**Proposed professional information for URBANOL**

## SCHEDULING STATUS

S5

## 1 NAME OF THE MEDICINE

URBANOL® 5 mg CAPSULES

URBANOL® 10 mg TABLETS

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

URBANOL 5 mg CAPSULES:

Each capsule contains 5 mg clobazam as active ingredient.

Contains sugar (lactose): 127 mg.

For a full list of excipients, see section 6.1.

URBANOL 10 mg TABLETS:

Each tablet contains 10 mg clobazam as active ingredient.

Contains sugar (lactose monohydrate): 72,3 mg.

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

URBANOL 5 mg CAPSULES

URBANOL 5 mg CAPSULES: opaque blue and white unprinted capsules (size no.4) containing a white powder.

**Clinical recommendation:** 23.05.2019 (received 21.08.2019). Date submitted: 22.01.2020

URBANOL 10 mg TABLETS

URBANOL 10 mg TABLETS: white bi-planar round tablets scored and engraved with “CBZ” and “10” on one side, and plain on the other side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

URBANOL is used in the treatment of anxiety in neurotic patients and for pre-operative medication. It may be effective in relieving the acute symptoms of alcohol withdrawal syndrome but has not specific usefulness in the treatment of psychotic patients.

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

### 4.2 Posology and method of administration

The normal adult dose ranges between 10 – 30 mg daily: doses of 20 mg and above should preferably be given at bedtime or in divided doses.

For elderly and debilitated patients as well as in children and light-weight patients, the daily dose should be halved.
Increased responsiveness and higher susceptibility to adverse effects may be present in these patients and low initial doses and gradual dose increments, under careful observation, are required.

Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded.

Dosage and duration of treatment must be adjusted to the indication, the severity of the condition and the individual clinical response. Due regard must be paid to the possibility of interference with alertness and reaction time. The fundamental principle is to keep the dose as low as possible.

**Patients with renal or hepatic impairment:**

Increased responsiveness and higher susceptibility to adverse effects may be present in these patients and require low initial doses and gradual dose increments under careful observation (see section 4.4).

**Secondary dose adjustment:**

After improvement of symptoms, the dose may be reduced.

**Duration of treatment:**

The duration of treatment should be as short as possible. The patient should be reassessed after a period, not exceeding 4 weeks, and regularly thereafter in order to evaluate the need for continued treatment, especially where the patient is free of symptoms. 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, using special expertise. It is strongly recommended that prolonged periods of uninterrupted treatment be avoided, since it may lead to dependence (see section 4.4).

**Discontinuation of treatment:**

It is strongly recommended that after prolonged treatment, URBANOL is not withdrawn suddenly, but rather that the dose is reduced gradually under medical supervision; otherwise, withdrawal symptoms may occur (see section 4.4).

**ADMINISTRATION:**

The 10 mg tablets can be divided into equal halves of 5 mg.

The capsules are to be swallowed without chewing with a generous amount of liquid (approximately 1 glass).

URBANOL can be given with or without food.

## 4.3 Contraindications

- Known hypersensitivity to benzodiazepines, or hypersensitivity to clobazam or any of the excipients of URBANOL
- Patients with any history of drug or alcohol dependence (increased risk of development of dependence)
- Myasthenia gravis (risk of aggravation of muscle weakness)
- Severe respiratory insufficiency (risk of deterioration)
- Sleep apnoea syndrome (risk of deterioration)
- Severe impairment of liver function (risk of precipitating encephalopathy)
- During the first trimester of pregnancy (see section 4.6, for use during second and third trimester)
- Breastfeeding women (see section 4.6)
- Benzodiazepines must not be given to children without careful assessment of the need for their use. URBANOL must not be used in children of age 3 years and younger.

## 4.4 Special warnings and precautions for use

**Amnesia:**

Anterograde amnesia may occur even if benzodiazepines are used in normal dose range, but especially at higher dose levels. In case of loss or bereavement psychological adjustment may be inhibited by
benzodiazepines.

**Muscle weakness:**

Clobazam can cause muscle weakness. Therefore, in patients with pre-existing muscle weakness or spinal or cerebellar ataxia or sleep apnoea, special observation is required, and a dose reduction may be necessary. Clobazam is contraindicated in patients with myasthenia gravis.

**Depression and personality disorders:**

Disinhibiting effects may be manifested in various ways. Suicide may be precipitated in patients who are depressed and aggressive behaviour towards self and others may be precipitated. Extreme caution should therefore be used in prescribing benzodiazepines in patients with personality disorders.

**Dependence:**

Benzodiazepines, including URBANOL, may lead to physical and psychological dependence. The risk of dependence increases with the dose and duration of treatment. However, this risk is present even with daily intake of URBANOL over periods of only a few weeks and applies not only to possible abuse with particularly high doses but also to the therapeutic dose range. The risk of dependence is increased in patients with a history of alcohol or drug abuse. Therefore, the duration of treatment should be as short as possible. (see section 4.2). The therapeutic benefit must be balanced against the risk of dependence during prolonged use.
Rebound phenomena are characterised by a recurrence in enhanced form of the symptoms which originally led to URBANOL treatment. This may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness.

Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment it is recommended that the dosage be decreased gradually.

Once physical dependence has developed, abrupt termination of URBANOL treatment will lead to withdrawal symptoms. These may include headaches, sleep disturbances, extreme anxiety, tension, restlessness, confusion, excitability and irritability.

In severe cases the following symptoms may occur:

derealisation, depersonalisation, hallucinations and symptomatic psychoses (e.g. withdrawal delirium), numbness and tingling sensations in the extremities, muscle pain, tremor, sweating, nausea, hyperacusis, hypersensitivity to light, noise and physical contact, as well as epileptic seizures.

A withdrawal syndrome may also occur when abruptly changing over from a benzodiazepine with a long duration of action (for example URBANOL) to one with a short duration of action.

**Pregnancy:**

Clobazam is not recommended during the first trimester of pregnancy and in women of childbearing potential not using contraception.

**Serious skin reaction:**

Serious skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported with clobazam in both children and adults during the post-marketing experience. A majority of the reported cases involved the concomitant use of other medicines, including anti-epileptic medicines that are associated with serious skin reactions. SJS/TEN could be associated with a fatal outcome. Patients should be closely monitored for signs or symptoms of SJS/TEN, especially during the first 8 weeks of treatment. Clobazam should be immediately discontinued when SJS/TEN is suspected. If signs or symptoms suggest

SJS/TEN, use of this medicine should not be resumed and alternative therapy should be considered (see section 4.8).

**Respiratory depression:**

Respiratory function should be monitored in patients with chronic or acute severe respiratory insufficiency and a dose reduction of clobazam may be necessary. Clobazam is contraindicated in patients with severe respiratory insufficiency (see section 4.3).

**Renal and hepatic impairment:**

In patients with impairment of renal or hepatic function, responsiveness to clobazam and susceptibility to adverse effects are increased, and a dose reduction may be necessary. In long-term treatment renal and hepatic function must be checked regularly.

**Elderly patients:**

In the elderly, due to the increased sensitivity to adverse reactions such as drowsiness, dizziness and muscle weakness, there is an increased risk of fall that may result in serious injury. A dose reduction is recommended.

**Tolerance in epilepsy:**

In the treatment of epilepsy with benzodiazepines – including clobazam – consideration must be given to the possibility of a decrease in anti-convulsant efficacy (development of tolerance) during the course of treatment.

**CYP2C19 poor metabolisers:**

In patients who are CYP2C19 poor metabolisers, levels of the active metabolite *N*-desmethylclobazam are expected to be increased as compared to extensive metabolisers. As this

may lead to increased side effects, dosage adjustment of clobazam may be necessary (e.g. low starting dose with careful dose titration – see section 5.2).

**Alcohol:**

It is recommended that patients abstain from drinking alcohol during treatment with URBANOL, as there is an increased risk of sedation and other adverse effects (see section 4.5).

**Concomitant use of opioids and benzodiazepines**

Concomitant use of opioids and benzodiazepines, including clobazam, may result in sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of opioids and benzodiazepines for use in patients for whom alternative treatment options are inadequate.

If a decision is made to prescribe clobazam concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation (see section 4.5).

URBANOL is not recommended for the primary treatment of psychotic illness. In patients with depression or anxiety associated with depression, URBANOL must be used only in conjunction with adequate concomitant treatment. Use of benzodiazepines (such as URBANOL) alone, can precipitate suicide in such patients.

Before treatment of anxiety states associated with emotional instability it must first be determined whether the patient suffers from a depressive disorder requiring adjunctive or different treatment.

In patients with schizophrenic or other psychotic illnesses, use of benzodiazepines is recommended only for adjunctive treatment, i.e. not for primary treatment.

Patients receiving barbiturates, antihistamines, narcotics or other central nervous system depressants. There is an additive risk of central nervous system depression when these medicines are taken together. Large doses may produce syncope.

**Duration of treatment:**

The duration of treatment should be as short as possible (see section 4.2) but should not exceed 8 – 12 weeks in case of anxiety, including the tapering-off process. Extension beyond these periods should not take place without re-evaluation of the situation. 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.

## 4.5 Interaction with other medicines and other forms of interaction

- **Alcohol**

Concomitant consumption of alcohol can increase the bioavailability of clobazam by 50 % (see section 5.2) and therefore lead to increased
clobazam effects (see section 4.4).

- **Central nervous system (CNS) depressant medication**

Especially when URBANOL is administered in higher doses, a mutually potentiating effect is to be expected if other CNS depressant medicines (such as antipsychotics, anxiolytics, certain antidepressant agents, anticonvulsant medicines, sedative antihistamines, anaesthetics, hypnotics or narcotic analgesics, or other sedatives) are taken at the same time. Special caution is also necessary when URBANOL is administered in cases of intoxication with such substances or with lithium.

- **Anticonvulsants**

If URBANOL is administered simultaneously with anticonvulsants, the dosage must be adjusted under regular medical supervision (EEG monitoring), as there may be interactions with the patient's anticonvulsant medication.

In patients receiving concomitant treatment with valproic acid, there may be a slight to moderate rise in plasma valproic acid concentration.
Phenytoin plasma levels may rise if patients receive concomitant treatment with URBANOL.

Where possible, it is recommended that blood levels of concomitantly administered valproic acid or phenytoin be monitored.

Carbamazepine and phenytoin may increase the metabolic conversion of clobazam to the active metabolite *N*-desmethylclobazam.

Stiripentol increases plasma levels of clobazam and its active metabolite, *N*-desmethylclobazam, through inhibition of CYP3A and CYP2C19. Monitoring of blood levels is recommended, prior to initiation of stiripentol and then once new steady-state concentration has been reached, i.e. after approximately 2 weeks.

- **Narcotic analgesics**

If URBANOL is used concomitantly with narcotic analgesics, possible euphoria may be enhanced; this may lead to increased psychological dependence.

- **Muscle relaxants**

The effects of muscle relaxants and nitrous oxide may be enhanced.

- **CYP2C19 inhibitors**

Strong and moderate inhibitors of CYP2C19 may result in increased exposure to *N*-desmethylclobazam (N-CLB), the active metabolite of clobazam. Dosage adjustment of URBANOL may be necessary when co-administered with strong (e.g., fluconazole, fluvoxamine, ticlopidine) or moderate (e.g. omeprazole) CYP2C19 inhibitors (see section 5.2).

- **CYP2D6 substrates**

Clobazam is a weak CYP2D6 inhibitor (see section 5.2).
Dose adjustment of medicines metabolised by CYP2D6 (e.g. dextromethorphan, pimozide, paroxetine, nebivolol) may be necessary.

## 4.6 Fertility, pregnancy and lactation

**Pregnancy:**

URBANOL should be used judiciously during pregnancy and preferably avoided.
Administration of URBANOL before or during childbirth can result in the occurrence of respiratory depression (including respiratory distress and apnoea), which may be associated with other disorders such as signs of sedation, hypothermia, hypotonia, feeding difficulties in the new-born and an increase in fetal heart rate (signs and symptoms of the so-called **"floppy infant syndrome"**). Moreover, infants born to mothers who have taken benzodiazepines over longer periods during the later stages of pregnancy may have developed physical dependence and may be at risk of developing a withdrawal syndrome in the postnatal period. Appropriate monitoring of the new-born in the postnatal period is recommended.

Generally, URBANOL must not be used in the first trimester of pregnancy (see section 4.3).
In the later stages of pregnancy, it must only be used if there are compelling indications.

**Lactation:**

URBANOL must not be used in breastfeeding women, since it passes into breast milk (see section 5.2).

## 4.7 Effects on ability to drive and use machines

Some adverse effects (e.g., sedation, muscle weakness) may impair the patient's ability to concentrate and react, and, therefore constitute a risk in situations where these abilities are of special importance (e.g., climbing dangerous heights, operating a vehicle or machinery).

## 4.8 Undesirable effects

*The following CIOMS frequency rating is used, when applicable: 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 (cannot be estimated from the available data).*

**Blood and lymphatic system disorders:**

*Not known:* blood dyscrasias have been reported.

**Metabolism and nutrition disorders:**

*Common:* decreased appetite

**Psychiatric disorders:**

*Common:* irritability, aggressiveness, restlessness, depression (pre-existing depression may be unmasked), drug tolerance (especially during prolonged use) (see section 4.4), acute agitation

*Uncommon:* abnormal behaviour, confusional state, anxiety, delusion, nightmare, loss of libido (particularly with high doses or in long-term treatment, and is reversible)

*Not known:* dependence (especially during prolonged use) (see section 4.4), initial insomnia, anger, fits of rage, nightmares, hallucination, psychotic disorder, poor sleep quality, difficulty in falling asleep or sleeping through suicidal ideation or tendencies. In the event of such reactions, treatment with URBANOL must be discontinued

Pre-existing depression may be unmasked during benzodiazepine use.

Tolerance and dependence may develop, especially during prolonged use (see section 4.4).

**Nervous system disorders:**

*Very common:* tiredness and sleepiness (somnolence), especially at the beginning of treatment and when higher doses are used

*Common:* sedation, dizziness, disturbance in attention, slowed or indistinct speech (disorders of articulation), (particularly with high doses or in long-term treatment, and is reversible), headache, tremor, ataxia or a fine tremor of the fingers may occur

*Uncommon*: numbed emotions, emotional poverty, anterograde amnesia may occur even if benzodiazepines are used in the normal dose range, but especially at higher dose levels, amnesia effects may be associated with inappropriate behaviour, memory impairment,

*Not known:* Slowed reaction time, drowsiness*, disorientation and confusion, muscle weakness, lethargy, cognitive disorder, impairment of consciousness (sometimes combined with respiratory disorders, may occur in very rare cases, particularly in elderly patients; these effects sometimes persist for a considerable length of time), nystagmus (particularly with high doses or in long-term treatment), unsteadiness of gait and other motor functions (such reactions occur particularly with high doses or in long-term treatment, and are

reversible).

*drowsiness is more common in elderly and debilitated patients and in patients receiving high doses.

**Eye disorders:**

*Uncommon:* visual disorders (diplopia). Such reactions occur particularly with high doses or in long-term treatment and are reversible.

**Respiratory, thoracic and mediastinal disorders:**

*Not known:* URBANOL may cause respiratory depression, especially if administered in high doses. Therefore, particularly in patients with pre-existing compromised respiratory function (e.g. in patients with bronchial asthma) or brain damage, respiratory insufficiency may occur or deteriorate.

**Gastrointestinal disorders:**

*Common:* dry mouth, constipation, decreased appetite, nausea/vomiting

**Hepato-biliary disorders:**

*Unknown:* hepatic dysfunction has been reported

**Skin and subcutaneous tissue disorders:**

*Uncommon:* cutaneous reactions, such as rash may develop in very rare cases

*Not known:* photosensitivity reactions, urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis (including some cases with fatal outcome)

**Musculoskeletal and connective tissue disorders:**

*Not known:* muscle spasms, muscle weakness

**General disorders and administration site disorders:**

*Very common*: fatigue, especially at the beginning of treatment and when higher doses are used

*Not known*: slow response to stimuli, hypothermia

*Uncommon:* weight gain (particularly with high doses or in long-term treatment, and is reversible)

**Injury, poisoning and procedural complications**

*Uncommon:* fall

**Reporting of suspected adverse reactions**

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:

- The Pharmacovigilance Unit at Sanofi: za.drugsafety@sanofi.com (email) or 011 256 3700 (tel.), or
- SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**" found online under SAHPRA's publications: http://www.sahpra.org.za/Publications/Index/8

## 4.9 Overdose

**Signs and symptoms:**

Overdose and intoxication with benzodiazepines, including URBANOL, may lead to central nervous system depression, associated with drowsiness, confusion and lethargy, possibly progressing to ataxia, respiratory depression, hypotension and, rarely, coma. The risk of a fatal outcome is increased in cases of combined poisoning with other CNS depressants, including alcohol.

**Management:**

In treatment for intoxication, it is recommended that the possible involvement of multiple agents be taken into consideration.

Gastric lavage, intravenous fluid replenishment and general supportive measures may be indicated in addition to monitoring of consciousness, respiration, pulse rate and blood pressure.

Secondary elimination of URBANOL (by forced diuresis or haemodialysis) is ineffective.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Category and class: A. 2.6 Tranquillisers

Pharmacotherapeutic group: Benzodiazepine derivatives

ATC Code: N05BA

Clobazam is a 1,5-benzodiazepine, with anxiolytic properties.

### 5.2 Pharmacokinetic properties

*Absorption:*

After oral administration, clobazam is well-absorbed. Relative bioavailability of clobazam capsules, tablets or solution (in propylene glycol) was not significantly different.

Time to peak plasma concentration ($T_{max}$) is achieved from 0,5 – 4 hours. The administration of URBANOL tablets with food slows the rate of absorption by approximately 1 hour but does not affect the overall extent of absorption.

Concomitant intake of alcohol can increase the bioavailability of clobazam by 50 % (see section 4.5).

*Distribution:*

After a single dose of 20 mg clobazam, marked interindividual variability in maximum plasma concentrations (222 to 709 ng/mL) was observed after 0,25 to 4 hours. Clobazam is lipophilic and

distributes rapidly throughout the body. Based on a population pharmacokinetic analysis, the apparent volume of distribution at steady state was approximately 102 L and is concentration independent over the therapeutic range. Approximately 80 – 90 % of clobazam is bound to plasma protein.

Clobazam accumulates approximately 2 – 3-fold to steady-state while the active metabolite N-desmethylclobazam (N-CLB) accumulates approximately 20-fold following clobazam twice-daily administration. Steady-state concentrations are reached within approximately 2 weeks.

*Metabolism:*

Clobazam is rapidly and extensively metabolised in the liver. Clobazam metabolism occurs primarily by hepatic demethylation to *N*-desmethylclobazam (N-CLB), mediated by CYP3A4 and to a lesser extent by CYP2C19. N-CLB is an active metabolite and the main circulating metabolite found in human plasma.

N-CLB undergoes further biotransformation in the liver to form 4-hydroxy-*N*-desmethylclobazam, primary mediated by CYP2C19.

CYP2C19 poor metabolisers exhibit a 5-fold higher plasma concentration of N-CLB compared to extensive metabolisers.

Clobazam is a weak CYP2D6 inhibitor. Co-administration with dextromethorphan led to increases of 90 % in AUC and 59 % in $C_{max}$ values for dextromethorphan.

*Elimination:*

Based on a population pharmacokinetic analysis, plasma elimination half-lives of clobazam and N-CLB were estimated to be 36 hours and 79 hours, respectively.

Clobazam is cleared mainly by hepatic metabolism with subsequent renal elimination. In a mass balance study, approximately 80 % of the administered dose was recovered in urine and about 11 % in the faeces.

Less than 1 % of unchanged clobazam and less than 10 % of unchanged N-CLB are excreted through the kidneys.

*Special populations:*

Clobazam crosses the placental barrier and appears in breast milk. Both in the fetal blood and in breast milk, effective concentrations may be reached.

**Elderly patients**

In the elderly, there is a tendency to a reduction in clearance
following oral administration; terminal half-life is prolonged, and the distribution volume increased. This may lead to a more extensive accumulation of the medicine, when administered on a multiple-dose basis than in younger subjects. The effect of age on the clearance and accumulation profile of clobazam seems also to apply to the
active metabolite.

**Hepatic impairment**

In patients with severe liver disease, the distribution volume of clobazam is increased and the terminal half-life is prolonged.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

URBANOL 5 mg CAPSULES:

Excipients:

Lactose

Talc

Magnesium stearate.

*Capsule shell:*

Gelatine

Titanium dioxide (E171)

Indigotin.

URBANOL 10 mg TABLETS:

Excipients:

Maize starch

Lactose monohydrate

Talc

Colloidal anhydrous silica

Magnesium stearate.

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf life

URBANOL® 5 mg CAPSULES: 3 years/36 months

URBANOL® 10 mg TABLETS: 2 years/24 months

## 6.4 Special precautions for storage

Store at or below 25 °C, in a dry place.

Protect from moisture.

### 6.5 Nature and contents of container

URBANOL is available as 5 mg capsules and 10 mg tablets packed into opaque white PVC/acetochloride and aluminium blister packs, inserted into outer printed cardboard cartons, containing 100 capsules/tablets each (5x 20 blister packs).

### 6.6 Special precautions for disposal

No special requirements.

## 7 HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd.

2 Bond Street,

Midrand,1685,

South Africa.

## 8 REGISTRATION NUMBER

URBANOL 5 mg CAPSULES : L/2.6/52

URBANOL 10 mg TABLETS : M/2.6/128

## 9 DATE OF FIRST AUTHORISATION

URBANOL 5 mg CAPSULES : 8 November 1978.

URBANOL 10 mg TABLETS : 20 July 1979.

## 10. DATE OF REVISION OF THE TEXT

To be allocated.

**Clinical recommendation:** 23.05.2019 (received 21.08.2019). Date submitted: 22.01.2020

**Reference:**

| Ref. | Description | Module |
|---|---|---|
| Ref. 1 | EU Summary of product characteristics for Frisium® 10 mg tablets (Clobazam 10 mg). Approved 15/01/2002; Revised: 04/07/2018, p. 1 – 12. | 1.3.1.2.1 |
| Ref. 2 | Approved shelf-life documentation:<br>Urbanol 5 mg: SAHPRA (MCC) approval letter & Annexure 10.1<br>Urbanol 10 mg: Annexure 10.1 | 1.3.1.2.2 |