SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

NOVAPRAZ XR 0,5 (extended release tablets)

NOVAPRAZ XR 1 (extended release tablets)

NOVAPRAZ XR 2 (extended release tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each NOVAPRAZ XR 0,5 extended release tablet contains 0,5 mg alprazolam.

Each NOVAPRAZ XR 1 extended release tablet contains 1 mg alprazolam.

Each NOVAPRAZ XR 2 extended release tablet contains 2 mg alprazolam.

For full list of excipients, see section 6.1

Contains sugar (lactose monohydrate).

3. PHARMACEUTICAL FORM

Extended release tablets (XR)

NOVAPRAZ XR 0,5: White to off-white, round, biconvex tablets with bevelled edge debossed with ‘X’ on one side and ‘70’ on the other side.

NOVAPRAZ XR 1: Yellow coloured, round, biconvex tablets with bevelled edge debossed with ‘X’ on one side and ‘73’ on the other side. The tablets may be mottled.

NOVAPRAZ XR 2: Blue coloured, round, biconvex tablets with bevelled edge debossed with ‘X’ on one side and ‘74’ on the other side. The tablets may be mottled.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NOVAPRAZ XR is indicated for the treatment of:

- SHORT-TERM RELIEF OF SYMPTOMS OF ANXIETY
- TREATMENT OF ANXIETY DISORDERS

- ANXIETY ASSOCIATED WITH DEPRESSION
- MIXED ANXIETY-DEPRESSION
- DEPRESSION
- PANIC DISORDERS

Short-term relief of symptoms of anxiety: treatment of anxiety disorders:

Anxiety disorder is a condition corresponding most closely to the latest APA Diagnostic and Statistical Manual [DSM] diagnosis of generalised anxiety disorder.

Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

Diagnostic criteria for Generalised Anxiety Disorder:

A. Generalised, persistent anxiety is manifested by symptoms from three of the following four categories:

1. Motor tension:

Shakiness, jitteriness, jumpiness, trembling, muscle aches, tension, eyelid twitch, inability to relax, furrowed brow, strained face, restlessness and easily startled.

2. Autonomic hyperactivity:

Heart pounding or racing, sweating, cold clammy hands, dry mouth, light-headedness, dizziness, paraesthesias, upset stomach, diarrhoea, discomfort in the pit of the stomach, hot or cold spells, lump in the throat, flushing, pallor, high resting pulse and respiration rate.

3. Apprehensive expectation:

Fear, anxiety, worry, rumination, and anticipation of misfortune to self and others.

4. Vigilance and scanning:

Hyper attentiveness resulting in distractibility, difficulty in concentrating, insomnia, feeling "on edge", impatience and irritability.

B. The anxious mood has been continuous for at least one month.

C. Not due to another mental disorder, such as Depressive Disorder or Schizophrenia.

D. At least 18 years of age.

Anxiety associated with depression; mixed anxiety depression; depression:

Depression can be variously described as neurotic depression, reactive depression, major depressive disorder, etc., depending upon local psychiatric nosology. Usage has not been established in depression with psychiatric features, in bipolar disorders or in "endogenous" depression (i.e., severely depressed inpatients).

Panic disorders:

This includes panic disorder with or without agoraphobia. The essential feature of panic disorder is the unexpected panic attack, a sudden onset of intense apprehension, fear, or terror.

Panic disorder is an illness characterised by recurrent panic attacks. Later in the course of this disturbance, certain issues, e.g. driving a car or being in a crowded place, may become associated with having a panic attack. These panic attacks are not triggered by situations in which the person is the focus of others' attention (as in social phobia).

Diagnostic criteria for Panic Disorder:

A. At least three panic attacks within a three-week period in circumstances other than during marked exertion or in a life-threatening situation. The attacks are not precipitated by exposure to a circumscribed phobic stimulus.

B. Panic attacks are manifested by discrete periods of apprehension or fear, and at least four of the following symptoms appear during each attack:

dyspnoea; palpitations; chest pain or discomfort; choking or smothering sensations; dizziness, vertigo, or unsteady feelings; feelings of unreality; paraesthesias (tingling in hands or feet); hot and cold flushes; sweating; faintness; trembling or shaking; smothering sensations, dizziness.

NOVAPRAZ XR is indicated for use of up to six months duration for anxiety and depression and for up to eight months in the treatment of panic disorder with or without some phobic avoidance. The effectiveness for long-term use, exceeding six months has not been established.

4.2 Posology and method of administration

Patients should be periodically re-assessed, and dosage adjustments made, as appropriate.

Posology

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

The optimum dose of NOVAPRAZ XR tablets should be individualised based upon the severity of the symptoms and individual patient response**.** In patients who require higher doses, dosage should be increased cautiously to avoid adverse effects.

When higher dosage is required, the evening dose should be increased before the daytime dose. In general, patients who have not previously received psychotropic medications will require somewhat lower doses than those previously treated with minor tranquillisers, antidepressants or hypnotics or those with a history of chronic alcoholism. It is recommended that the general principle of using the lowest effective dose be followed in elderly or debilitated patients to preclude the development of ataxia or over sedation.

NOVAPRAZ XR indicated for anxiety

Treatment should be as short as possible. The patient should be assessed regularly and the need for continued treatment should be re-evaluated especially when the patient is symptom-free. The overall duration of treatment, generally, should not be more than 8 to 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.

Table 1: NOVAPRAZ XR tablets starting dose and dose range

NOVAPRAZ XR tablets	**Usual starting dose***	**Usual dose range**
Anxiety	1 mg daily, in one or two doses	0,5 to 4,0 mg daily, in one or two doses
Mixed anxiety/depression Anxiety associated with depression	1 mg daily, in one or two doses	0,5 to 4,5 mg daily, in one or two doses

Panic Disorders	0,5 - 1,0 mg given at bedtime or 0,5 mg two times daily	In clinical trials the mean maintenance dose was between 5 and 6 mg per day given as a single daily dose or divided into two doses daily, with occasional patients needing up to 10 mg per day. The dose should be adjusted to patient response, with dose increments of no greater than 1 mg in the daily dose every three to four days.
Geriatric Patients	0,5 to 1,0 mg daily, given in one or two doses	0,5 to 1 mg daily; may be gradually increased if needed and tolerated.

* If side effects occur, the dose should be lowered. See section 4.4.

To discontinue treatment in patients taking NOVAPRAZ XR tablets, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of NOVAPRAZ XR be decreased by no more than 0,5 mg every three days. Some patients may require an even slower dosage reduction (see section 4.4).

Method of administration

Oral use.

NOVAPRAZ XR tablets may be administered once daily, preferably in the morning.

NOVAPRAZ XR tablets should be taken intact; they should not be chewed, crushed or broken.

4.3 Contraindications

NOVAPRAZ XR tablets are contraindicated in patients with known hypersensitivity to benzodiazepines, alprazolam, or to any component of these formulations.

NOVAPRAZ XR tablets are not recommended for patients whose primary diagnosis is schizophrenia.

Concomitant administration with antiretroviral protease inhibitors or with ketoconazole, as the elimination of NOVAPRAZ XR tablets are delayed several fold.

NOVAPRAZ XR tablets are also contraindicated in patients with

- myasthenia gravis,
- severe respiratory insufficiency,
- sleep apnoea syndrome and
- severe hepatic insufficiency.

4.4 Special warnings and precautions for use

Renal, hepatic and pulmonary impairment

NOVAPRAZ XR must be used with caution in patients with impaired renal function, hepatic insufficiency, pulmonary disease or limited pulmonary reserve.

NOVAPRAZ XR produces additive CNS depressant effects when co-administered with alcohol, barbiturates or other medicines producing CNS depression.

NOVAPRAZ XR is not recommended for the primary treatment of psychotic illness. NOVAPRAZ XR should not be used alone to treat depression, or anxiety with depression, as suicide may be precipitated in such patients. NOVAPRAZ XR should be used with extreme caution in patients with a history of alcohol or drug abuse.

Paediatric population

The safety and efficacy of NOVAPRAZ XR has not been established in children and adolescents under the age of 18 years.

Elderly patients

NOVAPRAZ XR tablets should be used with caution in elderly, due to the risk of sedation and/or musculoskeletal weakness that can promote falls, often with serious consequences in this population.
It is recommended that a general principle of using the lowest effective dose to be followed in the elderly and/or debilitated patients to preclude development of ataxia, over sedation or respiratory depression (see section 4.2).

Risk from concomitant use of opioids

Concomitant use of NOVAPRAZ XR 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 medicines such as NOVAPRAZ XR with opioids should be reserved for patients for whom alternative treatment options are not possible.

If a decision is made to prescribe NOVAPRAZ XR concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see 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 environment to be aware of these symptoms (see section 4.5)

Dependence

Habituation and emotional/physical dependence may occur with NOVAPRAZ XR. The risk of dependence increases with higher doses and long-term use and is further increased in patients with a history of alcoholism or drug abuse. Caution should be used when prescribing NOVAPRAZ XR to patients who are prone to abuse drugs (e.g. alcoholics and drug addicts) because of their predisposition to habituation and dependence (see section 4.8). Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability.

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

Pharmacodependency may occur at therapeutic doses and/or in patients with no individualised risk factor. There is an increased risk of pharmacodependency with the combined use of several benzodiazepines regardless of the anxiolytic or hypnotic indication. Cases of abuse have also been reported.

Withdrawal symptoms have occurred following rapid decrease or abrupt discontinuance of NOVAPRAZ XR. These can range from mild dysphoria and insomnia to a major syndrome which may include abdominal and muscle cramps, vomiting, sweating, tremor, and convulsions. In addition, withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy with NOVAPRAZ XR and special care must be taken in the treatment of epileptic patients. See section 4.2 for dose reduction during withdrawal period.

Rebound effects

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

Depression/anxiety

NOVAPRAZ XR usage has not been established in certain types of depression. See section 4.2.

Panic disorders have been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients. Therefore, the same precaution must be exercised when using the higher doses of NOVAPRAZ XR in treating patients with panic disorders as is exercised with the use of any psychotropic medicines in treating depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans.

In patients presenting with major depression or anxiety associated with depression NOVAPRAZ XR tablets should not be prescribed alone to treat depression as they may precipitate or increase the risk of suicide. Therefore, NOVAPRAZ XR should be used with caution and the prescription size should be limited in patients with signs and symptoms of a depressive disorder or suicidal tendencies.

NOVAPRAZ XR should be avoided in psychotic patients and patients suffering (see schizophrenia in section 4.1) from mental depression unless there is a marked component of anxiety in their illness.

Episodes of hypomania and mania have been reported in association with the use of NOVAPRAZ XR in patients with depression.

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 the tapering-off process.

Extension beyond these periods should not take place without re-evaluation of the patient. 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 is aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while the product is being discontinued.

Amnesia

Benzodiazepines as contained in NOVAPRAZ XR may induce anterograde amnesia. The condition occurs most often several hours after ingesting NOVAPRAZ XR and therefore to reduce the risk patients should ensure that they will be able to have uninterrupted sleep of 7-8 hours (see section 4.8).

Psychiatric and paradoxical reactions

Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other behavioural effects are known to occur when using benzodiazepines (e.g. NOVAPRAZ XR). Should this occur, use of NOVAPRAZ XR should be discontinued. They are more likely to occur in children and the elderly.

NOVAPRAZ XR tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Opioids

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

Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant medicines, narcotic analgesics, anti-epileptic medicines, anaesthetics and sedative antihistamines. In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychic dependence.

Pharmacokinetic interactions can occur when alprazolam is administered along with medicines that interfere with its metabolism.

CYP3A inhibitors

The steady state plasma concentrations of imipramine and desipramine have been reported to be increased an average of 31 and 20 %, respectively, by the concomitant administration of NOVAPRAZ XR tablets in doses up to 4 mg/day. The clinical significance of these changes is unknown (see section 5.2).

Pharmacokinetic interactions can occur when NOVAPRAZ XR is administered along with medicines that interfere with its metabolism. Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450IIIA4) may increase the concentration of NOVAPRAZ XR and enhance its activity. Data from clinical and *in vitro* studies with NOVAPRAZ XR, and clinical studies with medicines metabolised similarly to NOVAPRAZ XR provide evidence for varying degrees of interaction and possible interaction with NOVAPRAZ XR for a number of medicines. Based on the degree of interaction and the type of data available, the following recommendations are made:

- The co-administration of NOVAPRAZ XR with ketoconazole, itraconazole, or other azole-type antifungals is not recommended (see section 4.3).
- Caution and consideration of dose reduction is recommended when NOVAPRAZ XR is co-administered with nefazodone, fluvoxamine, and cimetidine.
- Caution is recommended when NOVAPRAZ XR is co-administered with fluoxetine, oral contraceptives, sertraline, diltiazem, or macrolide antibiotics such as erythromycin and troleandomycin.

CYPsA4 Inducers

Since alprazolam is metabolised by CYP3A4, inducers of this enzyme may enhance the metabolism of alprazolam. Interactions involving HIV protease inhibitors (e.g. ritonavir) and alprazolam are complex and time dependent. Short term, low doses of ritonavir resulted in a large impairment of alprazolam clearance, prolonged

its elimination half-life and enhanced clinical effects. Co-administration of NOVAPRAZ XR with HIV protease inhibitors is not recommended (see section 4.3).

Digoxin

Increased digoxin concentrations have been reported when NOVAPRAZ XR was given, especially in elderly (> 65 years of age). Patients who receive NOVAPRAZ XR and digoxin should therefore be monitored for signs and symptoms related to digoxin toxicity.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

If a patient becomes pregnant while taking NOVAPRAZ XR, the patient should be apprised of the potential hazard to the foetus.

Pregnancy

The safety of NOVAPRAZ XR during pregnancy and lactation has not been established. The potential for congenital malformations in children of patients who have received NOVAPRAZ XR during pregnancy exists. NOVAPRAZ XR should not be administered during labour. Given during labour, it crosses the placenta and may cause the floppy-infant syndrome characterised by central respiratory depression, hypothermia and poor sucking.

Breastfeeding

NOVAPRAZ XR should not be administered to mothers breastfeeding their infants, since NOVAPRAZ XR is excreted in human breast milk.

Fertility

In animal studies fertility was found to be negatively influenced in male rats (see section 5.3 *Fertility)*.

4.7 Effects on ability to drive and use machines

NOVAPRAZ XR has moderate to major influence on the ability to drive and use machines. NOVAPRAZ XR may cause sedation, somnolence, confusional state, impaired balance, abnormal coordination, dizziness, blurred vision, memory impairment, lethargy.

Patients should not drive, use machinery, or perform any tasks that require mental alertness, judgment and/or sound coordination and vision until they are certain that NOVAPRAZ XR does not adversely affect their ability to do so safely.

4.8 Undesirable effects

Summary of the safety profile

The most frequent undesirable effects associated with NOVAPRAZ XR therapy are over-sedation and somnolence. Drowsiness is more common in elderly and debilitated patients, and in those receiving high doses. Less frequently are decreased appetite, confusional state, depression of mood and affect, irritability, decreased libido, ataxia, impaired balance, abnormal coordination, dizziness, headache, memory impairment, dysarthria, hypersomnia, lethargy, blurred vision, constipation, nausea, dry mouth and fatigue.

Paradoxical reactions such as acute hyper-excitability with rage may occur. If these occur, the medicine should be discontinued.

Table 2: Tabulated summary of undesirable effects

MedDRA System Organ Class	**Frequency**	**Undesirable effects**
Metabolism and nutrition disorders	Frequent	Decreased appetite
Psychiatric disorders	Frequent	Confusional state, depression*, irritability, libido decreased
	Less frequent	Aggression, insomnia, loss of libido, mood disorder, nervousness, hallucinations, agitation, rage

Nervous system disorders	Frequent	Sedation, somnolence, ataxia, balance impaired, coordination abnormal, dizziness, headache, memory impairment, dysarthria, hypersomnia, lethargy
	Less frequent	Amnesia*, increased activity, tremor, intellectual impairment, slurred speech
Eye disorders	Frequent	Vision blurred
	Less frequent	Increased intraocular pressure
Gastrointestinal disorders	Frequent	Constipation, nausea, dry mouth
	Less frequent	Diarrhoea, vomiting
Hepato-biliary disorders	Less frequent	Abnormal liver function
Skin and subcutaneous tissue disorders	Less frequent	Dermatitis
Musculoskeletal and connective tissue disorders	Less frequent	Muscle twitching, muscle weakness
Renal and urinary disorders	Less frequent	Enuresis, urinary frequency, urinary retention
Reproductive system and breast disorders	Less frequent	Menstrual irregularities, sexual dysfunction
General disorder and administrative site conditions	Frequent	Fatigue
Investigations	Less frequent	Jaundice, weight decreased, weight increased

*See section “Description of selected adverse reactions”

Table 3: Post-marketing surveillance:

The following post-marketing events have been reported

MedDRA System Organ Class	**Frequency**	**Undesirable effects**
Endocrine disorders	Less frequent	Hyperprolactinaemia

Psychiatric disorders*	Less frequent	Hypomania, mania (see section 4.4), hallucination, anger, aggression, hostility, agitation, abnormal thinking, psychomotor hyperactivity
Nervous system disorders	Less frequent	Dystonia, Autonomic nervous system imbalance
Gastrointestinal disorders	Less frequent	Gastrointestinal disorder
Hepato-biliary disorders	Less frequent	Hepatitis, abnormal hepatic function, jaundice
Skin and subcutaneous tissue disorders	Less frequent	Dermatitis Angioedema
Renal and urinary disorders	Less frequent	Incontinence, urinary retention
Reproductive system and breast disorders	Less frequent	Sexual dysfunction, irregular menstruation, libido disorder
General disorders and administrative site conditions	Less frequent	Peripheral oedema
Investigations	Less frequent	Increased intraocular pressure

*See section "Description of selected adverse reactions"

Description of selected adverse reactions

Amnesia

Anterograde amnesia may occur at therapeutic dosages, the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour.

Depression

Pre-existing depression may be unmasked during benzodiazepine use.

Psychiatric and paradoxical reactions

Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines or benzodiazepine-like medicines. They may be quite severe with NOVAPRAZ XR.

In many of the spontaneous case reports of adverse behavioural effects, patients were receiving other CNS medicines concomitantly and/or were described as having underlying psychiatric conditions. Patients who have

borderline personality disorder, a prior history of violent or aggressive behaviour, or alcohol or substance abuse may be at risk of such events. Instances of irritability, hostility and intrusive thoughts have been reported during discontinuance of alprazolam in patients with post-traumatic stress disorder.

Dependence

Use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (see section 4.4). Psychic dependence may occur. Abuse of benzodiazepines has been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of NOVAPRAZ XR is important. It allows continued monitoring of the benefit/risk balance of NOVAPRAZ XR. 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

Symptoms of overdose with NOVAPRAZ XR are extensions of its pharmacological action and include drowsiness, slurred speech, motor in-coordination, somnolence, confusion, hypotension, coma, respiratory and cardiovascular depression. Serious sequelae are rare unless other medicines and/or ethanol are concomitantly ingested. Treatment of overdosage is primarily supportive of respiratory and cardiovascular function. The value of dialysis has not been determined. Flumazenil may be used as an adjunct to the management of respiratory and cardiovascular function associated with overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.6 Tranquilisers

Pharmacotherapeutic group: Benzodiazepine derivatives, ATC code: N05BA12

Alprazolam is an anxiolytic medicine of the benzodiazepine group. Benzodiazepines, including alprazolam, are thought to bind to central nervous system benzodiazepine receptors, thereby increasing the affinity of the

receptor for gamma-aminobutyric acid (GABA). GABA, an inhibitory neurotransmitter, modulates the activity of other neurotransmitter systems, including the noradrenergic system.

5.2 Pharmacokinetic properties

Absorption

Alprazolam is almost completely bioavailable following oral administration. Peak concentrations occur within 5 to 11 hours after a single dose of NOVAPRAZ XR tablets.

Steady-state plasma concentration is achieved within three to four days of continuous dosing.

Food has a significant influence on the bioavailability of alprazolam extended release tablets. A high-fat meal given up to 2 hours before dosing with alprazolam extended release tablets increased the mean C_{max} by about 25 %. The effect of this meal on T_{max} depended on the timing of the meal, with a reduction in T_{max} by about ⅓ for subjects eating immediately before dosing and an increase in T_{max} by about ⅓ for subjects eating 1 hour or more after dosing. The extent of exposure (AUC) and elimination half-life (t½) were not affected by eating.

There were significant differences in absorption rate for the alprazolam extended release tablets, depending on the time of day administered, with the C_{max} increased by 30 % and the T_{max} decreased by an hour following dosing at night, compared to morning dosing.

Distribution

In vitro, alprazolam is bound (80 %) to human serum protein.

Biotransformation

Alprazolam and its metabolites are excreted primarily in the urine. The predominant metabolites are alphahydroxy-alprazolam, 4-hydroxy alprazolam, and a benzophenone derived from alprazolam. Although they possess some pharmacological activity, the plasma levels of these metabolites are extremely low during chronic dosing.

Elimination

The plasma elimination half-life of alprazolam has been found to be about 11 to 15 hours in healthy adults.

Alprazolam clearance has been reported to be delayed in patients with impaired hepatic and renal function, alcoholism, in elderly or obese patients, and by the coadministration of certain medicines.

Multiple dose studies indicate that the metabolism and elimination of alprazolam are similar for the immediate-release and the extended-release products.

Linearity/non-linearity

The pharmacokinetics of alprazolam are linear over the recommended dosage range, with plasma concentrations being proportional to dose given.

Special populations

While pharmacokinetic studies have not been performed in special populations with alprazolam extended release tablets, the factors (such as age, gender, hepatic or renal impairment) that would affect the pharmacokinetics of alprazolam immediate release tablets would not be expected to be different with the administration of alprazolam extended release tablets.

Changes in the absorption, distribution, metabolism, and excretion of benzodiazepines have been reported in a variety of disease states including alcoholism, impaired hepatic function, and impaired renal function. Changes have also been demonstrated in geriatric patients. A mean half-life of alprazolam of 16,3 hours has been observed in healthy elderly subjects (range: 9,0–26,9 hours, n = 16) compared to 11,0 hours (range: 6,3–15,8 hours, n = 16) in healthy adult subjects. In patients with alcoholic liver disease the half-life of alprazolam ranged between 5,8 and 65,3 hours (mean: 19,7 hours, n = 17) as compared to between 6,3 and 26,9 hours (mean = 11,4 hours, n = 17) in healthy subjects. In an obese group of subjects, the half-life of alprazolam ranged between 9,9 and 40,4 hours (mean = 21,8 hours, n = 12) as compared to between 6,3 and 15,8 hours (mean = 10,6 hours, n = 12) in healthy subjects.

Because of its similarity to other benzodiazepines, it is assumed that alprazolam undergoes transplacental passage and that it is excreted in human milk.

Race — Maximal concentrations and half-life of alprazolam are approximately 15 % and 25 % higher in Asians compared to Caucasians.

Cigarette smoking — Alprazolam concentrations may be reduced by up to 50 % in smokers compared to non-smokers.

5.3 Preclinical safety data

Ocular effects

When rats were treated orally with alprazolam for 2 years, a tendency for a dose related increase in the number of cataracts (females) and corneal vascularization (males) was observed. These lesions did not appear until after 11 months of treatment.

Reproductive toxicity and fertility

In reproductive toxicity studies administration of alprazolam in rats and rabbits is associated at very high doses with developmental delay and an increased incidence of foetal death and skeletal malformations. In fertility studies, treatment of male rats at high doses prior to mating resulted in a decrease in the number of dams conceiving.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide

Hypromellose (Methocel K 4M-CR Premium)

Hypromellose (Methocel K 100 LV-CV Premium)

Lactose monohydrate

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

NOVAPRAZ XR 0,5, NOVAPRAZ XR 1 and NOVAPRAZ XR 2 are packed in white opaque round HDPE containers closed with white opaque polypropylene child resistant closures with wad having induction sealing liner. The HDPE containers also contain 2 g silica gel sachets and a cotton coil. The HDPE container is further packed in a pre-printed outer carton.

Pack size: 60 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novagen Pharma (Pty) Ltd.

Office 2, 100 Sovereign Drive, Route 21 Corporate Park

Nellmapius Drive, Irene, Pretoria

8. REGISTRATION NUMBER

51/2.6/0435/6/7

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08 December 2020

10. DATE OF REVISION OF THE TEXT

05 March 2021