SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Librocol Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances

Chlordiazepoxide, Clidinium bromide

Excipients with known effect: Lactose

Each capsule contains Lactose monohydrate (134 mg)

For the full list of excipients, see section 6.1.

3 Pharmaceutical form and amount of active ingredient per unit

1 coated tablet contains 5 mg chlordiazepoxide and 2.5 mg clidinium bromide

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of clinically significant disorders of the gastrointestinal and urogenital system when provoked or aggravated by anxiety and tension:

Digestive system: for example, irritable bowel, spastic colitis, and functional manifestations associated with hypersecretion and hypermotility of the gastrointestinal system such as diarrhoea, colitis, gastritis, duodenitis, gastric ulcer, ulcer duodenal and biliary dyskinesias.

Urogenital system: spasms and dyskinesias, nocturnal enuresis, functional cystodynia and dysmenorrhea.

Benzodiazepines should only be used when the severity of symptoms is clinically significant or strongly affects patient behaviour.

4.2 Posology and method of administration

Treatment should in any case be started at the lowest recommended dose, which can then be adjusted according to the response to treatment. The maximum dose should not be exceeded.

Usual dose

Adults: 3-4 filmed tablets per day.

Recommended mode of administration

It is preferable to take the medicine half an hour before the meal with liquid. The film-coated tablets can be swallowed entirely or crushed.

Duration of treatment

Treatment should be as short as possible. The indication must be reassessed regularly and the need for continued treatment must be verified, especially if the patient no longer has symptoms. The duration of treatment – from the start of treatment until the end of its gradual withdrawal phase – should not exceed 8 to 12 weeks.

In some patients, it may be necessary to prolong treatment beyond the recommended duration. This decision should only be taken after a competent reassessment of the patient's condition.

Special dosage instructions

Patients with impaired liver function and elderly patients

In elderly patients who are less than 75 years old, debilitated patients and patients with mild to moderate hepatic impairment, it is recommended to reduce the dose by approximately 50% (see "Contraindications").

Children and adolescents

It is recommended not to use Librocol in children as no studies have been carried out on the use of this medicine in children.

4.3 Contraindications

Hypersensitivity to chlordiazepoxide, clidinium bromide or to any of the excipients listed in section 6.1.,

multimorbidity in patients over 65,

patients over 75 years old,

glaucoma,

prostatic hypertrophy,

breastfeeding (see pregnancy and breastfeeding),

severe respiratory depression,

sleep apnoea syndrome

severe hepatic impairment,

myasthenia gravis.

4.4 Special warnings and precautions for use

This medication contains a benzodiazepine and an atropine spasmolytic. Their use in combination can lead to a synergy of their side effects and the risks of combination with other drugs – especially sedative and atropine-like effects – may be increased.

In the event of prolonged treatment, it is recommended to carry out monitoring of the blood count as well as renal and hepatic functions.

Duration of treatment

Treatment should be as short as possible. Its duration, including the gradual withdrawal phase, should not exceed 8 to 12 weeks. The treatment should not be extended without a reassessment of the situation.

When using a long-acting benzodiazepine such as chlordiazepoxide, a warning against switching to a long-acting benzodiazepine short-acting is needed because it may cause withdrawal symptoms.

Alcohol, medicines, or drugs abuse

The greatest caution is advised in patients who have already had a diagnosis of alcohol, drug or other substances abuse in the past.

Patients with episodes of depression

Benzodiazepines and similar drugs should not be prescribed to these patients as a sole treatment since depression may progress to cause a persistent or increased risk of suicide.

Tolerance

Some loss of the hypnotic effect of benzodiazepines after repeated use may develop within a few weeks.

Dependence

Taking benzodiazepines can cause physical and psychological dependence. Dependence of the drug may occur after use therapeutic doses and/or in patients without particular risk factors. This risk increases with the dose and duration of treatment. It is increased in patients with a history of substance abuse (alcohol, drugs).

Irrespective of the indication, the co-administration of several benzodiazepines increases the risk of drug dependence. Cases of misuse have been reported.

In order to minimize the risk of dependence as much as possible, benzodiazepines should only be prescribed after careful verification of the indication and the duration of treatment should be as short as possible (when used as a sleeping pill, treatment should not exceed four weeks). It is necessary to periodically assess the need for continued treatment. Prolonged treatment is only indicated in certain patients (panic attacks by example) and the benefit/risk balance is less clear.

Withdrawal symptoms

In the presence of dependence, withdrawal symptoms occur especially after an abrupt cessation. Symptoms seen include sleep disturbances, headaches, tremors, muscle pain and tension, restlessness, unusual anxiety, nervousness, confusion and irritability. In severe cases, one can observe symptoms such as distorted perception of the environment,

personality disorders, hyperacusis, tingling and numbness of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Withdrawal symptoms may appear within days of stopping treatment.

When withdrawal symptoms occur, close medical supervision and patient support are necessary.

Rebound symptoms

Discontinuation of treatment may be followed by transient rebound manifestations such as a reappearance, in an intensified form, of symptoms having initially led to treatment with a benzodiazepine. They may be accompanied by mood swings, anxiety, sleep disturbances or restlessness. Since the risk of withdrawal or discontinuation phenomena is higher after an abrupt discontinuation, it is recommended to discontinue the treatment gradually and reducing the dose in several stages.

Amnesia and alterations in psychomotor function

Benzodiazepines can cause anterograde amnesia. Amnesia and psychomotor alterations usually manifest within hours after taking the dose.

Psychiatric and "paradoxical" reactions

Benzodiazepines and other similar drugs may cause various changes in the state of consciousness, behavior and memory, for example: worsening insomnia, nightmares, irritation, nervousness, confusion, obsessions, confusion, psychotic symptoms, disinhibition with impulsive behavior, euphoria, irritability, anterograde amnesia and suggestibility.

This condition may be accompanied by potentially dangerous problems for the patient or for others, e.g. inappropriate behavior, aggressive behavior towards oneself or others (especially if friends or family members try to prevent patient activities) and automatic behavior with amnesia after the incident. If such reactions occur, treatment with Librocol should be abandoned. These reactions are more common in elderly patients. Great caution should be considered when prescribing benzodiazepines to patients with a personality disorder.

Special patient groups and risk of accumulation

In treatment with long-acting benzodiazepines such as chlordiazepoxide, patients should be monitored regularly at the start of treatment so that the dose or frequency of dosing can be reduced, if necessary, in order to prevent overdose due to accumulation.

In elderly patients (under 75 years of age), patients with renal insufficiency and patients with mild to moderate hepatic impairment, the half-life of benzodiazepines can be markedly prolonged. Dosage adjustment may be necessary (see "Posology and method of administration"). Librocol is contraindicated in patients over 75 years of age and patients with severe, acute or chronic hepatic impairment (see "Contraindications").

Due to the risk of sedation and/or muscle relaxation, benzodiazepines and other similar medicines should be used with caution in elderly patients, as these effects may cause falls which may have serious consequences in this patient population.

Risk from concomitant use of opioids

Concomitant use of Librocol and an opioid may cause sedation, respiratory depression, coma or death of the patient. Because of these risks, concomitant prescribing of sedative medicines – for example benzodiazepines or related medicines such as Librocol – with opioids is only indicated in patients for whom alternative treatment options are not possible. If however a prescription administration of Librocol and an opioid is deemed necessary, the lowest effective dose and the shortest duration of treatment possible should be chosen (see "Posology").

Patients should be closely monitored for signs and symptoms of respiratory depression and sedation. In this context, it strongly recommended to inform patients – and (if applicable) their relatives – about these symptoms (see 'Interactions').

Chlordiazepoxide Precautions

It may be wise to inform patients at the start of treatment that the treatment will be of limited duration, and to explain to them exactly how the dose will be gradually reduced. Patients should also be informed about possible withdrawal effects (see "Special warnings and precautions for use") so that these symptoms are less frightening to them if they occur after stopping the medication.

In cases of mild to moderate respiratory insufficiency, consideration should be given to the depressant effect of benzodiazepines and other similar medicines, especially since anxiety and excitement can also be signs of respiratory depression and thereby justify hospitalization under intensive care.

Clidinium Bromide Precautions

Librocol should be used with caution in the following cases:

- Enlarged prostate
- Mild to moderate renal or hepatic impairment
- Coronary insufficiency, cardiac arrhythmias, hyperthyroidism
- Chronic bronchitis due to increased viscosity of bronchial mucus
- Paralytic ileus, intestinal atony in elderly patients, toxic megacolon

Lactose, colorant

Librocol film-coated tablets contain lactose. Patients with galactose intolerance, total lactase deficiency or malabsorption of glucose and galactose (rare hereditary diseases) should not take Librocol film-coated tablets.

Hypersensitivity to colorant

Librocol contains the azo colorant E110. For this reason, the drug should be administered with caution to patients who may cause hypersensitivity reactions to azo dyes, acetylsalicylic acid and prostaglandin inhibitors.

4.5 Interactions

Interactions with chlordiazepoxide

Pharmacokinetic interactions

Drugs that inhibit liver enzymes

Chlordiazepoxide is hydroxylated by the CYP450 3A4 isoenzyme. Although there are no specific interaction studies, caution is recommended in the event of combination with medicinal products which inhibit this isoenzyme or which are metabolised by it (macrolide antibiotics, azole antifungals, calcium antagonists, protease inhibitors, ergot alkaloids, antidepressants) The metabolism of chlordiazepoxide can be inhibited by ketoconazole, cimetidine or disulfiram.

Concomitant administration of cimetidine leads to an increased risk of drowsiness. Patients should be warned of the increased risk when driving a vehicle or operating machinery.

Interactions pharmacodynamics

Caution should be exercised when Librocol is used in combination with medicinal products acting on the central nervous system (e.g. neuroleptics, tranquillizers, hypnotics, analgesics, antitussives, antihistamines with a sedative effect, centrally acting antihypertensives, antiepileptics, opiates or baclofen), since the depressant effect on the central nervous system may be enhanced.

Concomitant use of sedative medicines – eg benzodiazepines or related medicines such as Librocol – with opioids causes an additional depressant effect on the CNS and thus increases the risk of sedation, respiratory depression, coma and death. Dosage and duration co-administration should be limited (see "Special warnings and precautions for use").

In addition, the concomitant intake of opioids (narcotic analgesics) can reinforce the euphoric effect and thus cause the accelerated development of a psychological dependence.

Muscle relaxants may potentiate the effect of chlordiazepoxide.

The absorption of other medicines may be slowed by the effect on the gastrointestinal tract.

Barbiturates, morphine derivatives

Concomitant administration of a barbiturate or a morphine derivative carries an increased risk of respiratory depression. In the case of an overdose, it can lead to death.

Buprenorphine

Concomitant administration of buprenorphine also carries an increased risk of potentially fatal respiratory depression. The report benefits-risks of such a combination should be carefully weighed. Inform the patient of the need to strictly adhere to the dose prescribed.

Interactions with clidinium bromide

Pharmacokinetic interactions

When Librocol is combined with anticholinergic (atropine-like) substances, such as amantadine, some antihistamines (H1 antagonists), butyrophenone, phenothiazine, tricyclic and tetracyclic antidepressants, antiparkinson drugs, antiarrhythmics (quinidine, disopyramide), pirenzepine, anticholinergic spasmolytics or asthma treatments, the anticholinergic effect of clidinium is increased. There is therefore an increased risk of side effects such as urinary retention, progression of glaucoma, constipation, dry mouth, etc.

The consumption of alcohol should be refrained from during Librocol treatment because the detailed individual reaction is unpredictable.

4.6 Pregnancy/Breastfeeding

Contraception in men and women

Due to the genotoxic potential of chlordiazepoxide (see 'Preclinical data'), women of childbearing potential should use effective contraceptive measures during treatment with the drug and for at least 7 months after discontinuation of treatment.

If the patient thinks she may be pregnant or is planning to become pregnant, she should be advised to contact her physician to discuss discontinuation of the drug.

It is recommended that men use effective contraceptive measures and not have children during treatment with the medicine and for at least 4 months after stopping treatment.

Pregnancy

The risk to the human fetus is clearly demonstrated. Librocol should not be used during pregnancy, especially in the first and the last trimester of pregnancy, unless absolutely necessary.

The risk of malformations appears to be low when therapeutic doses of benzodiazepines are administered in early pregnancy. Some Epidemiological studies have, however, revealed an increased risk of cleft palate. There are a low number of cases of malformations and mental retardation in children with prenatal exposure following overdose or poisoning with chlordiazepoxide.

Neonatal symptoms such as hypothermia, hypotension and moderate respiratory depression have been reported when using benzodiazepines during the last trimester of pregnancy or during childbirth.

Infants whose mothers were on chronic benzodiazepine therapy during the late stages of pregnancy may have developed physical dependence, with the risk of withdrawal symptoms in the postnatal phase.

Librocol should be used with caution in late pregnancy because the active substance clidinium may cause anticholinergic effects in infant. (e.g. meconium ileus).

Breasfeeding

Clidinium bromide may reduce milk secretion and pass into breast milk. Chlordiazepoxide can also pass into breast milk.

The use of Librocol during lactation is therefore contraindicated.

4.7 Effect on ability to drive and use machines

Librocol has a strong influence on the ability to drive or use machines. Sedation, amnesia, reduced ability to concentrate and impaired muscle function may have a negative influence on the ability to use machines and drive a vehicle, especially after insufficient sleep time. The combination with other sedatives is not recommended and should be considered when driving a vehicle or the use of machinery.

4.8 Side effects

Security Profile Summary

The most common side effects are: sedation, dizziness, drowsiness, ataxia, fatigue and balance disorders. These side effects are dose-dependent and may persist overnight, even after a single dose. They mainly appear in start of treatment and usually resolve with continued treatment.

Elderly patients are particularly sensitive to drugs that exert a depressant effect on the central nervous system; that can cause them confusion, especially if they suffer from organic brain changes.

List of side effects

Side effects observed in patients taking Librocol are listed below by system organ class according to the MedDRA classification. Frequencies are defined as: very common (≥1/10), common (≥1/100 <1/10), uncommon (≥1/1000 <1/100), rare (≥1/10,000 <1/1,000), very rare (<1/10,000) and frequency not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Rare: myelosuppression (eg thrombocytopenia, leukopenia, agranulocytosis, pancytopenia).

Immune system disorders

Frequency not known: hypersensitivity reactions.

Metabolism and nutrition disorders

Uncommon: increased appetite

Psychiatric disorders

Frequency not known: amnesia, hallucinations, dependence, depression, agitation, irritability, nervousness, aggression, obsessions, nightmares, psychotic disorders, abnormal behavior, emotional disturbances, paradoxical reactions such as anxiety, sleep disturbances, insomnia, suicidal behavior, suicidal thoughts.

Nervous system disorders

Common: sedation, dizziness, somnolence, ataxia, balance disorders, confusional states.

Rare: headache, dizziness.

Frequency unknown: dysarthria, gait disturbances, extrapyramidal disorders (e.g. tremor, dyskinesia).

Eye disorders

Uncommon: reduced tear flow, accommodation disturbances, ocular disturbances, including diplopia.

Heart conditions

Frequency not known: tachycardia, palpitations.

Vascular disorders

Rare: hypotension.

Respiratory, thoracic and mediastinal disorders

Frequency not known: respiratory depression, increased viscosity of bronchial secretions.

Gastrointestinal disorders

Rare: gastrointestinal disorders, constipation.

Hepatobiliary disorders

Frequency not known: jaundice, increased level of bilirubin, increased levels of liver enzymes (transaminases, alkaline phosphatase).

Skin and subcutaneous tissue disorders

Rare: skin reactions (eg rash, pruritus).

Musculoskeletal and connective tissue disorders

Frequency not known: muscle weakness, asthenia.

Kidney and urinary disorders

Rare: micturition disorders (urinary retention).

Reproductive system and breast disorders

Rare: Changes in libido, erectile dysfunction, menstrual disorders.

Very rare: dysmenorrhea.

General disorders and administration site conditions

Common: fatigue.

Uncommon: dry mouth.

Reporting of suspected side effects after authorization is of great importance. It allows continuous monitoring of the risk-benefit ratio of the medication.

4.9 Overdose

Signs and symptoms

Symptoms of Chlordiazepoxide Overdose

As with other benzodiazepines, an overdose can be life threatening, especially in the setting of poly-intoxication in association with other medicines that have a depressant effect on the central nervous system (including alcohol). In the treatment of an overdose, it should be considered that the patient may have taken multiple medications.

An overdose of benzodiazepines usually causes central nervous system depression, the symptoms of which may range from feeling from mental numbness to a comatose state depending on the degree of severity. In mild cases, symptoms include numbness mental state, confusion and lethargy. In severe cases, ataxia, reduced muscle tone, hypotension and respiratory depression, in rare cases coma and very rarely death.

Symptoms of Clidinium Bromide Overdose

Clidinium bromide overdose may be manifested by anticholinergic effects such as urinary retention, dry mouth, tachycardia, mild light-headedness and transient ocular disturbances

(including mydriasis, paralysis of accommodation), skin flushing and inhibition of gastrointestinal motility. intestinal disorders, as well as more serious disorders such as changes in breathing and circulation, tachycardia, anger, nervousness, confusional state, hallucinations, delirium, respiratory depression and coma.

Treatment

Treatment of benzodiazepine overdose

Following an overdose of oral benzodiazepines, emesis should be induced within one hour if the patient is conscious. In unconscious patients, gastric lavage should be performed with corresponding protection of the respiratory tract. If stomach emptying is not promising, activated charcoal should be administered to reduce resorption. In the context of intensive care, particular attention is paid to the functions respiratory and cardiovascular.

Administration of flumazenil (Anexate®) may be useful in the diagnosis and/or treatment of accidental or intentional overdose of benzodiazepines.

The antagonization of the effects of benzodiazepines by flumazenil can however promote the onset of neurological problems (convulsions), especially in patients with epilepsy.

Treatment of clidinium bromide overdose

Symptomatic treatment with monitoring of vital functions in hospital.

5 Properties/Effects

5.1 Pharmacodynamic properties

ATC code

A03CA02

Mechanism of action and pharmacodynamics

Chlordiazepoxide and clidinium bromide have a complementary effect on the gastrointestinal and urogenital system. Chlordiazepoxide is a benzodiazepine which has an anxiolytic effect and relieves tension, in high doses, it is a muscle relaxant. This substance is indicated when anxiety or blood pressure influence the clinical picture, whether primary or secondary.

Clidinium bromide is a synthetic anticholinergic. It relieves smooth muscle spasms and inhibits secretions.

The combination of the two active substances simultaneously allows a peripheral and central action on the symptoms observed in case of disorders functions of the gastrointestinal and urogenital system. If the indication corresponds, the treatment makes it possible to obtain a stabilization of the vegetative functions troubled.

Clinical efficacy

no data available

5.2 Pharmacokinetics

Absorption

Chlordiazepoxide is almost completely absorbed after oral administration, it enters the bloodstream practically unchanged. Maximum plasma concentrations are reached on average in two to four hours.

Clidinium bromide is mainly absorbed unchanged in the small intestine.

Distribution

At steady state, chlordiazepoxide has a volume of distribution of 0.3–0.4 l/kg body weight. After administration of a new dose, the steady state of the unmodified chlordiazepoxide resolves within three days, while metabolites accumulate at a significantly slower rate. protein binding plasma represents 93 to 97%. The unmodified active ingredient as well as a major pharmacologically active metabolite, desmethylchlordiazepoxide quickly crosses the blood-brain barrier like the plasma barrier, it also passes, in small quantities, in breast milk.

A small part of orally administered clidinium bromide reaches the enterohepatic circulation in an unchanged form.

Metabolism

Dealkalization and hepatic hydroxylation of chlordiazepoxide produce the following pharmacologically active metabolites:

desmethylchlordiazepoxide, demoxepam and desmethyldiazepam.

Clidinium bromide is rapidly hydrolyzed to the corresponding hydrolyzed quaternary amino alcohol in the liver.

Elimination

The elimination half-life of chlordiazepoxide from plasma is about 15 minutes in the distribution phase and about ten hours in the of elimination. Total plasma clearance is between 0.3-0.5 ml/min/kg. Less than 1% of chlordiazepoxide dose given orally appears unchanged in the urine. Demoxepam and desmethyldiazepam are eliminated in an inactivated form of conjugated glucuronic acid.

The quaternary amino alcohol of clidinium bromide is eliminated in the urine and is also found unchanged in the faeces. Urinary elimination of the principle unchanged active occurs in two phases with average half-lives of 1½ to 20 hours respectively .

5.3 Preclinical data

Genotoxicity and carcinogenicity

In vivo and in vitro studies with chlordiazepoxide suggest a mutagenic effect. Similar test systems, however, provided results negatives. The relevance of the positive findings has not yet been clarified. In carcinogenicity studies in mice, high doses caused an increase in liver tumours, especially in males. However, no increased incidence of tumours was found in rats.

Reproductive toxicity

Animal experiments have revealed changes in the urogenital system, lung abnormalities and cranial malformations (exencephaly, palatoschizia) as well as behavioral disorders on the offspring as well as neurochemical changes. there is no data on this subject for clidinium bromide.

6. Pharmaceutical particulars

6.1 List of excipients

Povidone, Maize starch, Magnesium stearate, Talc,

Film-coating: Methycellulose, Shellac, Hypromellose, Titanium dioxide (E 171), Macrogol 400, Diethyl phthalate, E104, E110 (0.0056 mg), E132, E133.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

The medicine should not be used beyond the date shown after the word "Exp" on the packaging.

The medication should be stored in its original packaging, at room temperature (15-25°C), protected from light, out of reach of children.

6.5 Nature and contents of container

Librocol film coated tablets are contained in securitainer for solid dosage form

Pack size: 30

6.6 Special precautions for disposal

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Maketing Authorization Holder

Lagap SA

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6943 Vezia

Switzerland

8. Marketing Authorization Number

LAG/SWZ/44, 06225/07668/REN/2020

9. Date of First Authorization/Renewal of the Authorization

17/10/2016, 24-07-2021

10. Date of Revision of the Text

October 2022