Viatris South Africa (Pty)Ltd	Date of amendment: 14 June 2023	Response to SAHPRA Variations email – Application SAHPRA-1E0638 Rejected
LIBRAX® (tablets)	LIBRAX® contains 5 mg 7-Chloro-2-N-methylamino-5-phenyl-3H-1,4-benzodiazepine-4-oxide (chlordiazepoxide) active substances of Librium (Trademark) and 2,5 mg 1-methyl-3-benziloyloxyquinu-clidinium bromide (clidinium bromide) per sugar-coated tablet	

1.3.1.1 Annotated Professional Information for medicines for human use - clean

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

LIBRAX® (tablets)

2 QUALITIVE AND QUANTITIVE COMPOSITION

LIBRAX® contains 5 mg 7-Chloro-2-N-methylamino-5-phenyl-3H-1,4-benzodiazepine-4-oxide (chlordiazepoxide) active substances of Librium (Trademark) and 2,5 mg 1-methyl-3-benziloyloxyquinu-clidinium bromide (clidinium bromide) per sugar-coated tablet.

Excipients with known effect:

Contains sugar: Lactose anhydrous 131,025 mg, sucrose 130,838 mg

For full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Round, biconvex and green to yellow-green sugar-coated tablets.

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1.5.5.1 Annotated Professional Information for medicines for human use - clean

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

As an adjunct in the short-term treatment of non-ulcerated irritable bowel syndrome (IBS) associated with anxiety, tension or apprehension in adults.

LIBRAX® is only indicated when the disorder is severe, disabling or subjecting the individual to extreme stress.

4.2 Posology and method of administration

Posology

Treatment should be started with the lowest recommended dose.

The maximum dose should not be exceeded.

Treatment should be as short as possible.

The patient should be reassessed regularly and the need for continued treatment should be re-evaluated, especially in case the patient is symptom- free.

The overall duration of treatment generally should not be more than 8 – 12 weeks, including a tapering off process.

In certain cases, extension beyond the maximum treatment period may be necessary. If so, it should not take place without re-evaluation of the patient's status.

Adults:

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Due to the varied individual response to tranquillisers and anticholinergics, the optimum dosage of LIBRAX® varies with the diagnosis and response of the individual patient.

The usual dose is one (1) tablet three (3) or four (4) times a day administered before meals and at bedtime.

The dosage, therefore, should be individualised for maximum beneficial effects however, a maximum daily dose of 8 tablets should not be exceeded.

Special populations

Elderly and debilitated patients:

Initially one (1) tablet twice a day.

The dosage can be adjusted as needed and tolerated.

Paediatric population

The safety and efficacy of LIBRAX® in children has not been established.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to the active substances chlordiazepoxide, clidinium bromide, to other benzodiazepines, to any of the Belladonna alkaloids or to any of the excipients listed in section 6.1.
- Myasthenia gravis.
- LIBRAX® is also contraindicated in the presence of glaucoma, benign bladder, neck obstruction and paralytic ileus because of its anticholinergic component.
- Pregnancy and lactation.
- Severe respiratory failure.
- Sleep apnoea syndrome.
- Severe hepatic impairment.
- Myasthenia gravis.
- Prostatic hypertrophy.

4.4 Special warnings and precautions for use

Alcohol and drug abuse:

- Patients receiving LIBRAX® should be cautioned about possible combined effects with alcohol and other central nervous system (CNS) depressants.
- LIBRAX® should be used with extreme caution in patients with a history of alcohol or drug abuse.

- LIBRAX® is not recommended for the primary treatment of psychotic illness.
- LIBRAX® should not be used alone to treat depression or anxiety with depression as suicide may be precipitated in such patients.

Duration of treatment:

- The duration of treatment should be as short as possible (*see section 4.2*) but should not exceed eight to twelve weeks in case of anxiety, including tapering off process.
- Extension beyond these periods should not take place without re-evaluation of the situation (*see section 4.2)*.
- 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 product is being discontinued.
- When benzodiazepines as contained in LIBRAX® 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.

Specific patient groups and risk of accumulation :

- Particular caution should be exercised with the elderly and debilitated- who are at particular risk of over-sedation, respiratory depression and ataxia. (The initial oral dosage should be reduced in these patients).

  Caution should be exercised in the following patients:

  - patients suffering from impairment of renal or hepatic function;
  - patients suffering from anxiety accompanied by an underlying depressive disorder;
  - patients receiving barbiturates or other central nervous system depressants. There is an additive risk of central nervous system depression when these medicines are taken together;
  - patients should be cautioned regarding the additive effect of alcohol (*see sub-header 'Alcohol and drug abuse'*).
- In addition, LIBRAX® should be used with caution in the elderly due to the danger of precipitating undiagnosed glaucoma.
- Due to the risk of sedation and/or myorelaxant effects, LIBRAX® and similar medicines should be used with caution in elderly patients since they could lead to falls, frequently with serious sequelae in this patient population.

Tolerance:

Some loss of the hypnotic effects of LIBRAX® may develop after repeated use for a few weeks.

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Psychiatric and paradoxical reactions:

- In general, the concomitant administration of LIBRAX® and other psychotropic medicines is not recommended. If such combination therapy is indicated, careful consideration should be given to the pharmacology of the medicines to be employed – particularly when the known potentiating combinations such as monoamine oxide (MAO) inhibitors and phenothiazines are to be used.
- The usual precautions are indicated when LIBRAX® is used in patients with associated anxiety states and where there is any evidence of impending depression.
- Paradoxical reactions such as acute hyper-excitability with rage may occur.
- In some patients, LIBRAX® and similar medicines may cause various changes in the state of consciousness, as well as in behaviour and memory, such as: exacerbation of insomnia, nightmares, agitation, nervousness, confused state, delusions, confusion, psychotic symptoms, loss of inhibition with impulsive behaviour, euphoria, irritability, anterograde amnesia and suggestibility. This condition may be accompanied by potentially dangerous problems for the patient or others, such as inappropriate behaviour, aggressive behaviour against oneself or others, especially when friends and relatives try to prevent the patient's activities, as well as automatic behaviour with post-event amnesia.
- These reactions are more common in elderly patients.

- Extreme caution must be exercised when prescribing LIBRAX® to patients with personality disorders.
- If these occur, LIBRAX® should be discontinued.

Drug abuse and dependence:

- There is a potential for abuse and the development of physical and psychic dependence, especially with prolonged use and high doses.
- The risk of dependence is also greater in patients with a history of alcohol or drug abuse.
- Combining LIBRAX® with several benzodiazepines, regardless of the indication, increases the risk of drug dependence. Cases of abuse have been reported.
- To minimise the risk of dependence, LIBRAX® should be prescribed only after careful review of the indication and taken over the shortest possible duration. Checks must be performed periodically to determine whether it is necessary to continue treatment. Prolonged treatment is indicated only for certain patients (e.g. panic states).

Withdrawal symptoms:

- 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, hyper reactivity, extreme anxiety, tension, restlessness, confusion and irritability.

- In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Rebound effects:

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

Amnesia and changes in psychomotor function:

- LIBRAX® can cause anterograde amnesia. Amnesia along with psychomotor changes usually occur several hours after intake.

Risk due to concomitant use with opioids :

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1.5.5.1 Annotated Professional Information for medicines for human use - clean

- Concomitant use of LIBRAX® and opioids may lead to sedation, respiratory depression, coma and death. Due to these risks, concomitant prescription of opioids together with sedatives such as benzodiazepines, or related medicines such as LIBRAX®, is indicated only for those patients for whom there are no alternative treatment options. Nevertheless, if concomitant prescription of LIBRAX® together with opioids is deemed necessary, the lowest effective dose should be used and the duration of treatment should be as short as possible.
- Patients should be closely monitored for signs and symptoms of respiratory depression and sedation. In this regard, it is strongly recommended that patients and their caregivers (if applicable) be informed of these symptoms *(see section 4.5*).

Other :

- Although clinical studies have not established a cause and effect relationship, doctors should be aware that variable effects on blood coagulation have been reported infrequently in patients receiving oral anti-coagulants and chlordiazepoxide as contained in LIBRAX®.
- Medical conditions which may be affected by the use of LIBRAX® are :

- cardiac disease, coronary insufficiency,
- hiatus hernia with reflux oesophagitis,
- intestinal atony, paralytic ileus, toxic megacolon,
- obstruction in the gastro-intestinal or urinary tracts,

- ulcerative colitis or urinary retention,
- intestinal atony in elderly patients,
- chronic bronchitis due to increased viscosity of bronchial mucus,
- hyperthyroidism,
- prostatic hypertrophy,
- renal impairment or mild-to-moderate hepatic impairment.

Paediatric population :

- LIBRAX® is not recommended for children. (*see section 4.3*).

Lactose warning:

LIBRAX® contains lactose, which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption intolerance should not take LIBRAX®.

Sucrose warning:

LIBRAX® contains 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 sucrase-isomaltase insufficiency should not take LIBRAX®.

4.5 Interaction with other medicines and other forms of Interaction

- *Antacids or diarrhoea medicines containing kaolin or attapulgite:*
- May reduce blood levels and therefore the effects of LIBRAX®.
- These should therefore be taken at least 2-3 hours before or after LIBRAX®.
- *Ketoconazole:*
- LIBRAX® may reduce the blood levels and therefore should be taken at least 2 hours
- after ketoconazole.
- Diminished bowel motility with LIBRAX® may increase the liability to superficial ulceration of the stomach or bowel with potassium chloride.

- ***Interactions with chlordiazepoxide:***
- *Medicines with inhibitory activity on hepatic enzymes*
  - Chlordiazepoxide as contained in LIBRAX® is hydroxylated by the isoenzyme CYP450 3A4. In principle, although no specific interaction studies are available, caution should be exercised when co-administering medicines that inhibit – or are metabolised by – this isoenzyme (such as macrolide antibiotics, azole- type antifungal agents, calcium antagonists, protease inhibitors, ergot alkaloids and antidepressants).

- The metabolism of chlordiazepoxide as contained in LIBRAX® can be inhibited by ketoconazole, cimetidine or disulfiram. Concomitant ingestion of cimetidine leads to an increased risk of somnolence. The patient should be warned about this increased risk when driving or using machines (*see section 4.7)*.
- Caution should be exercised when combining LIBRAX® with centrally acting medicines (such as neuroleptics, sedatives, hypnotics, analgesics, antitussives, sedating antihistamines, centrally acting antihypertensive agents, antiepileptic agents, opiates or baclofen), since the central depressant effect may be enhanced.
- Concomitant use of opioids together with sedatives such as benzodiazepines or related medicines such as LIBRAX® increases the risk of sedation, respiratory depression, coma and death due to an additive central nervous system (CNS)-depressant effect. The dosage and duration of concomitant use should be restricted (*see section 4.4*). Additionally, concomitant intake of opioids (narcotic analgesics) may lead to an increase in the euphoric effect and thus to accelerated development of psychological dependence.
- Muscle relaxants may potentiate the effect of chlordiazepoxide.
- Absorption of other medicines may be slowed by the effect on the gastrointestinal tract.

- *Barbiturates, morphine derivatives*

- There is an increased risk of respiratory depression in patients concomitantly

taking barbiturates or morphine derivatives. This may be fatal in cases of overdose.

- *Buprenorphine*

o Concomitant intake with buprenorphine also leads to an increased risk of respiratory depression, which may be fatal. Inform the patient of the necessity of complying with the prescribed dose.

Interactions with clidinium bromide:

The anticholinergic effect of clidinium is potentiated when LIBRAX® is taken concomitantly with medicines with an anticholinergic (atropine-like) active component, for example amantadine, some antihistamines (H1 antagonists), butyrophenones, phenothiazines, tri- and tetracyclic antidepressants, antiparkinson agents, antiarrhythmic medicines (such as quinidine, disopyramide), pirenzepine, anticholinergic antispasmodic agents or asthma medicines. This may result in undesirable effects, e.g. urinary retention, progression of glaucoma, constipation, dry mouth, etc. Alcohol must not be consumed by persons under the influence of LIBRAX® since the individual reaction in each case is unpredictable.

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4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

Due to the genotoxic potential of chlordiazepoxide as contained in LIBRAX®, women of childbearing potential should use effective contraceptive measures while being treated with LIBRAX® and for 7 months following completion of treatment.

If the patient suspects to be pregnant or intends to become pregnant, she should be warned to contact her doctor to discuss discontinuation of LIBRAX®.

Men are recommended to use effective contraceptive measures and to not father a child while receiving LIBRAX® and for 4 months following completion of treatment.

Pregnancy

LIBRAX® should not be used during pregnancy. During labour LIBRAX® crosses the placenta and may cause the “floppy-infant” syndrome characterised by central respiratory depression, hypothermia and poor sucking.

Breastfeeding

LIBRAX® should not be administered to lactating mothers.

Fertility

No effect on fertility expected.

4.7 Effects on ability to drive and use machines

Patients should be advised, particularly at the initiation of therapy, not to drive a motor vehicle or operate dangerous machinery or perform potentially hazardous tasks where impaired decision making could lead to accidents.

LIBRAX® may cause drowsiness, sedation, amnesia, impaired concentration, impaired muscular function (*see section 4.8*), and have a noticeable effect on mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

Combination with other sedative medicines should not be recommended or considered when driving cars or using machines *(see section 4.5*).

4.8 Undesirable effects

Since LIBRAX® contains chlordiazepoxide and clidinium bromide, the possibility of untoward effects which may be seen with either of these two active substances cannot be excluded.

The side effects most frequently encountered are drowsiness and over-sedation. Drowsiness is more common in elderly and debilitated patients, and in those receiving high doses. Less common are depression of mood and affect, disorientation or confusion, lethargy, ataxia, constipation, nausea, diarrhoea and changes in libido.

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Summary of the safety profile

Tabulated list of adverse reactions

Body System	**Undesirable effect**				
	Common	**Uncommon**	**Rare**	**Very Rare**	**Frequency not known**
Blood and the lymphatic system disorders:			bone marrow depression (e.g. thrombocytopenia, leucopenia, agranulocytosis, pancytopenia)		
Immune system disorders:					hypersensitivity
Metabolism and nutrition disorders:		increased appetite			
Psychiatric disorders:					amnesia, hallucination, dependence, depression, restlessness, agitation, irritability, depressed level of consciousness, aggression, delusion, nightmares,

					psychotic disorders, abnormal behaviour, emotional disturbances, paradoxical medicine reaction (e.g. anxiety, sleep disorders, insomnia, suicide attempt, suicidal ideation)
Nervous system disorders:	sedation, dizziness, somnolence, ataxia, balance disorder, confusional state, drowsiness[1]		headache, vertigo		dysarthria, gait disturbance, extrapyramidal disorder (e.g tremor, dyskinesia)
Eye disorders:		decreased lacrimation, accommodation disorders	visual impairment incl. diplopia, blurring of vision[1]		
Cardiac disorders:					tachycardia, palpitations
Vascular disorders:			hypotension		
Respiratory, thoracic and mediastinal disorders:					respiratory depression, increased viscosity of bronchial secretion

Gastrointestinal disorders:			gastrointestinal disorders, constipation[1]		
Hepato-biliary disorders:					jaundice, hepatic dysfunction, haematological disturbances, increased blood bilirubin, increased transaminases, increased blood alkaline phosphatase
Skin and subcutaneous tissue disorders:			skin reactions (e.g. rash, pruritus)		
Musculoskeletal, connective tissue and bone disorders:					muscular weakness, asthenia
Renal and urinary disorders:			urinary retention[1]		
Reproductive system and breast disorders:			libido disorder, erectile dysfunction, menstrual disorder	dysmenorrhoea	
General disorders and administrative site conditions:	fatigue	dry mouth[1]			

[1] These side effects are usually mild and transient and may be minimised by dosage adjustment.

Tabulated list of adverse reactions of chlordiazepoxide

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Body System	Undesirable effect
	Less frequent[2]
Nervous system disorders:	extrapyramidal symptoms (e.g tremor, dyskinesia)
Gastrointestinal disorders:	nausea and constipation
Skin and subcutaneous tissue disorders:	skin eruptions, oedema
Reproductive system and breast disorders:	minor menstrual irregularities, increased and decreased libido

[2] These side effects have been reported less frequently and are generally controlled with reduction of dosage.

Reporting suspected adverse reactions after authorisation of the medicine is important.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (*see section 4.8)*.

The signs and symptoms of LIBRAX® overdosage may be produced by either of its components.

Overdose associated with chlordiazepoxide

Clinical signs and symptoms:

- Usually, such symptoms will probably be overshadowed by the anticholinergic actions of clidinium bromide (*see below*).
- As with other benzodiazepines, an overdose of LIBRAX® can be life-threatening, especially in cases of multiple intoxication with other centrally depressant medicines (including alcohol).
- LIBRAX® overdose usually leads to depression of the central nervous system, the symptoms of which, depending on severity, may manifest as drowsiness to comatose states, as mentioned above. In mild cases, symptoms include drowsiness, confusion and lethargy. In severe cases, ataxia, decreased muscle tone, hypotension and respiratory depression may occur; coma is rare and fatal in very rare cases.
- *Treatment:*
- Treatment is systematic and supportive.

Overdose associated with clidinium bromide

Clinical signs and symptoms:

Clidinium bromide overdose may be manifested by anticholinergic effects such as excessive dryness of mouth, urinary hesitancy and constipation tachycardia, mild drowsiness and transient disturbances of vision (including blurring of vision, mydriasis and 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:

- Treatment is systematic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION:

A11.2 Gastro-intestinal anti-spasmodic and cholinolytic (anti-cholinergics)

Pharmacotherapeutic group: Synthetic anticholinergic agents in combination with psycholeptics ATC code: A03CA02 (clidinium and psycholeptics)

Pharmacodynamic effects:

LIBRAX® has anticholinergic/spasmolytic action and anxiolytic effect.

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6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Lactose anhydrous

White corn starch

Talc

Magnesium stearate

Sugar-coating:

Acacia gum spray-dried

Indigo carmine 85 %

Yellow iron oxide

Rice starch

Oil of paraffin of low viscosity

Paraffinum sodium FP 50/52

Crystallized sugar

Talcum Luzenac 00

6.2 Incompatibilities

Not applicable.

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6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original package/container.

6.5 Nature and contents of container

Sugar coated tablets in amber glass bottles containing 30, 100 or 500 tablets.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Any unused product or waste material should be disposed of in accordance with local requirements.

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Viatris South Africa (Pty) Ltd

4 Brewery Street

Isando

1600

Republic of South Africa

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8 REGISTRATION NUMBER(S)

B/11.2/994

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 June 1998

10 DATE OF REVISION OF TEXT

TBA