impairments of various organs caused or exacerbated by anxiety and tension:

Cardiovascular and Respiratory Systems: (e.g. pseudoangina pectoris, precordial anxiety, tachycardia, emotiogenic hypertension, dyspnea, and hyperventilation);

Gastrointestinal tract: (e.g. irritable bowel syndrome, ulcerative colitis, epigastric pain, spasm, bloating, and diarrhea);

Urogenital tract: (e.g. irritable bladder, urinary frequency, dysmenorrhea);

Other Psychosomatic Disturbances: (e.g. psychogenic headache, psychogenic dermatoses).

Lexotanil is also suitable for treatment of anxiety and tension states due to chronic organic disease and as an adjuvant to psychotherapy in psychoneurosis.

Contraindications
Lexotanil is contraindicated in patients with known hypersensitivity to benzodiazepines, severe respiratory failure, sleep apnea syndrome, myasthenia gravis, and severe liver failure (benzodiazepines are contraindicated in severe liver failure because they can exacerbate hepatic encephalopathy).

Benzodiazepines are not suitable for the primary treatment of psychotic disorders. Benzodiazepines should not be used as sole agents for the treatment of depression or anxiety associated with depression (this can lead the patient to commit suicide). Patients known or presumed to be dependent on alcohol, medicines, or drugs should not take benzodiazepines.

Side Effects
The following side effects can occur: tiredness, drowsiness, muscle weakness, blunting of feelings, reduced alertness, confusion, headache, dizziness, ataxia, and diplopia. These effects occur predominantly at the start of treatment and generally dis-
Depending on the duration of action of the substance concerned, withdrawal phenomena commence a few hours to a week or more after discontinuation of treatment. In order to minimize the risk of dependence, benzodiazepines should be prescribed only after a careful consideration of the indication and should be taken for as short a period as possible (generally no longer than four weeks when used as a hypnotic, for example). The need for continuation of treatment should be reviewed regularly. The risk-benefit relationship of more prolonged treatment is less clear hence it is indicated only in certain patients (e.g. those with panic attacks).

In order to avoid withdrawal phenomena the drug should be discontinued by tapering off the dose in all patients. Should withdrawal phenomena occur, close medical monitoring and support of the patient are required.

Pregnancy and Lactation
The safety of bromazepam in pregnant women has not been established. Spontaneous reports do not suggest a higher incidence of adverse drug reactions than would be expected in a similar untreated group of female patients. A number of studies refer to an increased risk of congenital malformations in the child when tranquilizers (diazepam, meprobamate, and chlordiazepoxide) are taken during the first trimester of pregnancy. Bromazepam should not be taken during pregnancy unless there is a compelling indication for its use and no safer therapeutic alternative is available.

Women of childbearing age who are prescribed the drug should be instructed to inform the doctor if they plan to become pregnant, or suspect that they may be pregnant, in order that the drug can be discontinued. Bromazepam may be taken during the last trimester of pregnancy or during confinement only if there is a compelling indication for its use and no safer therapeutic alternative is available.

Furthermore, children of mothers who took benzodiazepines regularly during late pregnancy may have

appear with continuation of treatment. There have been occasional reports of gastrointestinal disturbances, loss of libido, and skin reactions.

Therapeutic dosage may lead to anterograde amnesia, the risk of which increases with increasing dosage. The amnesia may be accompanied by inappropriate behavior. Preexisting depression may become manifest during treatment with benzodiazepines. Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusions, fits of rage, nightmares, hallucinations, psychoses, inappropriate behavior, and other behavioral disturbances are known to occur with use of benzodiazepines and benzodiazepine-like substances (see Precautions). Such reactions, which occur more commonly in children and elderly patients, call for discontinuation of treatment. Prolonged use (even in therapeutic doses) can lead to physical dependence. Discontinuation of the drug can then lead to the appearance of withdrawal or rebound phenomena (see Precautions). Psychologic dependence can also occur. There are reports of abuse of benzodiazepines.

Precautions
Relative Restrictions on Use
Caution is required in patients with chronic respiratory failure, as they are at risk of respiratory depression.

Alertness, Reactive Capacity
Sedation, amnesia, and impairment of muscle function can impair the ability to drive a motor vehicle or operate machines. These effects are exacerbated by alcohol.

Dependence
Use of benzodiazepines can lead to dependence. This risk increases with dose and duration of treatment and is higher in predisposed patients. Withdrawal phenomena occur especially after abrupt discontinuation and in milder cases are limited to tremor, restlessness, insomnia, anxiety, headache, and impairment of concentration, though symptoms such as sweating, muscle pain, abdominal pain, disturbances of perception, and in rare cases delirium and convulsions may occur.

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Women of childbearing age who are prescribed the drug should be instructed to inform the doctor if they plan to become pregnant, or suspect that they may be pregnant, in order that the drug can be discontinued. Bromazepam may be taken during the last trimester of pregnancy or during confinement only if there is a compelling indication for its use, as because of its pharmacologic action effects such as hypotension, and moderately severe respiratory depression are to be expected in the neonate. Furthermore, children of mothers who took benzodiazepines regularly during late pregnancy may have
developed physical dependence and are therefore at risk of developing withdrawal phenomena after birth. As benzodiazepines are excreted in breast milk, nursing mothers should not take Lexotanil.

**Overdosage**
As with other benzodiazepines, intentional or accidental overdosage of Lexotanil is seldom life-threatening unless other CNS depressants (including alcohol) have been taken simultaneously. Overdosage of benzodiazepines generally manifests itself in the form of CNS depression ranging from drowsiness to coma. In mild cases symptoms such as drowsiness, contusion, and lethargy occur. In most cases it is sufficient to monitor vital functions and await recovery.

Higher overdoses, especially in combination with other centrally acting drugs, can result in ataxia, reduced muscle tonus, hypotension, respiratory depression, in rare cases coma, and very rarely death.

In the treatment of overdoses of medications it should be borne in mind that a number of substances may have been taken. Provided that they are conscious, patients who have taken an overdose of benzodiazepines should be made to vomit (within an hour); unconscious patients should undergo gastric lavage with maintenance of a clear airway. Where no benefit is to be expected from evacuation of the stomach, activated charcoal should be administered to reduce intestinal absorption. The patient’s respiration and cardiac function should be particularly closely monitored. Anexate (flumazenil) can be useful as an antagonist.

**Stability**
This medicine should not be used after the expiry date (EXP) shown on the pack.

**Drug Interactions**
As with all psychoactive substances, the effect of Lexotanil may be intensified by alcohol. Simultaneous intake of alcohol should be avoided. When Lexotanil is combined with other centrally acting drugs such as antidepressants, hypnotics, narcotic analgesics, neuroleptics, anxiolytics/sedatives, antiepileptics, sedative antihistamines, or anesthetics, its CNS sedative effect may be increased. There is an increased risk of respiratory depression. In the case of narcotic analgesics euphoria, and hence also psychologic dependence, may be increased.

In patients taking muscle relaxants the risk of muscle weakness is increased. Although no such effect is known to occur with Lexotanil, drugs that inhibit certain hepatic enzymes (in particular cytochrome P450) can potentiate the effect of benzodiazepines that are metabolized by these enzymes. By increasing its rate of absorption, cisapride can cause transient potentiation of the effects of Lexotanil.

**Dosage and Administration**

**Standard Dosage**
*Average dose for outpatient therapy:* 1.5-3 mg up to three times daily.
*Severe cases, especially in hospitals:* 6-12 mg two or three times daily.

These amounts are general recommendations, and dosage should be individually determined. Treatment of outpatients should begin with low doses, gradually increasing to the optimum level. The duration of treatment should be as short as possible. The patient’s condition should be reassessed at regular intervals and the need for continued treatment determined, especially if the patient no longer has any symptoms. In general, the total duration of treatment should not exceed 8-12 weeks including a tapering-off period. In certain cases treatment may need to be continued beyond the maximum recommended duration, but only after a careful reassessment of the patient’s condition and the indications.

**Special Dosage Instructions**
Lexotanil is generally not indicated in children. Should the doctor nevertheless consider treatment with Lexotanil to be indicated, the dosage should be adjusted to the lower body weight of the child. Elderly patients and patients with disturbances of hepatic and/or renal function require lower doses
because of differences in reactivity and pharmacokinetics.

At the start of treatment the patient should be checked regularly in order to keep the dose and/or dose frequency as low as possible and avoid the risk of overdosage of the drug as a result of accumulation.

**Duration of Treatment**

At the start of treatment it may be useful to inform the patient that the duration of treatment will be limited and that the dose will be tapered off at the end of treatment.

It is important that the patient be aware that rebound and withdrawal phenomena may occur during withdrawal of the drug. Withdrawal phenomena can also occur when a benzodiazepine is replaced by another benzodiazepine with a significantly shorter elimination half-life.