SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICALPRODUCT

Bralix 5 mg/2.5 mg coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains 2.5 mg clidinium bromide and 5 mg chlordiazepoxide.

Excipient(s) with known effect
This product contains 101.5 mg lactose, 71.391 mg sucrose and 0.057 mg tartrazine E102.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated Tablet.

Green, round, coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of severe and/or incapacitating signs of anxiety accompanied by digestive function disorders with a spasmodic component.

4.2 Posology and method of administration

Posology

In all cases, treatment should be initiated at the lowest dose indicated, subsequently increasing it, if necessary, after having tested the individual's response. The maximum dose should not be exceeded.

Adults
The usual dosage for adults is 1-2 tablets, 2 to 4 times a day.

The tablets should be swallowed with a little water.

They may be taken with meals, when going to bed or when experiencing pain.

Paediatric population
Not recommended in children and adolescents from 6 to 18 years, owing to a lack of studies. If necessary, it is recommended that the dosage should be reduced, by half for example. In children under 6 years of age the medicinal product is contraindicated (see section 4.3).

Special patient groups
In elderly patients under 75 years of age and in patients with renal or mild to moderate hepatic insufficiency it is recommended that the dosage should be reduced, by half for example (see section 4.3).

Duration
Treatment must be as brief as possible. The indication will be re-evaluated regularly, especially in the absence of symptoms. The total duration of treatment should not exceed 8 to 12 weeks for the majority of patients, including the posology reduction period (see section 4.4).

In some cases, it may be necessary to prolong treatment beyond the recommended periods. This assumes accurate and repeated evaluations of the patient's condition.

Method of administration
Oral administration. To be swallowed with water.

4.3 Contraindications

Bralix is contraindicated for patients with:

- hypersensitivity to active substances or to any of the excipients listed in section 6.1.
- poly-pathological subjects aged over 65 years.
- patients aged over 75 years.
- children under 6 years.
- risk of angle-closure glaucoma.
- risk of urinary retention associated with urethroprostatic disorders.
- breast-feeding (see section 4.6).
- severe respiratory insufficiency.
- sleep apnoea syndrome.
- severe, acute or chronic hepatic insufficiency (risk of occurrence of encephalopathy).
- myasthenia gravis.

4.4 Special warnings and precautions for use

Warnings

This medicinal product contains both a benzodiazepine and an atropinic antispasmodic agent. Being associated, their undesirable effects may synergise and multiply the risks with other medicinal products, especially the sedative and/or atropinic actions (see section 4.5).

Duration of treatment
The duration of treatment should be as short as possible but should not exceed 8 to 12 weeks, including tapering off process. Extension beyond these periods should not take place without re-evaluation of the situation.

When benzodiazepines with a long duration of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Alcohol and drug abuse
The greatest care is recommended if there is a history of alcoholism or other dependences, drug related or otherwise (see section 4.5).

In subjects with major depressive episodes
Benzodiazepines and similar products should not be prescribed alone since they allow depression to develop separately with a persistent or increased risk of suicide.

Tolerance
Some loss of efficacy to the hypnotic effects of benzodiazepines may develop after repeated use for a few weeks.

Dependence
Use of benzodiazepines may lead to the development of physical and psychic dependence upon these products. Drug dependence may occur at therapeutic doses and/or in patients without any distinct risk factor. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse. Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of insomnia, headaches, muscle pain, muscle tension, hyperreactivity, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures. Withdrawal symptoms may be manifested in the days following the cessation of treatment. Combining several benzodiazepines, whatever the anxiolytic or hypnotic indication, risks increasing the risk of drug dependence. Cases of abuse have also been reported.

Rebound reactions
Upon the discontinuation of treatment a transient syndrome may occur whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. Since the risk of withdrawal/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

Amnesia and alteration in psychomotor function
Benzodiazepines may induce anterograde amnesia. Anterograde amnesia along with alterations in psychomotor functions occurs most often several hours after ingesting the drug.

Psychiatric and paradoxical reactions
In some subjects, benzodiazepines and similar products, may give rise to a combination of an alteration in the state of consciousness, behavioural and memory problems. The following may be observed:

- aggravation of insomnia, nightmares, agitation, nervousness.
- delirious thoughts, hallucinations, confusional-oneiric state, psychotic type symptoms.
- loss of inhibitions with impulsiveness.
- euphoria, irritability.
- anterograde amnesia.
- suggestibility.

This syndrome may be accompanied by potentially dangerous problems for the patient or for other people, of the following types:
- unusual behaviour for the patient.
- auto- or hetero-aggressive behaviour, in particular if friends and relations attempt to hamper the patient's activities.
- automatic behaviour with post-event amnesia.

If these reactions should occur during treatment with Bralix, administration must be suspended. These reactions are more frequent in the elderly. Extreme caution should be used prescribing benzodiazepins to patients with personality disorders.

Specific patient groups and risk of accumulation
Given that chlordiazepoxide is a long-acting benzodiazepine, the patient should be monitored regularly to decrease, if necessary, the dose or frequency of administration to prevent overdose due to accumulation.

In elderly people under 75 or people suffering from renal or mild to moderate hepatic insufficiency, the half-life of benzodiazepines may be considerably extended. A dosage adaptation may be necessary (see section 4.2). People aged 75 years and older and patients with severe, acute or chronic hepatic insufficiency are contraindicated (see section 4.3).

Benzodiazepines and similar products should be used with care in elderly subjects owing to the risk of sedation and/or myorelaxant effect, which might lead to falls with consequences which are often serious in this population.

Precautions for use (associated with chlordiazepoxide)

It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased. Moreover it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while the medicinal product is being discontinued.

In the case of mild to moderate respiratory insufficiency, account should be taken of the depressant effect of benzodiazepines and similar products (especially as anxiety and agitation may constitute signs indicating decompensation of the respiratory function, justifying admission to an intensive care unit).

Pediatric population
Not recommended in children and adolescents from 6 to 18 years and contraindicated in children under 6 years.If treatment is imperative in children 6 years of age and

olderthe risk/benefit ratio should be scrupulously evaluated and the duration of treatment should be as short as possible. No clinical studies have been conducted on children with clidinium bromide and chlordiazepoxide.

Precautions for use (associated with clidinium bromide)

Use with care in the case of:
- prostate hypertrophy.
- renal or hepatic insufficiency.
- coronary insufficiency, heart rate problems, hyperthyroidism.
- chronic bronchitis owing to an increase in the viscosity of bronchial secretions.
- paralytic ileus, intestinal atonia in elderly subjects, toxic megacolon.

Risk from concomitant use of opioids
Concomitant use of Bralix and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as Bralix with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Bralix concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see section 4.5).

Bralix contains lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Bralix contains sucrose
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

Bralix contains tartrazine E102
May cause allergic reactions.

4.5 Interaction with other medicinal productsand other forms of interaction

Interactions with chlordiazepoxide

If Bralix is combined with centrally-acting drugs such as neuroleptics, tranquilisers, antidepressants, hypnotics, analgesics, anaesthetics, antitussives, sedative anti-histamines, central antihypertensives, and baclofen the central depressive effects are likely to be intensified. In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychic dependence.

Barbiturates
Increased risk of respiratory depression, which may be fatal in the event of overdose.

Buprenorphine
With buprenorphine used as substitution treatment: increased risk of respiratory depression which may be fatal. Carefully evaluate the risk-benefit ratio of this combination. Inform the patient of the need to observe the prescribed doses.

Cimetidine
Increased risk of drowsiness. Warn patients of the increased risk when driving cars and using machines.

Products derived from morphine
Increased risk of respiratory depression, which may be fatal in the event of overdose.

Product which inhibit hepatic enzymes
Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines. To a lesser degree this also applies to benzodiazepines that are metabolised only by conjugation.

Opioids
The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Bralix with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

Interactions with clidinium bromide

Atropine-like substances may add their side effects and may more easily induce urinary retention, advance of glaucoma, constipation, dry mouth, etc.
Drugs considered as atropine-like are those substances having anticholinergic action belonging to the following therapeutic groups: antidepressants, antihistamine (H_1 antagonists), antiparkinsonian agents, anticholinergics, other atropinic antispasmodics, dispopyramide, phenothiazine neuroleptics, clozapine and amantadine.

4.6Fertility, pregnancy and lactation

Pregnancy
There is no evidence of drug safety in human pregnancy or evidence from animals that it is free from hazard. Therefore, do not use during pregnancy, especially during the first and last trimesters, unless there are compelling reasons.
If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician to discuss discontinuation of the product if she intends to become or suspects that she is pregnant.
If, for compelling medical reasons, the product is administered during the late phase of pregnancy, or during labour at high doses, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression, can be expected, due to the pharmacological action of the compound. Moreover, infants born to mothers who took benzodiazepines chronically during the later stages of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period.

Due to the clidinium, Bralix should be administered with care at the end of pregnancy due to risk of atropinic effects in the child (meconium ileus).

Lactation
Clidinium may decrease lacteal secretion and may also pass into milk resulting in atropinic effects in the child. Chlordiazepoxide may also appear in breast milk. Therefore, the use of Bralix is not recommended during breast-feeding (see section 4.3).

4.7 Effects on ability to drive and use machines

This medicinal product can cause drowsiness which impairs the ability to drive or use machine. Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or to use machines. Combination with other sedative medicinal products should not be recommended or considered when driving cars or using machines (see section 4.5). If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased.

4.8 Undesirable effects

Most common adverse effects include sedation, dizziness, somnolence, ataxia, fatigue and balance disorder. These adverse effects are dose-related and may persist into the following day even after a single dose. However, these phenomena occur predominantly at the start of therapy and usually disappear with repeated administration. The elderly are particularly sensitive to the effects of centrally-depressant drugs and may experience confusion, especially if organic brain changes are present.

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories:

- Very common (≥ 1/10)
- Common (≥ 1/100 to < 1/10)
- Uncommon (≥ 1/1 000 to < 1/100)
- Rare (≥ 1/10 000 to < 1/1 000)
- Very rare (< 1/10 000)
- Not known (Frequency cannot be estimated from the available data).

Organ Class	**Effect**
Blood and lymphatic system	Rare: bone marrow depression (e.g. thrombocytopenia, leucopenia, agranulocytosis, pancytopenia)
Immune system disorders	Frequency not known: hypersensitivity
Metabolism and nutrition disorders	Uncommon: increased appetite

Psychiatric disorders	Frequency not known: amnesia, hallucinations, dependence, depression, restlessness, agitation, irritability, depressed level of consciousness, aggression, delusion, nightmares, psychotic disorder, abnormal behaviour, emotional disturbances, paradoxical drug reaction (e.g. anxiety, sleep disorders, insomnia, suicide attempt, suicidal ideation)
Nervous system disorders	Common: sedation, dizziness, somnolence, ataxia, balance disorder, confusional state Rare: headache, vertigo Frequency not known: dysarthria, gait disturbance, extrapyramidal disorder (e.g. tremor, dyskinesia)
Eye disorders	Uncommon: Lacrimation decreased, accommodation disorders Rare: visual impairment incl. diplopia
Cardiac disorders	Frequency not known: tachycardia, palpitations
Vascular disorders	Rare: hypotension
Respiratory, thoracic and mediastinal disorders	Frequency not known: respiratory depression, increased viscosity of bronchial secretion
Gastrointestinal disorders	Rare: gastrointestinal disorder, constipation
Hepato-biliary disorders	Frequency not known: jaundice, blood bilirubin increased, transaminases increased, blood alkaline phosphatase increased
Skin and subcutaneous tissues disorders	Rare: skin reaction (e.g. rash, pruritus)
Musculoskeletal, connective tissue disorders	Frequency not known: Muscular weakness, asthenia
Renal and urinary disorders	Rare: urinary retention
Reproductive system and breast disorders	Rare: libido disorder, erectile dysfunction, menstrual disorder Very rare: dysmenorrhoea

General disorders and administration site conditions	Common: fatigue Uncommon: dry mouth

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactionsvia the national reporting system.

4.9 Overdose

Associated with chlordiazepoxide

Clinical signs and symptoms
As with other benzodiazepines, overdose can be life threatening, in particular in the event of polyintoxication involving other central nervous system depressants (including alcohol). In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death.

Treatment
Following overdose with oral benzodiazepines, vomiting should be induced (within one hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care.

The administration of flumazenil may be useful in the diagnosis and/or treatment of intentional or accidental overdose with benzodiazepines. The antagonism by flumazenil of the effect of benzodiazepines may encourage the appearance of neurological problems (convulsions), in particular in epileptic patients.

Associated with clidinium bromide

Clinical signs and symptoms
Clidinium bromide overdose may be manifested by anticholinergic effects such as urinary retention, dry mouth, tachycardia, mild drowsiness and transient disturbances of vision(including mydriasis, accommodation paralysis), redness of the skin, inhibition of gastrointestinal motility, and more serious disturbances such as circulatory and respiratory alterations, tachycardia, arousal state, agitation, confusion and hallucination, delirium, respiratory depression and coma.

Treatment
Symptomatic with cardiac and respiratory monitoring in a hospital environment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for functional gastrointestinal disorders, Antispasmodics in combination with psycholeptics, ATC code: A03CA02

Mechanism of action and pharmacodynamic effects
Chlordiazepoxide is an anxiolytic belonging to the class of benzodiazepines.
Pharmacologically its properties are those of the class of benzodiazepines: anxiolytic, sedative, hypnotic, anticonvulsant, myorelaxant and amnestic. These effects are associated with a specific agonist action on a central receptor forming part of the GABA-OMEGA macromolecular receptors complex (also known as BZ1 and BZ2) modulating the opening of the chlorine channel.
Drug dependence may be observed in animals and in humans.

Clidinium bromide is a synthetic anticholinergic that has a spasmolytic effect on smooth muscle and also inhibits secretions.

5.2 Pharmacokinetic properties

Chlordiazepoxide

Chlordiazepoxide is well absorbed, with peak blood levels being achieved one or two hours after administration. The bioavailability after oral dose is close to 100%. The drug has a half-life of 6-30 hours. Steady-state levels are usually reached within three days.
Chlordiazepoxide is metabolised into desmethyl-chlordiazepoxide. It is also metabolised to a much lesser extent to the active metabolite demoxapam. The demoxepam is itself metabolised into an active metabolite, oxazepam, but in very small proportions (less than 1% of the chlordiazepoxide ingested results in the formation of oxazepam).
Urinary elimination takes the form of demoxepam and oxazepam. The half-life is 20 to 24 hours.
Foeto-placental crossover and passing into the mother's milk have been demonstrated for benzodiazepines.
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.

Clidinium bromide

Clidinium bromide is metabolised into 3-hydroxy-1-methylquinuclidinium bromide, which is the principal form found in the urine of humans. Clidinium bromide and its metabolites are found in faeces. Marked carbon studies show that this substance is not metabolised by N-demethylation.

5.3 Preclinical safety data

Mutagenic and tumorigenic potential
In in-vivo and in-vitro studies with chlordiazepoxide there are indications for a mutagenic effect. Nevertheless, in similar test systems results are negative. The relevance of the positive findings is currently unclear.
In carcinogenicity studies in mice an increase of liver tumors was seen at high doses, especially in males, whereas no increase of tumor incidence was seen in rats.

Reproductive toxicity
Observations in humans have shown no clear evidence of a teratogenic effect of chlordiazepoxide up to now, whereas in animal studies changes in the urogenital tract, lung anomalies and malformations of the skull (exencephaly, cleft palate), behavioral disorders and neurochemical changes have been observed in the offspring. The malformation risk with administration of therapeutic doses of benzodiazepines in early pregnancy appears to be low, although some epidemiological studies have found evidence of an increased risk for the occurrence of cleft palate and there are few case reports of malformations and mental retardation of prenatally exposed children after chlordiazepoxide overdose and poisoning.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Cellulose, microcrystalline
Starch, pregelatinised
Lactose monohydrate
Maize starch
Povidone
Silica, colloidal anhydrous
Magnesium stearate
Talc

Coating
Hypromellose
Macrogol 400
Titanium dioxide
Gelatin
Sucrose
Macrogol 6000
Povidone
Talc
Calcium carbonate
Tartrazine E102
Indigotine, indigo carmine E132

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 25 ºC. Protect from light and moisture.

6.5 Nature and contents of container

PVC/Aluminium blisters. Pack sizes of 30, 100 and 1000 coated tablets.
PP containers with PE closure. Pack size of 1000 coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Remedica Ltd
Aharnon Str., Limassol Industrial Estate,
3056 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER(S)

07943/08539/REN/2022

9.DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of latest renewal: 10-10-2022

10. DATE OF REVISION OF THE TEXT

04/07/2023