for Patients: When lidocaine and prilocaine cream is used, the patient should be aware that the production of dermal analgesia may be accompanied by the block of all sensations in the treated skin. For this reason, the patient should avoid inadvertent trauma to the treated area by scratching, rubbing, or exposure to extreme hot or cold temperatures until complete sensation has returned.

Lidocaine and prilocaine cream should not be applied near the eyes or on open wounds.

Drug Interactions: Lidocaine and prilocaine cream should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the toxic effects are additive and potentially synergistic.

Prilocaine may contribute to the formation of methemoglobin in patients treated with other drugs known to cause this condition (see Methemoglobinemia subsection of WARNINGS).

Specific interaction studies with lidocaine/prilocaine and class III anti-arrhythmic drugs (e.g., amiodarone, bretylium, sotalol, doetilide) have not been performed, but caution is advised (see WARNINGS).

Should lidocaine and prilocaine cream be used concomitantly with other products containing lidocaine and/or prilocaine, cumulative doses from all formulations must be considered.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Long-term studies in animals designed to evaluate the carcinogenic potential of lidocaine and prilocaine have not been conducted.

Metabolites of prilocaine have been shown to be carcinogenic in laboratory animals. In the animal studies reported below, doses or blood levels are compared with the Single Dermal Administration (SDA) of 60 g of lidocaine and prilocaine cream to 400 cm^2 for 3 hours to a small person (50 kg). The typical application of lidocaine and prilocaine cream for one or two treatments for venipuncture sites (2.5 or 5 g) would be 1/24 or 1/12 of that dose in an adult or about the same mg/kg dose in an infant.

Chronic oral toxicity studies of *ortho*-toluidine, a metabolite of prilocaine, in mice (450 to 7200 mg/m^2; 60 to 960 times SDA) and rats (900 to 4,800 mg/m^2; 60 to 320 times SDA) have shown that *ortho*-toluidine is a carcinogen in both species. The tumors included hepatocarcinomas/adenomas in female mice, multiple occurrences of hemangiosarcomas/hemangiomas in both sexes of mice, sarcomas of multiple organs, transitional-cell carcinomas/papillomas of urinary bladder in both sexes of rats, subcutaneous fibromas/fibrosarcomas and mesotheliomas in male rats, and mammary gland fibroadenomas/adenomas in female rats. The lowest dose tested (450 mg/m^2 in mice, 900 mg/m^2 in rats; 60 times SDA) was carcinogenic in both species. Thus the no-effect dose must be less than 60 times SDA. The animal studies were conducted at 150 to 2,400 mg/kg in mice and at 150 to 800 mg/kg in rats. The dosages have been converted to mg/m^2 for the SDA calculations above.

Mutagenesis: The mutagenic potential of lidocaine HCl has been tested in a bacterial reverse (Ames) assay in Salmonella, an *in vitro* chromosomal aberration assay using human lymphocytes an *in vivo* micronucleus test in mice. There was no indication of mutagenicity or structural damage to chromosomes in these tests.

Ortho-toluidine, a metabolite of prilocaine, at a concentration of 0.5 µg/mL, was genotoxic in *Escherichia coli* DNA repair and phage-induction assays. Urine concentrates from rats treated with *ortho*-toluidine (300 mg/kg orally; 300 times SDA) were mutagenic when examined in *Salmonella typhimurium* in the presence of metabolic activation. Several other tests on *ortho*-toluidine, including reverse mutations in five different *Salmonella typhimurium* strains in the presence or absence of metabolic activation and a study to detect single strand breaks in DNA of V79 Chinese hamster cells, were negative.

Impairment of Fertility: See Use in Pregnancy.

Use in Pregnancy: Teratogenic Effects: Pregnancy Category B.

Reproduction studies with lidocaine have been performed in rats and have revealed no evidence of harm to the fetus (30 mg/kg subcutaneously; 22 times SDA). Reproduction studies with prilocaine have been performed in rats and have revealed no evidence of

impaired fertility or harm to the fetus (300 mg/kg intramuscularly; 188 times SDA). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, lidocaine and prilocaine cream should be used during pregnancy only if clearly needed.

Reproduction studies have been performed in rats receiving subcutaneous administration of an aqueous mixture containing lidocaine HCl and prilocaine HCl at 1:1 (w/w). At 40 mg/kg each, a dose equivalent to 29 times SDA lidocaine and 25 times SDA prilocaine, no teratogenic, embryotoxic or fetotoxic effects were observed.

Labor and Delivery: Neither lidocaine nor prilocaine are contraindicated in labor and delivery. Should lidocaine and prilocaine cream be used concomitantly with other products containing lidocaine and/or prilocaine, cumulative doses from all formulations must be considered.

Nursing Mothers: Lidocaine, and probably prilocaine, are excreted in human milk. Therefore, caution should be exercised when lidocaine and prilocaine cream is administered to a nursing mother since the milk:plasma ratio of lidocaine is 0.4 and is not determined for prilocaine.

Pediatric Use: Controlled studies of lidocaine and prilocaine cream in children under the age of seven years have shown less overall benefit than in older children or adults. These results illustrate the importance of emotional and psychological support of younger children undergoing medical or surgical procedures.

Lidocaine and prilocaine cream should be used with care in patients with conditions or therapy associated with methemoglobinemia (see Methemoglobinemia subsection of WARNINGS).

When using lidocaine and prilocaine cream in young children, especially infants under the age of 3 months, care must be taken to insure that the caregiver understands the need to limit the dose and area of application, and to prevent accidental ingestion (see DOSAGE AND ADMINISTRATION and Methemoglobinemia).

In neonates (minimum gestation age: 37 weeks) and children weighing less than 20 kg, the area and duration of application should be limited (see TABLE 2 in Individualization of Dose).

Studies have not demonstrated the efficacy of lidocaine and prilocaine cream for heel lancing in neonates.

Geriatric Use: Of the total number of patients in clinical studies of lidocaine and prilocaine cream, 180 were age 65 to 74 and 138 were 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Plasma levels of lidocaine and prilocaine in geriatric and non-geriatric patients following application of a thick layer of lidocaine and prilocaine cream are very low and well below potentially toxic levels. However, there are no sufficient data to evaluate quantitative differences in systemic plasma levels of lidocaine and prilocaine between geriatric and non-geriatric patients following application of lidocaine and prilocaine cream.

Consideration should be given for those elderly patients who have enhanced sensitivity

to systemic absorption (see PRECAUTIONS).

After intravenous dosing, the elimination half-life of lidocaine is significantly longer in elderly patients (2.5 hours) than in younger patients (1.5 hours). (See CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS

Localized Reactions: During or immediately after treatment with lidocaine and prilocaine cream on intact skin, the skin at the site of treatment may develop erythema or edema or may be the locus of abnormal sensation. Rare cases of discrete purpuric or petechial reactions at the application site have been reported. Rare cases of hyperpigmentation following the use of lidocaine and prilocaine cream have been reported. The relationship to lidocaine and prilocaine cream or the underlying procedure has not been established. In clinical studies on intact skin involving over 1,300 lidocaine and prilocaine cream-treated subjects, one or more such local reactions were noted in 56% of patients, and were generally mild and transient, resolving spontaneously within 1 or 2 hours. There were no serious reactions that were ascribed to lidocaine and prilocaine cream.

Two recent reports describe blistering on the foreskin in neonates about to undergo circumcision. Both neonates received 1.0 g of lidocaine and prilocaine cream.

In patients treated with lidocaine and prilocaine cream on intact skin, local effects observed in the trials included: paleness (pallor or blanching) 37%, redness (erythema) 30%, alterations in temperature sensations 7%, edema 6%, itching 2% and rash, less than 1%.

In clinical studies on genital mucous membranes involving 378 lidocaine and prilocaine cream-treated patients, one or more application site reactions, usually mild and transient, were noted in 41% of patients. The most common application site reactions were redness (21%), burning sensation (17%) and edema (10%).

Allergic Reactions: Allergic and anaphylactoid reactions associated with lidocaine or prilocaine can occur. They are characterized by urticaria, angioedema, bronchospasm, and shock. If they occur they should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Systemic (Dose Related) Reactions: Systemic adverse reactions following appropriate use of lidocaine and prilocaine cream are unlikely due to the small dose absorbed (see Pharmacokinetics subsection of CLINICAL PHARMACOLOGY). Systemic adverse effects of lidocaine and/or prilocaine are similar in nature to those observed with other amide local anesthetic agents including CNS excitation and/or depression (light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest). Excitatory CNS reactions may be brief or not occur at all, in which case the first manifestation may be drowsiness merging into unconsciousness. Cardiovascular manifestations may include bradycardia, hypotension and cardiovascular collapse leading to arrest.

OVERDOSAGE

Peak blood levels following a 60 g application to 400 cm^2 of intact skin for 3 hours are 0.05 to 0.16 µg/mL for lidocaine and 0.02 to 0.10 µg/mL for prilocaine. Toxic levels of lidocaine (>5 µg/mL) and/or prilocaine (>6 µg/mL) cause decreases in cardiac output, total peripheral resistance and mean arterial pressure. These changes may be attributable to direct depressant effects of these local anesthetic agents on the cardiovascular system. In the absence of massive topical overdose or oral ingestion, evaluation should include evaluation of other etiologies for the clinical effects or overdosage from other sources of lidocaine, prilocaine or other local anesthetics. Consult the package inserts for parenteral Xylocaine (lidocaine HCl) or Citanest (prilocaine HCl) for further information for the management of overdose.

DOSAGE AND ADMINISTRATION

Adult Patients-Intact Skin

A thick layer of lidocaine and prilocaine cream is applied to intact skin and covered with an occlusive dressing (see INSTRUCTIONS FOR APPLICATION).

Minor Dermal Procedures: For minor procedures such as intravenous cannulation and venipuncture, apply 2.5 grams of lidocaine and prilocaine cream (1/2 the 5 g tube) over 20 to 25 cm^2 of skin surface for at least 1 hour. In controlled clinical trials using lidocaine and prilocaine cream, two sites were usually prepared in case there was a technical problem with cannulation or venipuncture at the first site.

Major Dermal Procedures: For more painful dermatological procedures involving a larger skin area such as split thickness skin graft harvesting, apply 2 grams of lidocaine and prilocaine cream per 10 cm^2 of skin and allow to remain in contact with the skin for at least 2 hours.

Adult Male Genital Skin: As an adjunct prior to local anesthetic infiltration, apply a thick layer of lidocaine and prilocaine cream (1 g/10 cm^2) to the skin surface for 15 minutes. Local anesthetic infiltration should be performed immediately after removal of lidocaine and prilocaine cream.

Dermal analgesia can be expected to increase for up to 3 hours under occlusive dressing and persist for 1 to 2 hours after removal of the cream. The amount of lidocaine and prilocaine absorbed during the period of application can be estimated from the information in Table 2, ** footnote, in Individualization of Dose.

Adult Female Patients-Genital Mucous Membranes

For minor procedures on the female external genitalia, such as removal of condylomata acuminata, as well as for use as pretreatment for anesthetic infiltration, apply a thick layer (5 to 10 grams) of lidocaine and prilocaine cream for 5 to 10 minutes.

Occlusion is not necessary for absorption, but may be helpful to keep the cream in place. Patients should be lying down during the lidocaine and prilocaine cream application, especially if no occlusion is used. The procedure or the local anesthetic infiltration should be performed immediately after the removal of lidocaine and prilocaine cream.

Pediatric Patients-Intact Skin

The following are the maximum recommended doses, application areas and application times for lidocaine and prilocaine cream based on a child's age and weight:

Age and Body Weight Requirements	Maximum Total Dose of Lidocaine and Prilocaine Cream	Maximum Application Area	Maximum Application Time
0 up to 3 months or < 5 kg	1 g	10 cm^2	1 hour
3 up to 12 months and > 5 kg	2 g	20 cm^2	4 hours
1 to 6 years and > 10 kg	10 g	100 cm^2	4 hours
7 to 12 years and > 20 kg	20 g	200 cm^2	4 hours

Please note: If a patient greater than 3 months old does not meet the minimum weight requirement, the maximum total dose of lidocaine and prilocaine cream should be restricted to that which corresponds to the patient's **weight** (see INSTRUCTIONS FOR APPLICATION).

Practitioners should carefully instruct caregivers to avoid application of excessive amounts of lidocaine and prilocaine cream (see PRECAUTIONS).

When applying lidocaine and prilocaine cream to the skin of young children, care must be taken to maintain careful observation of the child to prevent accidental ingestion of lidocaine and prilocaine cream or the occlusive dressing. A secondary protective covering to prevent inadvertent disruption of the application site may be useful.

Lidocaine and prilocaine cream should not be used in neonates with a gestational age less than 37 weeks nor in infants under the age of 12 months who are receiving treatment with methemoglobin-inducing agents (see Methemoglobinemia subsection of WARNINGS).

When lidocaine and prilocaine cream (lidocaine 2.5% and prilocaine 2.5%) is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered (see Individualization of Dose). The amount absorbed in the case of lidocaine and prilocaine cream is determined by the area over which it is applied and the duration of application under occlusion (see Table 2, ** footnote, in Individualization of Dose).

Although the incidence of systemic adverse reactions with lidocaine and prilocaine cream is very low, caution should be exercised, particularly when applying it over large areas and leaving it on for longer than 2 hours. The incidence of systemic adverse reactions can be expected to be directly proportional to the area and time of exposure (see Individualization of Dose).

INSTRUCTIONS FOR APPLICATION:

To measure 1 gram of lidocaine and prilocaine cream, the Cream should be gently squeezed out of the tube as a narrow strip that is 1.5 inches (3.8 cm) long and 0.2 inches (5 mm) wide. The strip of lidocaine and prilocaine cream should be contained

within the lines of the diagram shown below.

Use the number of strips that equals your dose, like the examples in the table below.

Dosing Information

1 gram = 1 strip

2 grams = 2 strips

2.5 grams = 2.5 strips

For adult and pediatric patients, apply ONLY as prescribed by your physician.

If your child is below the age of 3 months or small for their age, please inform your doctor before applying lidocaine and prilocaine cream, which can be harmful, if applied over too much skin at one time in young children.

When applying lidocaine and prilocaine cream to the intact skin of young children, it is important that they be carefully observed by an adult in order to prevent the accidental ingestion of or eye contact with lidocaine and prilocaine cream.

Lidocaine and prilocaine cream must be applied to intact skin at least 1 hour before the start of a routine procedure and for 2 hours before the start of a painful procedure. A protective covering of the cream is not necessary for absorption but may be helpful to keep the cream in place.

If using a protective covering, your doctor will remove it, wipe off the lidocaine and prilocaine cream, and clean the entire area with an antiseptic solution before the procedure. The duration of effective skin anesthesia will be at least 1 hour after removal of the protective covering.

Precautions

1. Do not apply near eyes or open wounds.
2. Keep out of the reach of children.
3. If your child becomes very dizzy, excessively sleepy, or develops duskiness of the face or lips after applying lidocaine and prilocaine cream, remove the cream and contact the child's physician at once.

HOW SUPPLIED

Lidocaine 2.5% and Prilocaine 2.5% Cream, USP:

NDC 0591-2070-30

Strength 30 gram/tube

packed individually, in a child-resistant tube.

NOT FOR OPHTHALMIC USE.

KEEP CONTAINER TIGHTLY CLOSED AT ALL TIMES WHEN NOT IN USE.

Storage: Store at 20º to 25ºC (68º to 77ºF); excursions permitted between 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Rx Only

Keep out of the reach of children.

For all medical inquiries contact:
ACTAVIS
Medical Communications
Parsippany, NJ 07054
1-800-272-5525

Manufactured by:
Teligent Pharma, Inc.
Buena, NJ 08310 USA

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Parsippany, NJ 07054 USA

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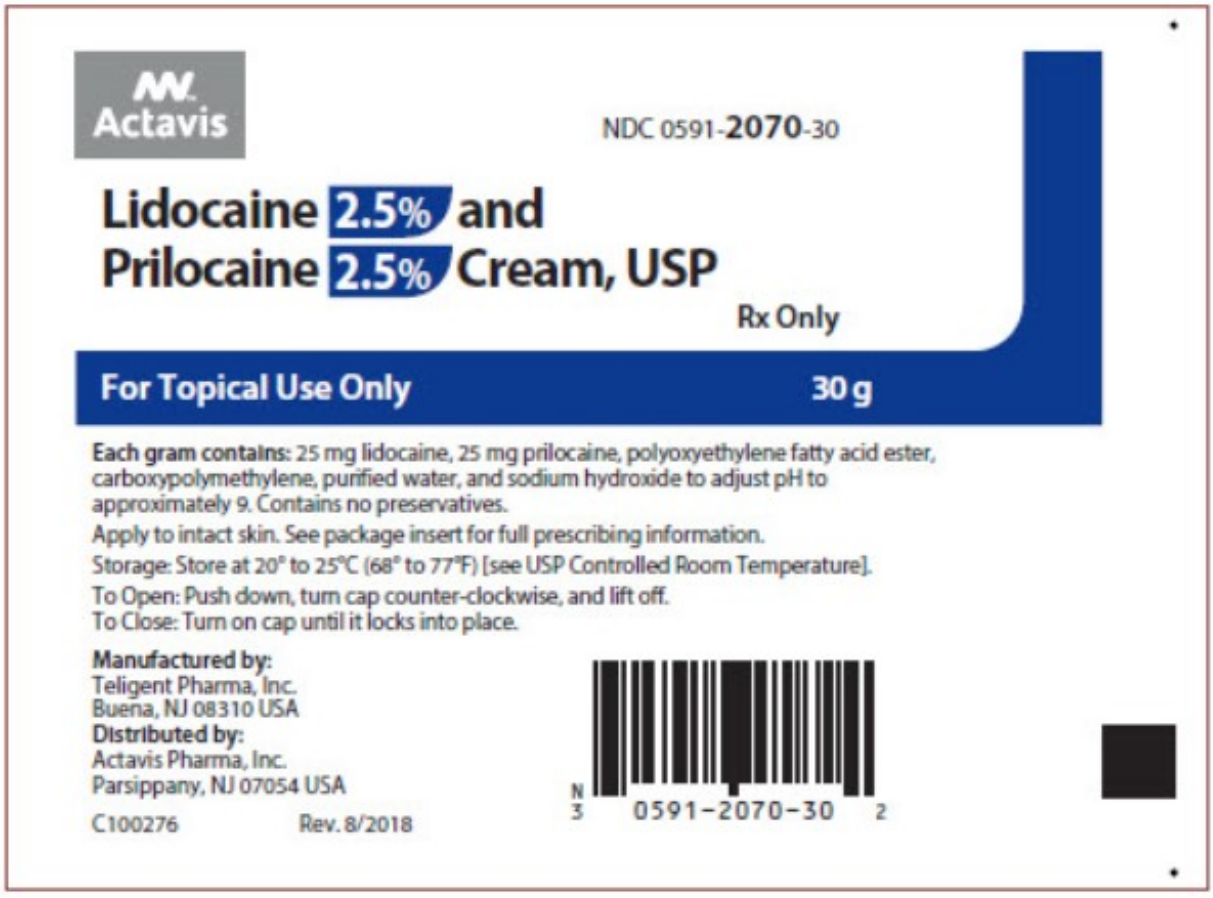
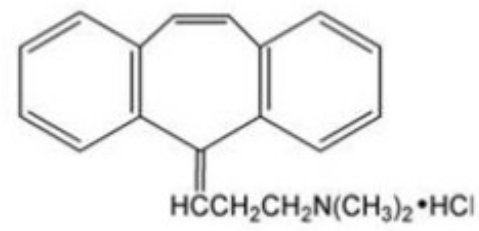


DESCRIPTION

Cyclobenzaprine hydrochloride, USP is a tricyclic amine salt which is white to off white, odourless, crystalline powder with the molecular formula C 20H 21N • HCl and a molecular weight of 311.9. It has a melting point of 217°C, and a pKa of 8.47 at 25°C. It is freely soluble in water, in alcohol and in methanol, sparingly soluble in isopropanol, slightly soluble in chloroform and in methylene chloride, insoluble in n-hexane. If aqueous

solutions are made alkaline, the free base separates. Cyclobenzaprine hydrochloride is designated chemically as 3-(5H -dibenzo[a,d] cycloheptен-5-ylidene)- N,N-dimethyl-1-propanamine hydrochloride, and has the following structural formula:



Cyclobenzaprine hydrochloride tablets, USP are available as 5 mg, 7.5 mg and 10 mg tablets for oral administration. Each 5 mg, 7.5 mg and 10 mg tablet contains cyclobenzaprine hydrochloride and the following inactive ingredients: crospovidone, hypromellose, lactose anhydrous, macrogol, magnesium stearate, polysorbate 80, pregelatinized starch, silicified microcrystalline cellulose, titanium dioxide. The tablets of 5 mg and 10 mg also contain D&C Yellow #10 Aluminum Lake and FD&C Yellow #6 Sunset Yellow FCF Aluminum Lake. In addition, the 5 mg tablets contain FD&C Blue #2/INDIGO Carmine Aluminum Lake.

CLINICAL PHARMACOLOGY

Cyclobenzaprine hydrochloride relieves skeletal muscle spasm of local origin without interfering with muscle function. It is ineffective in muscle spasm due to central nervous system disease.

Cyclobenzaprine reduced or abolished skeletal muscle hyperactivity in several animal models. Animal studies indicate that cyclobenzaprine does not act at the neuromuscular junction or directly on skeletal muscle. Such studies show that cyclobenzaprine acts primarily within the central nervous system at brain stem as opposed to spinal cord levels, although its action on the latter may contribute to its overall skeletal muscle relaxant activity. Evidence suggests that the net effect of cyclobenzaprine is a reduction of tonic somatic motor activity, influencing both gamma (γ) and alpha (α) motor systems.

Pharmacological studies in animals showed a similarity between the effects of cyclobenzaprine and the structurally related tricyclic antidepressants, including reserpine antagonism, norepinephrine potentiation, potent peripheral and central anticholinergic effects, and sedation. Cyclobenzaprine caused slight to moderate increase in heart rate in animals.

Pharmacokinetics

Estimates of mean oral bioavailability of cyclobenzaprine range from 33% to 55%. Cyclobenzaprine exhibits linear pharmacokinetics over the dose range 2.5 mg to 10 mg, and is subject to enterohepatic circulation. It is highly bound to plasma proteins. Drug accumulates when dosed 3 times a day, reaching steady-state within 3 to 4 days at plasma concentrations about 4-fold higher than after a single dose. At steady-state in healthy subjects receiving 10 mg t.i.d. (n = 18), peak plasma concentration was 25.9 ng/mL (range, 12.8 to 46.1 ng/mL), and area under the concentration-time (AUC) curve over an 8-hour dosing interval was 177 ng·hr/mL (range, 80 to 319 ng·hr/mL).

Cyclobenzaprine is extensively metabolized, and is excreted primarily as glucuronides via the kidney. Cytochromes P450 3A4, 1A2, and, to a lesser extent, 2D6, mediate N-demethylation, one of the oxidative pathways for cyclobenzaprine. Cyclobenzaprine is eliminated quite slowly, with an effective half-life of 18 hours (range 8 to 37 hours; n = 18); plasma clearance is 0.7 L/min.

The plasma concentration of cyclobenzaprine is generally higher in the elderly and in patients with hepatic impairment (see PRECAUTIONS: Use in the Elderly and PRECAUTIONS: Impaired Hepatic Function).

Elderly

In a pharmacokinetic study in elderly individuals (≥ 65 yrs old), mean (n = 10) steady-state cyclobenzaprine AUC values were approximately 1.7-fold (171 ng·hr/mL, range 96.1 to 255.3) higher than those seen in a group of 18 younger adults (101.4 ng·hr/mL, range 36.1 to 182.9) from another study. Elderly male subjects had the highest observed mean increase, approximately 2.4-fold (198.3 ng·hr/mL, range 155.6 to 255.3 vs. 83.2 ng·hr/mL, range 41.1 to 142.5 for younger males) while levels in elderly females were increased to a much lesser extent, approximately 1.2-fold (143.8 ng·hr/mL, range 96.1 to 196.3 vs. 115.9 ng·hr/mL, range 36.1 to 182.9 for younger females).

In light of these findings, therapy with cyclobenzaprine in the elderly should be initiated with a 5 mg dose and titrated slowly upward.

Hepatic Impairment

In a pharmacokinetic study of 16 subjects with hepatic impairment (15 mild, 1 moderate per Child-Pugh score), both AUC and C_{max} were approximately double the values seen in the healthy control group. Based on the findings, cyclobenzaprine should be used with caution in subjects with mild hepatic impairment starting with the 5 mg dose and titrating slowly upward. Due to the lack of data in subjects with more severe hepatic insufficiency, the use of cyclobenzaprine in subjects with moderate to severe impairment is not recommended.

No significant effect on plasma levels or bioavailability of cyclobenzaprine or aspirin was noted when single or multiple doses of the two drugs were administered concomitantly. Concomitant administration of cyclobenzaprine and naproxen or diflunisal was well tolerated with no reported unexpected adverse effects. However combination therapy of cyclobenzaprine with naproxen was associated with more side effects than therapy with naproxen alone, primarily in the form of drowsiness. No well controlled studies have been performed to indicate that cyclobenzaprine enhances the clinical effect of aspirin or other analgesics, or whether analgesics enhance the clinical effect of cyclobenzaprine in acute musculoskeletal conditions.

Clinical Studies

Eight double-blind controlled clinical studies were performed in 642 patients comparing cyclobenzaprine hydrochloride 10 mg, diazepam, and placebo. Muscle spasm, local pain and tenderness, limitation of motion, and restriction in activities of daily living were evaluated. In three of these studies there was a significantly greater improvement with cyclobenzaprine than with diazepam, while in the other studies the improvement following both treatments was comparable.

Although the frequency and severity of adverse reactions observed in patients treated with cyclobenzaprine were comparable to those observed in patients treated with

diazepam, dry mouth was observed more frequently in patients treated with cyclobenzaprine and dizziness more frequently in those treated with diazepam. The incidence of drowsiness, the most frequent adverse reaction, was similar with both drugs.

The efficacy of cyclobenzaprine hydrochloride 5 mg was demonstrated in two 7-day, double-blind, controlled clinical trials enrolling 1,405 patients. One study compared cyclobenzaprine hydrochloride 5 mg and 10 mg t.i.d. to placebo; and a second study compared cyclobenzaprine hydrochloride 5 mg and 2.5 mg t.i.d. to placebo. Primary endpoints for both trials were determined by patient-generated data and included global impression of change, medication helpfulness, and relief from starting backache. Each endpoint consisted of a score on a 5-point rating scale (from 0 or worst outcome to 4 or best outcome). Secondary endpoints included a physician's evaluation of the presence and extent of palpable muscle spasm.

Comparisons of cyclobenzaprine hydrochloride 5 mg and placebo groups in both trials established the statistically significant superiority of the 5 mg dose for all three primary endpoints at day 8 and, in the study comparing 5 mg and 10 mg, at day 3 or 4 as well. A similar effect was observed with cyclobenzaprine hydrochloride 10 mg (all endpoints). Physician-assessed secondary endpoints also showed that cyclobenzaprine hydrochloride 5 mg was associated with a greater reduction in palpable muscle spasm than placebo.

Analysis of the data from controlled studies shows that cyclobenzaprine produces clinical improvement whether or not sedation occurs.

Surveillance Program

A post-marketing surveillance program was carried out in 7,607 patients with acute musculoskeletal disorders, and included 297 patients treated with cyclobenzaprine hydrochloride 10 mg for 30 days or longer. The overall effectiveness of cyclobenzaprine was similar to that observed in the double-blind controlled studies; the overall incidence of adverse effects was less (see ADVERSE REACTIONS).

INDICATIONS AND USAGE

Cyclobenzaprine hydrochloride tablets, USP are indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions.

Improvement is manifested by relief of muscle spasm and its associated signs and symptoms, namely, pain, tenderness, limitation of motion, and restriction in activities of daily living.

Cyclobenzaprine hydrochloride tablets should be used only for short periods (up to 2 or 3 weeks) because adequate evidence of effectiveness for more prolonged use is not available and because muscle spasm associated with acute, painful musculoskeletal conditions is generally of short duration and specific therapy for longer periods is seldom warranted.

Cyclobenzaprine hydrochloride tablets have not been found effective in the treatment of spasticity associated with cerebral or spinal cord disease, or in children with cerebral palsy.

CONTRAINDICATIONS

Hypersensitivity to any component of this product.

Concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation. Hyperpyretic crisis seizures and deaths have occurred in patients receiving cyclobenzaprine (or structurally similar tricyclic antidepressants) concomitantly with MAO inhibitor drugs.

Acute recovery phase of myocardial infarction, and patients with arrhythmias, heart block or conduction disturbances, or congestive heart failure.

Hyperthyroidism.

WARNINGS

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with cyclobenzaprine hydrochloride when used in combination with other drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), tramadol, bupropion, meperidine, verapamil, or (MAO) inhibitors. The concomitant use of cyclobenzaprine hydrochloride with MAO inhibitors is contraindicated (see CONTRAINDICATIONS). Serotonin syndrome symptoms may include mental status changes (e.g., confusion, agitation, hallucinations), autonomic instability (e.g., diaphoresis, tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., tremor, ataxia, hyperreflexia, clonus, muscle rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Treatment with cyclobenzaprine hydrochloride and any concomitant serotonergic agents should be discontinued immediately if the above reactions occur and supportive symptomatic treatment should be initiated. If concomitant treatment with cyclobenzaprine hydrochloride and other serotonergic drugs is clinically warranted, careful observation is advised, particularly during treatment initiation or dose increases (see PRECAUTIONS: Drug Interactions).

Cyclobenzaprine is closely related to the tricyclic antidepressants, e.g., amitriptyline and imipramine. In short term studies for indications other than muscle spasm associated with acute musculoskeletal conditions, and usually at doses somewhat greater than those recommended for skeletal muscle spasm, some of the more serious central nervous system reactions noted with the tricyclic antidepressants have occurred (see WARNINGS, below, and ADVERSE REACTIONS).

Tricyclic antidepressants have been reported to produce arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke.

Cyclobenzaprine may enhance the effects of alcohol, barbiturates, and other CNS depressants.

PRECAUTIONS

General

Because of its atropine-like action, cyclobenzaprine should be used with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure, and in patients taking anticholinergic medication.

Impaired Hepatic Function

The plasma concentration of cyclobenzaprine is increased in patients with hepatic impairment (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Hepatic Impairment). These patients are generally more susceptible to drugs with potentially sedating effects, including cyclobenzaprine. Cyclobenzaprine hydrochloride should be used with caution in subjects with mild hepatic impairment starting with a 5 mg dose and titrating slowly upward. Due to the lack of data in subjects with more severe hepatic insufficiency, the use of cyclobenzaprine in subjects with moderate to severe impairment is not recommended.

Information for Patients

Cyclobenzaprine, especially when used with alcohol or other CNS depressants, may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle. In the elderly, the frequency and severity of adverse events associated with the use of cyclobenzaprine, with or without concomitant medications, is increased. In elderly patients, cyclobenzaprine hydrochloride should be initiated with a 5 mg dose and titrated slowly upward.

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of cyclobenzaprine hydrochloride and other drugs, such as SSRIs, SNRIs, TCAs, tramadol, bupropion, meperidine, verapamil or MAO inhibitors. Patients should be advised of the signs and symptoms of serotonin syndrome, and be instructed to seek medical care immediately if they experience these symptoms (see WARNINGS and PRECAUTIONS: Drug Interactions).

Drug Interactions

Cyclobenzaprine may have life-threatening interactions with MAO inhibitors (see CONTRAINDICATIONS). Postmarketing cases of serotonin syndrome have been reported during combined use of cyclobenzaprine hydrochloride and other drugs, such as SSRIs, SNRIs, TCAs, tramadol, bupropion, meperidine, verapamil or MAO inhibitors. If concomitant treatment with cyclobenzaprine hydrochloride and other serotonergic drugs is clinically warranted, careful observation is advised, particularly during treatment initiation or dose increases (see WARNINGS).

Cyclobenzaprine may enhance the effects of alcohol, barbiturates, and other CNS depressants.

Tricyclic antidepressants may block the antihypertensive action of guanethidine and similarly acting compounds.

Tricyclic antidepressants may enhance the seizure risk in patients taking tramadol.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In rats treated with cyclobenzaprine for up to 67 weeks at doses of approximately 5 to 40 times the maximum recommended human dose, pale, sometimes enlarged, livers were noted and there was a dose-related hepatocyte vacuolation with lipidosis. In the higher dose groups this microscopic change was seen after 26 weeks and even earlier in rats which died prior to 26 weeks; at lower doses, the change was not seen until after

26 weeks.

Cyclobenzaprine did not affect the onset, incidence or distribution of neoplasia in an 81-week study in the mouse or in a 105-week study in the rat.

At oral doses of up to 10 times the human dose, cyclobenzaprine did not adversely affect the reproductive performance or fertility of male or female rats. Cyclobenzaprine did not demonstrate mutagenic activity in the male mouse at dose levels of up to 20 times the human dose.

Pregnancy

Teratogenic Effects. Pregnancy Category B

Reproduction studies have been performed in rats, mice and rabbits at doses up to 20 times the human dose, and have revealed no evidence of impaired fertility or harm to the fetus due to cyclobenzaprine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because cyclobenzaprine is closely related to the tricyclic antidepressants, some of which are known to be excreted in human milk, caution should be exercised when cyclobenzaprine hydrochloride is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of cyclobenzaprine in pediatric patients below 15 years of age have not been established.

Use in the Elderly

The plasma concentration of cyclobenzaprine is increased in the elderly (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Elderly). The elderly may also be more at risk for CNS adverse events such as hallucinations and confusion, cardiac events resulting in falls or other sequelae, drug-drug and drug-disease interactions. For these reasons, in the elderly, cyclobenzaprine should be used only if clearly needed. In such patients cyclobenzaprine hydrochloride should be initiated with a 5 mg dose and titrated slowly upward.

ADVERSE REACTIONS

Incidence of most common adverse reactions in the two double-blind*, placebo-controlled 5 mg studies (incidence of > 3% on cyclobenzaprine hydrochloride 5 mg):

	Cyclobenzaprine Hydrochloride 5 mg N = 464	Cyclobenzaprine Hydrochloride 10 mg N = 249	Placebo N = 469
Drowsiness	29%	38%	10%
Dry Mouth	21%	32%	7%

Fatigue	6%	6%	3%
Headache	5%	5%	8%

*Note: Cyclobenzaprine hydrochloride 10 mg data are from one clinical trial. Cyclobenzaprine hydrochloride 5 mg and placebo data are from two studies.

Adverse reactions which were reported in 1% to 3% of the patients were: abdominal pain, acid regurgitation, constipation, diarrhea, dizziness, nausea, irritability, mental acuity decreased, nervousness, upper respiratory infection, and pharyngitis.

The following list of adverse reactions is based on the experience in 473 patients treated with cyclobenzaprine hydrochloride 10 mg in additional controlled clinical studies, 7,607 patients in the postmarketing surveillance program, and reports received since the drug was marketed. The overall incidence of adverse reactions among patients in the surveillance program was less than the incidence in the controlled clinical studies.

The adverse reactions reported most frequently with cyclobenzaprine were drowsiness, dry mouth and dizziness. The incidence of these common adverse reactions was lower in the surveillance program than in the controlled clinical studies:

	Clinical Studies with Cyclobenzaprine hydrochloride 10 mg	Surveillance Program with Cyclobenzaprine hydrochloride 10 mg
Drowsiness	39%	16%
Dry Mouth	27%	7%
Dizziness	11%	3%

Among the less frequent adverse reactions, there was no appreciable difference in incidence in controlled clinical studies or in the surveillance program. Adverse reactions which were reported in 1% to 3% of the patients were: fatigue/tiredness, asthenia, nausea, constipation, dyspepsia, unpleasant taste, blurred vision, headache, nervousness, and confusion.

The following adverse reactions have been reported in postmarketing experience or with an incidence of less than 1% of patients in clinical trials with the 10 mg tablet:

Body as a Whole: Syncope; malaise.

Cardiovascular: Tachycardia; arrhythmia; vasodilatation; palpitation; hypotension.

Digestive: Vomiting; anorexia; diarrhea; gastrointestinal pain; gastritis; thirst; flatulence; edema of the tongue; abnormal liver function and rare reports of hepatitis, jaundice and cholestasis.

Hypersensitivity: Anaphylaxis; angioedema; pruritus; facial edema; urticaria; rash.

Musculoskeletal: Local weakness.

Nervous System and Psychiatric: Seizures; ataxia; vertigo; dysarthria; tremors; hypertonia; convulsions; muscle twitching; disorientation; insomnia; depressed mood; abnormal sensations; anxiety; agitation; psychosis; abnormal thinking and dreaming;

hallucinations; excitement; paresthesia; diplopia, serotonin syndrome.

Skin: Sweating.

Special Senses: Ageusia; tinnitus.

Urogenital: Urinary frequency and/or retention.

Causal Relationship Unknown

Other reactions, reported rarely for cyclobenzaprine under circumstances where a causal relationship could not be established or reported for other tricyclic drugs, are listed to serve as alerting information to physicians:

Body as a Whole: Chest pain; edema.

Cardiovascular: Hypertension; myocardial infarction; heart block; stroke.

Digestive: Paralytic ileus; tongue discoloration; stomatitis; parotid swelling.

Endocrine: Inappropriate ADH syndrome.

Hematic and Lymphatic: Purpura; bone marrow depression; leukopenia; eosinophilia; thrombocytopenia.

Metabolic, Nutritional and Immune: Elevation and lowering of blood sugar levels; weight gain or loss.

Musculoskeletal: Myalgia.

Nervous System and Psychiatric: Decreased or increased libido; abnormal gait; delusions; aggressive behavior; paranoia; peripheral neuropathy; Bell's palsy; alteration in EEG patterns; extrapyramidal symptoms.

Respiratory: Dyspnea.

Skin: Photosensitization; alopecia.

Urogenital: Impaired urination; dilatation of urinary tract; impotence; testicular swelling; gynecomastia; breast enlargement; galactorrhea.

Pharmacologic similarities among the tricyclic drugs require that certain withdrawal symptoms be considered when cyclobenzaprine is administered, even though they have not been reported to occur with this drug. Abrupt cessation of treatment after prolonged administration rarely may produce nausea, headache, and malaise. These are not indicative of addiction.

OVERDOSAGE

Although rare, deaths may occur from overdosage with cyclobenzaprine. Multiple drug ingestion (including alcohol) is common in deliberate cyclobenzaprine overdose. **As management of overdose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment**. Signs and symptoms of toxicity may develop rapidly after cyclobenzaprine overdose; therefore, hospital monitoring is required as soon as possible. The acute oral LD_{50} of cyclobenzaprine is approximately 338 and 425 mg/kg in mice and rats, respectively.

Manifestations

The most common effects associated with cyclobenzaprine overdose are drowsiness and tachycardia. Less frequent manifestations include tremor, agitation, coma, ataxia, hypertension, slurred speech, confusion, dizziness, nausea, vomiting, and hallucinations. Rare but potentially critical manifestations of overdose are cardiac arrest, chest pain, cardiac dysrhythmias, severe hypotension, seizures, and neuroleptic malignant syndrome.

Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of cyclobenzaprine toxicity. Other potential effects of overdosage include any of the symptoms listed under ADVERSE REACTIONS.

Management

General

As management of overdose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment.

In order to protect against the rare but potentially critical manifestations described above, obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate gastric decontamination. Observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. Monitoring of plasma drug levels should not guide management of the patient. Dialysis is probably of no value because of low plasma concentrations of the drug.

Gastrointestinal Decontamination

All patients suspected of an overdose with cyclobenzaprine should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage and emesis is contraindicated.

Cardiovascular

A maximal limb-lead QRS duration of ≥ 0.10 seconds may be the best indication of the severity of the overdose. Serum alkalinization, to a pH of 7.45 to 7.55, using intravenous sodium bicarbonate and hyperventilation (as needed), should be instituted for patients with dysrhythmias and/or QRS widening. A pH > 7.60 or a pCO_2 < 20 mmHg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

CNS

In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines or, if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in close consultation with a poison control center.

Psychiatric Follow-up

Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

Pediatric Management

The principles of management of child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

ADVERSE REACTIONS

Incidence of most common adverse reactions in the two double-blind*, placebo-controlled 5 mg studies (incidence of > 3% on cyclobenzaprine hydrochloride 5 mg):

	Cyclobenzaprine Hydrochloride 5 mg N = 464	Cyclobenzaprine Hydrochloride 10 mg N = 249	Placebo N = 469
Drowsiness	29%	38%	10%
Dry Mouth	21%	32%	7%
Fatigue	6%	6%	3%
Headache	5%	5%	8%

*Note: Cyclobenzaprine hydrochloride 10 mg data are from one clinical trial. Cyclobenzaprine hydrochloride 5 mg and placebo data are from two studies.

Adverse reactions which were reported in 1% to 3% of the patients were: abdominal pain, acid regurgitation, constipation, diarrhea, dizziness, nausea, irritability, mental acuity decreased, nervousness, upper respiratory infection, and pharyngitis.

The following list of adverse reactions is based on the experience in 473 patients treated with cyclobenzaprine hydrochloride 10 mg in additional controlled clinical studies, 7,607 patients in the postmarketing surveillance program, and reports received since the drug was marketed. The overall incidence of adverse reactions among patients in the surveillance program was less than the incidence in the controlled clinical studies.

The adverse reactions reported most frequently with cyclobenzaprine were drowsiness, dry mouth and dizziness. The incidence of these common adverse reactions was lower in the surveillance program than in the controlled clinical studies:

Clinical Studies with

DOSAGE AND ADMINISTRATION

For most patients, the recommended dose of cyclobenzaprine hydrochloride tablets is 5 mg three times a day. Based on individual patient response, the dose may be increased to 10 mg three times a day. Use of cyclobenzaprine hydrochloride tablets for periods longer than 2 or 3 weeks is not recommended (see INDICATIONS AND USAGE).

Less frequent dosing should be considered for hepatically impaired or elderly patients (see PRECAUTIONS: Impaired Hepatic Function, and Use in the Elderly).

HOW SUPPLIED

Cyclobenzaprine Hydrochloride Tablets, USP are available containing 5 mg, 7.5 mg or 10 mg of cyclobenzaprine hydrochloride, USP.

The 5 mg tablets are butter scotch yellow film-coated, round tablets debossed with 020 on one side and plain on other side. They are available as follows:

NDC 52817-330-10

bottles of 100 tablets

Store at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature.]

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Distributed By:

TruPharma, LLC

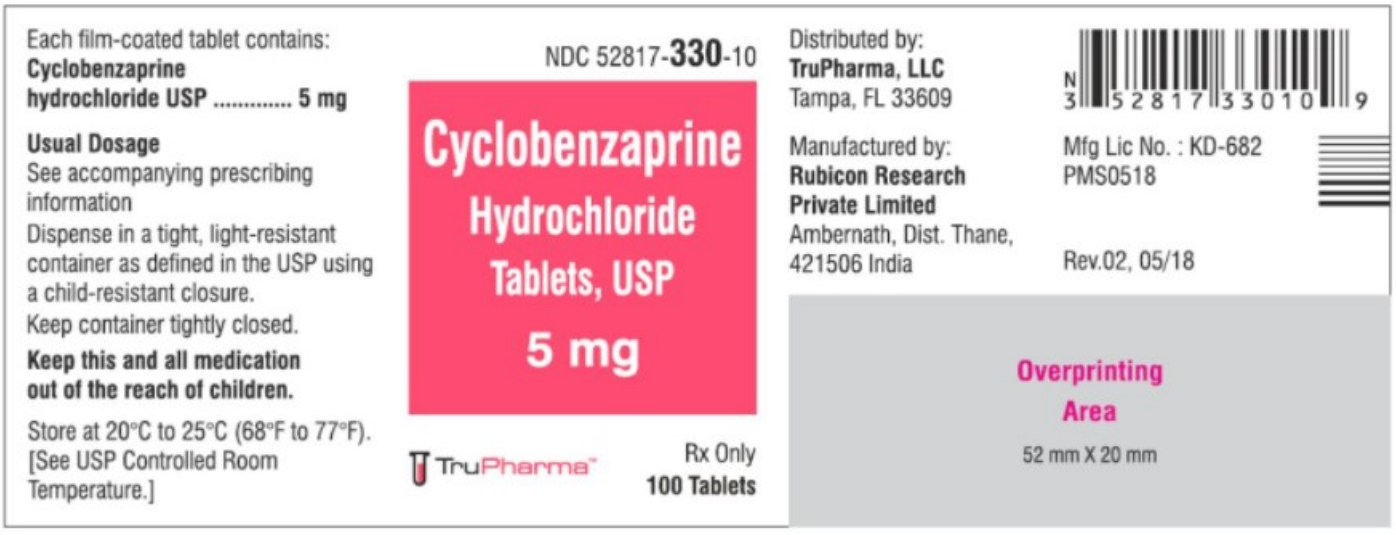
Tampa,FL 33609

Manufactured by:

Rubicon Research Private Limited,

Ambernath,Dist. Thane,421506 India

Rev. 02, June 2018

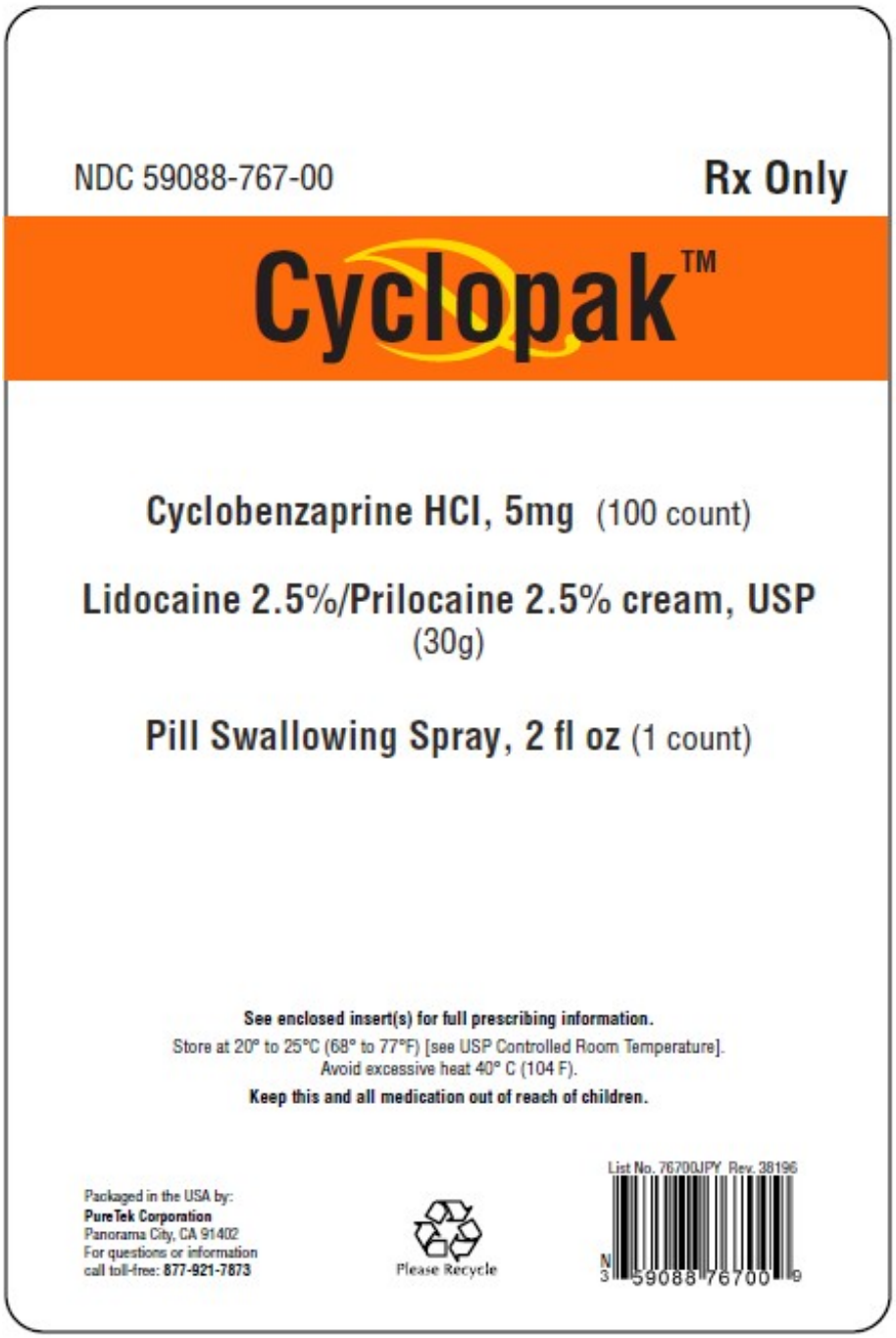


PHARMAPURERX PILL SWALLOWING SPRAY

Cyclopak

Cyclobenzaprine HCl, 5mg (100 count)
Lidocaine 2.5%/Prilocaine 2.5% cream, USP (30g)
Pill Swallowing Spray, 2 fl oz (1 count)

Packaged in the USA by:
PureTek Corporation
Panorama City, CA 91402
For questions or information
call toll-free: 877-921-7873



CYCLOPAK

cyclobenzaprine hydrochloride tablet , lidocaine and prilocaine, kit

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:59088-767

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:59088-767-00	1 in 1 PACKAGE; Type 0: Not a Combination Product	11/30/2020	04/30/2024

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1	3 TUBE	90 g
Part 2	1 BOTTLE	100

Part 1 of 2

LIDOCAINE AND PRILOCAINE

lidocaine and prilocaine cream

Product Information	
Item Code (Source)	NDC:0591-2070
Route of Administration	TOPICAL

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
LIDOCAINE (UNII: 98PI200987) (LIDOCAINE - UNII:98PI200987)	LIDOCAINE	25 mg in 1 g
PRILOCAINE (UNII: 046O35D44R) (PRILOCAINE - UNII:046O35D44R)	PRILOCAINE	25 mg in 1 g

Inactive Ingredients	
Ingredient Name	**Strength**
CARBOMER HOMOPOLYMER TYPE B (ALLYL SUCROSE CROSSLINKED) (UNII: Z135WT9208)	
WATER (UNII: 059QF0KO0R)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
PEG-55 HYDROGENATED CASTOR OIL (UNII: 0WZF1506N9)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0591-2070-30	1 in 1 CARTON		
1		30 g in 1 TUBE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA019941	11/12/2012	

Part 2 of 2

CYCLOBENZAPRINE HYDROCHLORIDE

cyclobenzaprine hydrochloride tablet, film coated

Product Information	
Item Code (Source)	NDC:52817-330
Route of Administration	ORAL

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CYCLOBENZAPRINE HYDROCHLORIDE (UNII: 0VE05JYS2P) (CYCLOBENZAPRINE - UNII:69O5WQQ5TI)	CYCLOBENZAPRINE HYDROCHLORIDE	5 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
CROSPOVIDONE (15 MPA.S AT 5%) (UNII: 68401960MK)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
STARCH, CORN (UNII: O8232NY3SJ)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	

Product Characteristics			
Color	yellow (BUTTER SCOTCH)	**Score**	no score
Shape	ROUND	**Size**	8mm
Flavor		**Imprint Code**	020
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:52817-330-10	100 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA208170	05/31/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
unapproved drug other		11/30/2020	04/30/2024

Labeler - PureTek Corporation (785961046)

Establishment

Name	Address	ID/FEI	Business Operations
PureTek Corporation		785961046	pack(59088-767)

Revised: 1/2024 PureTek Corporation