1.3.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

PROPRIETARY NAME AND DOSAGE FORM

BENCLOPRO 15 extended release capsule

BENCLOPRO 30 extended release capsule

COMPOSITION

BENCLOPRO 15

Each extended release capsule contains cyclobenzaprine 15 mg as cyclobenzaprine hydrochloride.

List of excipients: ethylcellulose, diethyl phthalate, gelatin, hypromellose, polyethylene glycol, red iron oxide, sugar spheres, titanium dioxide and yellow iron oxide

Contains sugar (sucrose in the form of sugar spheres): 109,7 mg.

BENCLOPRO 30

Each extended release capsule contains cyclobenzaprine 30 mg as cyclobenzaprine hydrochloride.

List of excipients: ethylcellulose, diethyl phthalate, FD & C Blue No. 1, FD & C Red No. 40, FD&C Yellow No. 6, gelatin, hypromellose, polyethylene glycol, sugar spheres and titanium dioxide

Contains sugar (sucrose in the form of Sugar Spheres): 87,6 mg.

CATEGORY AND CLASS

A 17.3 Medicines acting on muscular system. Others

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Cyclobenzaprine has muscle relaxing properties. Animal studies have shown that cyclobenzaprine acts primarily within the central nervous system at the brain stem as opposed to the spinal cord level. An overlapping 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 demonstrated 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.

Pharmacokinetic properties

Absorption

In a single-dose study comprised of healthy adult males (n=15), the dose adjusted ratios of the arithmetic means of AUC_{0-168} and

$AUC_{0-\infty}$ indicated that exposure of 30 mg of cyclobenzaprine hydrochloride was about 16 % and 10 % higher than that of 15 mg of cyclobenzaprine hydrochloride, respectively. The dose-adjusted ratios of the arithmetic means of C_{max} indicated that the peak plasma concentration of 30 mg of cyclobenzaprine hydrochloride was about 20 % higher than that of 15 mg of cyclobenzaprine hydrochloride. The half-lives and time to peak plasma cyclobenzaprine concentration were similar for both strengths, that is: cyclobenzaprine 15 mg and 30 mg.

A food effect study conducted in healthy adult subjects (n=15) utilising a single dose of 30 mg of cyclobenzaprine hydrochloride demonstrated a statistically significant increase in bioavailability when 30 mg of cyclobenzaprine hydrochloride was given with food relative to the fasted state. There was a 35 % increase in peak plasma cyclobenzaprine concentration (C_{max}) and a 20 % increase in exposure (AUC_{0-168} and $AUC_{0-\infty}$) in the presence of food. No effect, however, was noted in T_{lag}, T_{max}, or the shape of the mean plasma cyclobenzaprine concentration versus time profile. Cyclobenzaprine in plasma was first detectable in both the fed and fasted states at 1,5 hours.

In a multiple-dose study utilising 30 mg of cyclobenzaprine hydrochloride administered once daily for 7 days in a group of healthy adult volunteers (n=35) a 2,5-fold accumulation of plasma cyclobenzaprine levels was noted at steady-state.

Metabolism and elimination

Cyclobenzaprine is extensively metabolised and is excreted primarily as glucuronides via the kidney. Cytochromes P-450 3A4, 1A2 and, to a lesser extent, 2D6, mediate N-demethylation, one of the oxidative pathways for cyclobenzaprine. Cyclobenzaprine has an elimination half-life of 32 hours (range 8 to 37 hours; n=18); plasma clearance is 0,7 L/min following single dose administration of cyclobenzaprine hydrochloride.

Special populations

Elderly:

Cyclobenzaprine plasma AUC is increased by 40 % and the plasma half-life of cyclobenzaprine is prolonged in elderly subjects greater than 65 years of age (50 hours) a single dose of cyclobenzaprine hydrochloride compared to younger subjects (32 hours). Pharmacokinetic characteristics of cyclobenzaprine following multiple-dose administration of cyclobenzaprine hydrochloride in the elderly were not evaluated.

Hepatic impairment

In a pharmacokinetic study of immediate release cyclobenzaprine in sixteen 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. The pharmacokinetics of cyclobenzaprine in subjects with severe hepatic impairment is not known.

INDICATIONS

BENCLOPRO is indicated as an adjunct to rest and physiotherapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions.

BENCLOPRO should be used only for short periods (up to two or three 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.

BENCLOPRO has been found to be not effective in the treatment of spasticity associated with cerebral or spinal cord disease or in children with cerebral palsy.

CONTRAINDICATIONS

- Hypersensitivity to cyclobenzaprine or to any of the list of excipients of **BENCLOPRO** (see **COMPOSITION**).
- Patients with dysrhythmias, heart block conduction disturbances, or congestive heart failure. During the acute recovery phase of myocardial infarction.
- Hyperthyroidism.
- Concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation (see **INTERACTIONS**).
- Use of **BENCLOPRO** is not recommended in patients with mild, moderate or severe hepatic impairment. This is as a result of a two-fold higher cyclobenzaprine plasma level in subjects with mild hepatic impairment, as compared to healthy subjects, following administration of immediate release cyclobenzaprine and because there is limited dosing flexibility with **BENCLOPRO**.
- Use of **BENCLOPRO** is not recommended in the elderly. This is due to a 40 % increase in cyclobenzaprine plasma levels and a 56 % increase in plasma half-life following administration of **BENCLOPRO** in elderly subjects as compared to young adults.

WARNINGS AND SPECIAL PRECAUTIONS

Cyclobenzaprine is structurally related to the tricyclic antidepressants, e.g., amitriptyline and imipramine. As a result, some of the more serious central nervous system reactions noted with the tricyclic antidepressants have occurred.

The cardiotoxic potential of tricyclic antidepressants is widely acknowledged. They have been reported to produce dysrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke.

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

Hyperpyretic crisis seizures and deaths have occurred in patients receiving **BENCLOPRO** concomitantly with MAO inhibitor medicines

(see **CONTRAINDICATIONS** and **INTERACTIONS**).

Paediatric use

Safety and effectiveness of **BENCLOPRO** has not been established in paediatric patients.

Use in the elderly

The plasma concentration and half-life of cyclobenzaprine are substantially increased in the elderly (see **Pharmacokinetic properties,** *Elderly* and **CONTRAINDICATIONS**). Accordingly, **BENCLOPRO** should not be used in the elderly.

General

The antimuscarinic-like effects of **BENCLOPRO** (cyclobenzaprine

hydrochloride extended release capsules) warrant care in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure and in patients taking anticholinergic medication.

The epileptogenic potential requires care in patients with a history of epilepsy.

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 vacoulation with lipidosis. In the higher dose groups, this microscopic change was seen after 26 weeks and even earlier in rats that 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.

Effects on ability to drive and use machines

As **BENCLOPRO** frequently causes drowsiness, patients using **BENCLOPRO** should not drive or operate machinery.

Contains sugar

BENCLOPRO contains sugar (sucrose) which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrose-isomaltase insufficiency should not take **BENCLOPRO**.

INTERACTIONS

MAOI: **BENCLOPRO** is contraindicated in patients receiving mono-amine oxidase inhibitors, and for at least 14 days after discontinuation of the MAOI's. Life-threatening interactions may occur (see **CONTRAINDICATIONS**).

Alcohol, barbiturates, CNS depressants: **BENCLOPRO** may enhance the effects of alcohol, barbiturates, and other CNS depressants.

Guanethidine: **BENCLOPRO** may block the antihypertensive action of guanethidine and similarly acting compounds.

Tramadol: **BENCLOPRO** may enhance the risk of seizures in patients taking tramadol.

HUMAN REPRODUCTION

The safe use of **BENCLOPRO** has not been established in pregnancy or lactation.

DOSAGE AND DIRECTIONS FOR USE

Doses must be taken at approximately the same time each day. Use of **BENCLOPRO** for periods longer than two or three weeks is not recommended (see **INDICATIONS**).

Dosage considerations for special patient populations

BENCLOPRO should not be used in the elderly or in patients with impaired hepatic function. (see **WARNINGS AND SPECIAL PRECAUTIONS**).

The recommended adult dose is one (1) **BENCLOPRO 15** capsule taken once daily. Some patients may require up to 30 mg/day, given as one (1) **BENCLOPRO 30** capsule taken once daily or as two (2) **BENCLOPRO 15** capsules taken once daily.

SIDE EFFECTS

The following side effects may occur:

Table 1: Incidence of the most common adverse reactions occurring in ≥ 3 % of subjects in any treatment group in the two phase 3, double- blind BENCLOPRO trials.

	BENCLOPRO 15 N=127	**BENCLOPRO 30 N=126**	**Placebo N=128**
Dry mouth	6 %	14 %	2 %
Dizziness	3 %	6 %	2 %
Fatigue	3 %	3 %	2 %
Constipation	1 %	3 %	0 %
Somnolence	1 %	2 %	0 %
Nausea	3 %	3 %	1 %
Dyspepsia	0 %	4 %	1 %

Table 2: Incidence of the most common adverse reactions occurring in ≥ 3 % of subjects in any treatment group in the seven -day pharmacokinetic study of BENCLOPRO.

	BENCLOPRO 30 N = 36

Somnolence	100 %
Dry mouth	58 %
Headache NOS	17 %
Dizziness	19 %
Vision blurred	3 %
Nausea	8 %
Dysgeusia	6 %
Palpitations	6 %
Tremor	6 %
Dry throat	8 %
Acne NOS	6 %
Disturbance in attention	6 %
Insomnia	0 %

Post marketing surveillance

In a post marketing surveillance program (7 607 patients treated with cyclobenzaprine 10 mg TID), the adverse reactions reported most frequently were drowsiness, dry mouth and dizziness. 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 post marketing experience or with an incidence of less than 1 % of patients in clinical trials with the 10 mg TID tablet:

Blood and lymphatic system disorders

The following side effects have been reported and frequencies are unknown:

Purpura; bone marrow depression; leucopenia; eosinophilia; thrombocytopenia.

Immune system disorders

Less frequent: anaphylaxis; angioedema.

Endocrine disorders

The following side effect has been reported and frequencies are unknown:

Inappropriate ADH syndrome.

Metabolism and nutrition disorders

The following side effects have been reported and frequencies are unknown:

Elevation and lowering of blood sugar levels; weight gain or loss.

Nervous system disorders

Less frequent: 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; tinnitus; decreased or increased libido; abnormal gait; delusions; aggressive behavior; paranoia; peripheral neuropathy; Bell's palsy; alteration in EEG patterns; extrapyramidal symptoms.

Cardiac disorders

The following side effects have been reported and frequencies are unknown:

Tachycardia; dysrhythmia; vasodilatation; palpitation; hypotension, syncope; chest pain; myocardial infarction; heart block; stroke; dyspnoea.

Vascular disorders

The following side effects have been reported and frequencies are unknown:

Hypertension; oedema

Gastrointestinal disorders

Less frequent: vomiting; anorexia; diarrhoea; gastrointestinal pain; gastritis; thirst; flatulence; edema of the tongue; ageusia; paralytic ileus; tongue discolouration; stomatitis; parotid swelling.

Hepato-biliary disorders

Less frequent: reports of hepatitis; jaundice and cholestasis.

Skin and subcutaneous tissue disorders

Less frequent: photosensitisation; alopecia; pruritus; facial edema; urticaria; rash.

Musculoskeletal, connective tissue and bone disorders

The following side effects have been reported and frequencies are unknown:

Local weakness; myalgia.

Renal and urinary disorders

Less frequent: urinary frequency and/or retention; impaired urination; dilatation of urinary tract.

Reproductive system and breast disorders

The following side effects have been reported and frequencies are unknown:

Impotence; testicular swelling; gynaecomastia; breast enlargement; galactorrhoea.

Investigations

The following side effect has been reported and frequencies are unknown:

Abnormal liver function.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms

The most common effects associated with cyclobenzaprine overdose are drowsiness and tachycardia. Less frequent symptoms include tremor, agitation, coma, ataxia, hypertension,

slurred speech, confusion, dizziness, nausea, vomiting and hallucinations. Rare but potentially critical symptoms 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 "**SIDE EFFECTS**".

Treatment

Treatment is symptomatic and supportive. Medical professionals to consult the nearest poison control centre. Signs and symptoms of toxicity may develop rapidly after cyclobenzaprine overdose; therefore, hospital monitoring is required as soon as possible. The acute oral LD50 of cyclobenzaprine is approximately 338 and 425 mg/kg in mice and rats, respectively.

General

Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line, and initiate gastric lavage. 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 medicine levels should not guide management of the patient. Dialysis is probably of no value because of low plasma concentrations of the medicine.

Gastric lavage

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 alkalinisation, 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 antidysrhythmics 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 centre.

Psychiatric follow-up

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

Paediatric management

The principles of management of child and adult overdosage are similar. It is strongly recommended that the medical practitioner contact the local poison control center for specific paediatric treatment.

IDENTIFICATION

BENCLOPRO 15: Light orange opaque, hard gelatin body with blue ink imprint "1002-15" and Light Orange opaque cap with blue ink

imprint "EUR" containing spherical beads that are white to yellow in colour.

BENCLOPRO 30: Dark blue opaque, hard gelatin body with white ink imprint "1002-30" and red opaque hard gelatin cap with white ink imprint "EUR" containing spherical beads that are white to yellow in colour.

PRESENTATION

White HDPE bottles with white polypropylene caps containing 30 capsules per bottle.

Blister packs consisting of PVC forming film and Aluminium lidding material containing 15 capsules per card.

STORAGE INSTRUCTIONS

Store at or below 25 ºC.

HDPE bottles: Keep in the original container.

Keep container well closed.

Blister packs: Keep the blisters in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

BENCLOPRO 15: 57/17.1/0701

BENCLOPRO 30: 57/17.1/0702

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