

## MODEX

Tablets

### Composition

Each tablet contains:

Clinidium bromide	2.5 mg
Chlordiazepoxide	5 mg

### Action

Modex combines the anticholinergic action of Clinidium bromide with the anxiolytic effect of Chlordiazepoxide.

Chlordiazepoxide has anxiolytic and central muscle relaxant properties. It has little autonomic activity. Chlordiazepoxide acts as depressant of the central nervous system producing all levels of CNS depression, from mild sedation to hypnosis, to coma depending on the dose. The precise sites and mechanisms of action have not been fully established but various mechanisms have been proposed. It is believed that chlordiazepoxide enhances or facilitates the inhibitory neurotransmitter action of gamma-aminobutyric acid (GABA) which mediates both pre- and post synaptic inhibition in all regions of the CNS following interaction between chlordiazepoxide and a specific neuronal membrane receptor. Anti-anxiety action of chlordiazepoxide is believed to result from stimulation of GABA receptors in the ascending reticular activating system, since GABA in inhibitory receptor stimulation increases inhibition and blocks both cortical and limbic arousal following stimulation of the brainstem reticular formation.

The exact mechanism of action of chlordiazepoxide is not fully established. Skeletal muscle relaxation primarily occurs by inhibiting spinal polysynaptic afferent pathways but it may also inhibit monosynaptic afferent pathways.

### Pharmacokinetics

Chlordiazepoxide is well absorbed with peak blood levels being achieved one or two hours after administration. Rate of absorption is age-related and tends to be delayed in the elderly. After absorption it is highly bound to plasma proteins. The drug has a half-life of 6-30 hours. Steady state levels are usually reached within 3 days.

Chlordiazepoxide is extensively metabolised in the liver by hepatic microsomal enzymes and exhibits capacity limited, protein binding sensitive, hepatic clearance.

Pharmacologically active metabolites of chlordiazepoxide include desmethylchlordiazepoxide, demoxepam, desmethyldiazepam and oxazepam.

The active metabolite desmethylchlordiazepoxide has an accumulation half-life of 10-18 hours and Demoxepam has an accumulation half-life of approximately 21-78 hours. Steady state levels of these active metabolites are reached after 10-15 days with metabolite concentrations which are similar to those of the parent drug.

Chlordiazepoxide is distributed in the CSF corresponding to the free fraction of chlordiazepoxide. It enters the brain following a rapid distribution phase in grey matter with its high blood flow, followed by a longer accumulation phase of chlordiazepoxide and its metabolites in the white matter. The accumulation is more marked following repeated dosage. Chlordiazepoxide has a high affinity for lipids.

Chlordiazepoxide is excreted mainly in the urine mainly in the form of its metabolites; only a small percent of this is in free form most being excreted as conjugates with glucuronide or sulphate. There is no biliary excretion.

### Indications

Control of hypersecretion, hypermotility and emotional factors associated with gastrointestinal disorders due to anxiety and tension states.

### **Contraindications**

- Known hypersensitivity to either of the components of the preparation.
- Presence of glaucoma, and in patients with prostatic hypertrophy and benign bladder neck obstruction.
- During the first trimester of pregnancy and in breastfeeding.

### **Warnings**

Because of the benzodiazepine component, prolonged use may cause dependence.

Withdrawal symptoms similar in character to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of benzodiazepine drugs. These symptoms include convulsions, tremor, abdominal and muscle cramps, vomiting and sweating.

When discontinuing therapy in patients who have been treated with this preparation for prolonged periods, the dosage should be decreased gradually to avoid the possibility of withdrawal symptoms.

Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, rage, insomnia, sleep disturbances and stimulation have been reported. Should these occur, use of the drug should be discontinued.

### **Pregnancy**

#### *Category D*

There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

### **Nursing Mothers**

Chlordiazepoxide or its metabolites may be excreted in breast milk, and use by nursing mothers may cause sedation in the infant.

Clinidium may tend to inhibit lactation.

Modex should not be administered to nursing mothers.

### **Adverse Reactions**

Adverse effects relevant to Clinidium are those typical of anticholinergic agents, e.g. dryness of the mouth, constipation and urinary hesitancy, especially at the beginning of the treatment.

In common with other benzodiazepines, the following side effects have been occasionally reported: drowsiness, fatigue, ataxia, hypotension, gastrointestinal disturbances, visual disturbances, skin rash, urinary retention, headache, confusion, vertigo, change in libido, blood dyscrasias, jaundice, minor menstrual irregularities, extrapyramidal symptoms, changes in EEG patterns (low voltage fast activity) and paradoxical reactions such as acute hyper-excitation states .

In a few instances, syncope has been reported.

Drowsiness and fatigue, if they occur, are usually observed at the beginning of therapy. Usually, they diminish during continued treatment, or when the dosage is decreased.

### **Precautions**

In elderly or debilitated patients, the initial dose should be low. Dosage increments should be made gradually, according to the response of the patient, in order to preclude drowsiness, ataxia, excessive sedation or confusion.

Although hypotension has rarely occurred, this drug should be administered with caution to patients in whom a drop of blood pressure might lead to cardiac complications.

Caution should be exercised in patients with impaired renal or hepatic function. When Modex treatment is protracted, periodic blood counts and liver function tests are recommended.

Patients who experience drowsiness during treatment should be warned that their ability to perform potentially hazardous tasks requiring mental alertness or physical coordination, such as driving a vehicle or operating machinery, might be impaired.

### **Drug Interactions**

*Modex / Alcohol/ General Anaesthetics/ CNS Depressants/ Monoamine Oxidase Inhibitors/ Phenothiazines/ Tricyclic Antidepressants*

Concurrent use may intensify sedative and atropine like effects.

### **Dosage and Administration**

Because of the varied individual responses to tranquilizers and anticholinergics, the optimum dosage of Modex varies according to the diagnosis and response of each individual patient.

Therefore, the dosage should be individualized for maximum beneficial effects. The usual maintenance dosage is 1 or 2 tablets, 3 or 4 times a day, administered before meals and at bedtime. In elderly and debilitated patients, it is recommended that the initial dosage should not exceed 2 Modex tablets per day, to be increased gradually as needed and tolerated.

### **Over Dosage**

#### **Manifestations**

Manifestations of chlordiazepoxide over dosage include somnolence, confusion, coma and diminished reflexes. Respiration, pulse and blood pressure should be monitored, as in all cases of drug over dosage, although, in general, these effects have been minimal following chlordiazepoxide over dosage.

While either of its components may produce the signs and symptoms of Modex over dosage, usually the symptoms due to the anticholinergic effects of Clinidium bromide will be most prominent. The symptoms of Clinidium over dosage are excessive dryness of mouth, blurring of vision, urinary hesitancy and constipation.

#### **Treatment**

General supportive measures should be employed, along with immediate gastric lavage.

0.5-2 mg of Physostigmine should be administered I.V. at a rate of no more than 1 mg/min. This may be repeated in 1-4 mg doses if arrhythmias, convulsions or deep coma recur. Intravenous fluids should be administered, and an adequate airway maintained.

Hypotension may be combated by the use of noradrenaline or metaraminol.

Methylphenidate or caffeine and sodium benzoate may be administered to combat CNS-depressive effects. Dialysis is of limited value. If excitation occurs, barbiturates should not be used.

### **Presentation**

Box of 20 tablets.