G.P.-S.004-0466 GW.12/1(MBR1)

ANNEXURE 1

AMENDED 28 JANUARY 1999

NAME OF APPLICANT:	CIPLA-MEDPRO (PTY) LTD
NAME OF MEDICINE:	ZOPAX 0,5
DOSAGE FORM:	TABLETS

A. The undermentioned information with regard to this medicine shall appear on the package insert. The information shall be presented in the format stipulated: Provided that the Council may authorise any deviation from such information or such format.

1. Scheduling status.
2. Proprietary name (and dosage form).
3. Composition.
4. Pharmacological classification.
5. Pharmacological action.
6. Indications.
7. Contra-indications.
8. Warnings.
9. Dosage and directions for use.
10. Side-effects and special precautions.
11. Known symptoms of overdosage and particulars of its treatment.
12. Conditions of registration.
13. Identification.
14. Presentation.
15. Storage instructions.
16. Registration number (or reference number).
17. Applicant.
18. Date of publication.

B. The following is a facsimile or specimen of the label:

The attached documents refer:

Package Insert
Immediate and Outer Container Labels

PACKAGE INSERT

1999 -01- 28

SCHEDULING STATUS: S5

PROPRIETARY NAME (AND DOSAGE FORM):

ZOPAX 0,5 Tablets

COMPOSITION:

Each tablet contains 0,5 mg alprazolam.

Preservatives:	Methylparaben	0,09% m/m
	Propylparaben	0,009% m/m

PHARMACOLOGICAL CLASSIFICATION:

A 2.6 Tranquillisers

PHARMACOLOGICAL ACTION:

Alprazolam is an anxiolytic agent of the benzodiazepine group. It is believed that benzodiazepines enhance or facilitate the inhibitory neurotransmitter action of gamma-aminobutyric acid (GABA), which is one of the major inhibitory neurotransmitters in the brain and mediates both pre- and post-synaptic inhibition in all regions of the central nervous system, following interaction between the benzodiazepine and a specific neuronal membrane receptor.

Following oral administration, alprazolam is readily absorbed from the gastrointestinal tract, usually within 1 to 2 hours. The half-life in plasma is 12 to 15 hours. Alprazolam is 70 to 80% bound to plasma protein. Steady-state plasma concentrations are usually attained within a few days. Alprazolam undergoes oxidative metabolism to metabolites and is eliminated as glucuronide conjugates primarily in the urine.

INDICATIONS:

ZOPAX is indicated for the management of anxiety disorders and the short-term relief of symptoms of anxiety. Anxiety associated with depression is also responsive to **ZOPAX.**

ZOPAX is also indicated for the treatment of panic disorders for up to eight months. The doctor should periodically re-assess the usefulness of **ZOPAX** for the individual patient.

ZOPAX is only indicated when the anxiety is severe, disabling or subjecting the individual to extreme stress.

CONTRA-INDICATIONS:

The safety of **ZOPAX** (alprazolam) in pregnancy has not been established. **ZOPAX should not be administered during pregnancy. Do not administer 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.**

ZOPAX (alprazolam) should not be administered to nursing mothers, since alprazolam is excreted in human breast milk.

ZOPAX (alprazolam) is contra-indicated in patients with known hypersensitivity to the benzodiazepines and in acute narrow angle glaucoma.

ZOPAX (alprazolam) is not recommended for use in patients whose primary diagnosis is schizophrenia, psychotic patients and patients suffering from mental depression or suicidal tendencies, unless there is a marked component of anxiety in their illness.
ZOPAX (alprazolam) is contra-indicated in patients with pre-existing central nervous system depression or coma, acute pulmonary insufficiency, sleep apnoea, myasthenia gravis, porphyria and in children.

WARNINGS:

There is potential for abuse and dependence. Withdrawal symptoms may occur after periods of ordinary therapeutic doses. Individuals who are prone to abuse medicines such as alcoholics and drug addicts or patients on other central nervous system depressants, should be under careful surveillance while receiving a benzodiazepine because of the predisposition of such patients to habituation and dependence.

Patients receiving **ZOPAX** (alprazolam) should be advised not to drive or operate machinery, or climb dangerous heights until it is established that they do not become drowsy or dizzy while receiving **ZOPAX.** In these situations, impaired decision making could lead to accidents.

DOSAGE AND DIRECTIONS FOR USE:

Treatment should be as short as possible. The patient should be reassessed regularly and the need for continued treatment should be 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 with special expertise.

A maximum dosage of 4 mg should not be exceeded, except in the treatment of panic disorders. The optimum dosage of **ZOPAX** (alprazolam), should be individualized 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 a higher dosage is required, the evening dose should be increased before the day-time doses. In general, patients who have not previously received psychotropic medications, will require 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. Patients should be periodically re-assessed and dosage adjustments made as appropriate.

Discontinuation therapy:
The dosage should be reduced slowly to reduce withdrawal symptoms. It is suggested that the daily dosage of **ZOPAX** be decreased by no more than 0,5 mg every three days. Some patients may require an even slower dosage reduction.

	Usual starting dosage*	Usual dosage range
Anxiety	0,25 to 0,5 mg given three times daily	0,5 to 4,0 mg daily given in divided doses
Depression associated with anxiety	0,5 mg given three times daily	1,5 mg to 4,0 mg daily given in divided doses
*Geriatric patients or in the presence of debilitating disease	0,25 mg given two or three times daily	0,5 to 0,75 mg daily given in divided doses to be gradually increased if needed and tolerated
Panic-related disorders	0,5 to 1,0 mg given at bedtime	The dose should be adjusted to patient response. Dosage adjustments should be in increments no greater than 1 mg every 3 to 4 days. Additional doses can be added until a three times daily of four times daily schedule is achieved

* If side-effects occur, the dose should be lowered.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Drowsiness, sedation and ataxia are the most frequent side-effect of alprazolam use. These effects generally decrease on continued administration and are a consequence of central nervous system depression.

Less frequent side-effects include vertigo, headache, confusion, mental depression, slurred speech or dysathria, changes in libido, tremor, visual disturbances, urinary retention or incontinence, gastro-intestinal disturbances, changes in salivation, amnesia and paradoxical excitation and dis-inhibition. Jaundice, blood disorders and hypersensitivity reactions have been reported less frequently.

Respiratory depression and hypotension occur with high dosage.

Precautions

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

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. 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, hyperacousia, 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 alprazolam 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.

Duration of treatment: The duration of treatment should be as short as possible (see Dosage), but should not exceed 8 - 12 weeks, including 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.

Caution is required in elderly patients or debilitated patients who may be more prone to adverse effects. Caution is required in patients with impaired liver or kidney function.
Sedation or respiratory and cardiovascular depression may be enhanced by other medicines with central nervous system depressant properties; these include alcohol, antidepressants, antihistamines, general anaesthetics, other hypnotics or sedatives, neuroleptics and opioid analgesics.

Interactions
ZOPAX (alprazolam) produces additive central nervous system depressant effects when co-administered with medicines such as barbiturates, alcohol or other central nervous system depressants. Patients should be cautioned regarding the additive effect of alcohol.

The steady state plasma concentrations of imipramine and desipramine have been reported to be increased on average of 31% and 20% respectively by the concomitant administration of **ZOPAX** (alprazolam). Pharmacokinetic interactions of **ZOPAX** with other have been reported. The clearance of **ZOPAX** can be delayed by the co-administration of cimetidine or macrolide antibiotics.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

See "Side-effects and Special Precautions".
Overdosage can produce central nervous system depression and coma.
Treatment is symptomatic and supportive.
The antidote flumazenil may be administered.

IDENTIFICATION:

Pink, round, flat, bevelled tablets, smooth on one side with central breakline on the other side.

PRESENTATION:

Blister strips of 10 tablets packaged in 5 x 10's.

STORAGE INSTRUCTIONS:

Store below 30°C and protect from light.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

30/2.6/0357

1999 -01- 28

NAME AND BUSINESS ADDRESS OF APPLICANT:

Cipla-Medpro (Pty) Ltd
Rosen Heights
Pasita Street
Rosenpark
BELLVILLE
7530

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

1999 -01- 28

VOUBILJET

SKEDULERINGSTATUS: S5

EIENDOMSNAAM (EN DOSEERVORM):

ZOPAX 0,5 Tablette

SAMESTELLING:

Elke tablet bevat 0,5 mg Alprasolam

Preserveermiddel:	Metielparaben	0,09% m/m
	Propielparaben	0,009% m/m

FARMAKOLOGIESE KLASSIFIKASIE:

A 2.6 Bedaarmiddels (Berustingsmiddels)

FARMAKOLOGIESE WERKING:

Alprasolam is 'n anksiolitiese middel van die bensodiasepiengroep. Dit word aanvaar dat bensodiasepiene die inhiberende neurotransmitter werking van gamma-aminobottersuur (GABS), wat een van die hoof inhiberende neurotransmitters in die brein is, en beide pre- en post sinaptiese inhibering in alle areas van die sentrale senuweestelsel bemiddel na die interaksie tussen die bensodiasepiene en 'n spesifieke neuronale membraanreseptor, versterk of aanhelp.

Alprasolam word geredelik na orale toediening van die gastro-intestinale stelsel geabsorbeer; gewoonlik tussen 1 tot 2 ure. Die halfleeftyd in plasma is 12 - 15 ure. Alprasolam is 70 - 80% gebind aan plasma proteïene. Vaste toestand plasmakonsentrasie word gewoonlik binne 'n paar dae verkry. Alprasolam ondergaan oksidatiewe metabolisme na metaboliete en word as glikuroniede konjugate in die uriene geëlimineer.

INDIKASIES:

ZOPAX word aangedui vir die behandeling van angsversteurings en die korttermyn verligting van simptome van angs. Angs geassosieer met depressie reageer ook op **ZOPAX.**

ZOPAX is ook aangedui vir die behandeling van paniekversteurings vir tot agt maande lank. Die geneesheer moet die bruikbaarheid van **ZOPAX** by individuele pasiënte gereeld herevalueer.

ZOPAX word slegs aangedui wanneer die angs ernstig is, die individu belemmer of aan uiterste stres blootstel.

KONTRA-INDIKASIES:

Die veiligheid van **ZOPAX** tydends swangerskap is nog nie vasgestel nie. **ZOPAX moet nie tydens swangerskap toegedien word nie. Moet nie tydens kraam toegedien word nie. Wanneer tydens kraam toegedien, kruis dit die plasenta en kan die slapbabasindroom wat gekenmerk word deur sentrale respiratoriese depressie, hipotermie en swak suiging veroorsaak.**

ZOPAX (alprasolam) moet nie by borsvoedende moeders gebruik word nie, aangesien alprasolam in menslike borsmelk uitgeskei word.

ZOPAX (alprasolam) word teenaangedui by pasiënte met bekende hipersensitiwiteit vir die bensodiasepiene en by akute smalhoek gloukoom.

Die gebruik van **ZOPAX** (alprasolam) word nie by pasiënte met 'n primêre diagnose van skisofrene, psigotiese pasiënte en pasiënte wat aan geestesdepressie ly of selfmoordneigings het, tensy daar 'n merkbare komponent van angs in hulle toestand is, aanbeveel nie.

ZOPAX (alprasolam) word teenaangedui by pasiënte met vooraf bestaande sentrale senuweestelsel onderdrukking of koma, akute pulmonêre ontoerekenheid, slaapapnee, myasthenia gravis, porfirie en by kinders.

WAARSKUWINGS:

Daar bestaan 'n moontlikheid van misbruik en afhanklikheid. Onttrekkingsimptome kan voorkom na periodes van normale terapeutiese dosisse. Individue wat geneig is tot die misbruik van medisyne soos alkoholiste, dwelmverslaafdes of pasiënte op ander sentrale senuweestelselonderdrukkers, moet sorgvuldig dopgehou word wanneer hulle bensodiasepiene gebruik, omdat daar by sulke pasiënte 'n neiging tot gewoontevorming en afhanklikheid bestaan.

Pasiënte wat **ZOPAX** (alprasolam) gebruik moet aangesê word om nie motorvoertuie te bestuur, masjinerie te hanteer, of op gevaarlike hoogtes te klim nie, totdat daar vasgestel is dat hulle nie lomerig of duiselig word terwyl hulle **ZOPAX** neem nie. Sulke situasies kan besluitneming belemmer en ongelukke veroorsaak.

DOSIS EN GEBRUIKSAANWYSINGS:

Behandeling moet so kort as moontlik wees. Die pasiënt moet gereeld geherevalueer word en die nodigheid vir volgehoue behandeling moet ge-evalueer word, veral waar die pasiënt simptoomvry is. Die totale duur van behandeling moet gewoonlik nie meer as 8 - 12 weke wees nie, insluitende die afskaling van die dosering.

In sekere gevalle kan verlenging van die maksimum behandelingsperiode nodig wees; indien dit die geval is, moet dit nie plaasvind sonder herevaluering van die pasiëntstatus met spesiale kundigheid nie.

'n Maksimum dosis van 4 mg moet nie oorskry word nie, behalwe by die behandeling van paniekversteurings. Die optimale dosis **ZOPAX** (alprazolam) moet geïndividualiseer word, gebaseer op die erns van die simptome en individuele pasiëntreaksie. By pasiënte wat hoër dosisse benodig, moet die dosering versigtig verhoog word om ongunstige reaksies te vermy.

Wanneer hoër dosisse benodig word, moet die aanddosering voor die dagdosering verhoog word. Oor die algemeen sal pasiënte wat nie voorheen psigotrope medikasie ontvang het nie, ietwat laer dosisse benodig as wat voorheen met susmiddels, antidepressante of hipnotika behandel is, of diegene met 'n geskiedenis van chroniese alkoholisme.

Dit word aanbeveel dat die algemene beginsel om die laagste effektiewe dosis te gebruik, gevolg moet word. Pasiënte moet periodiek geherevalueer word om sodoende die nodige dosisaanpassing te doen.

Onttrekkingsterapie:
Die dosis moet stadig verminder word om onttrekkingssimptome te verminder. Dit word aanbeveel dat die daaglikse dosering van **ZOPAX** met nie meer as 0,5 mg elke 3 dae verminder word nie. Sommige pasiënte kan nog selfs 'n meer geleidelike vermindering in dosering benodig.

	*Gebruiklike Aanvangsdosis	Gewone Dosisreeks
Angs	0,25 - 0,5 mg drie keer per dag	0,5 - 4,0 mg daagliks in verdeelde dosisse
Depressie geassosieer met angs	0,5 mg drie keer per dag	1,5 - 4,0 mg daagliks, in verdeelde dosisse
Geriatriese pasiënte of in die teenwoordigheid van 'n verswakkende siekte	0,25 mg twee tot drie keer per dag	0,5 - 0,75 mg daagliks in verdeelde dosisse om geleidelik verhoog te word indien nodig en verdra kan word.
Paniekverwante versteurings	0,5 - 1,0 mg net voor slapenstyd	Die dosis moet na gelang van pasiëntreaksie aangepas word. Dosis aanpassings moet geleidelik plaasvind - nie meer as 1 mg elke 3 - 4 dae nie. Addisionele dosisse kan bygevoeg word totdat 'n drie keer per dag of vier keer per dag skedule bereik is.

* Indien newe effekte voorkom, moet die dosis verminder word.

NEWE-EFFEKTE EN SPESIALE VOORSORGMAATREëLS:

Lomerigheid, sedasie en ataksie is die mees algemene newe-effekte met alprasolam gebruik. Hierdie effekte verminder gewoonlik met volgehoue toediening en is 'n gevolg van sentrale senustelsel onderdrukking.

Minder algemene newe-effekte sluit duiseligheid, hoofpyn, verwarring, geestesdepressie, sleepspraak of uitspraaksteurnis, verandering in libido, tremor, visuele steurings, urinêre retensie of inkontinensie, gastro-intestinale versteurings, verandering in salivering, amnesie en paradoksale eksitasie en disinhibisie. Geelsug, bloedafwykings en hipersensitiwiteitsreaksies is minder dikwels aangemeld.

Asemhalingsonderdrukking en lae bloeddruk kom met hoë dosisse voor.

Voorsorgmaatreëls:

Alprasolam word nie aanbeveel vir die primêre behandeling van psigotiese toestande nie. Alprasolam moet nie alleen gebruik word in die behandeling van depressie of angs met depressie nie (selfmoord kan by sulke pasiënte voorkom). Alprasolam moet met groot versigtigheid by pasiënte met 'n geskiedenis van alkohol of geneesmiddel misbruik gebruik word.

Afhanklikheid

Daar is 'n moontlikheid vir misbruik en die ontwikkeling van fisiese en psigiese afhanklikheid, veral met verlengde gebruik en hoë dosisse. Die gevaar van afhanklikheid is ook groter in pasiënte met 'n geskiedenis van alkohol of geneesmiddel misbruik. As fisiese afhanklikheid ontwikkel het sal skielike staking van behandeling met onttrekkingssimptome gepaard gaan. Dit kan hoofpyne, spierpyne, uitermatige angs, spanning, rusteloosheid, verwarring en prikkelbaarheid insluit.

In angstige gevalle kan die volgende simptome voorkom: werklikheidsverlies, verontpersoonliking, gehooroorgevoeligheid, gevoelloosheid en tinteling van uiteindes, hipersensitiwiteit vir lig, geraas en fisiese kontak, hallusinasies of epileptiese aanvalle.

Terugslageffek

'n Oorgangssindroom waarby die simptome wat tot die behandeling met alprasolam gelei het, kan in 'n versteekte mate terugkom tydens onttrekking van die behandeling. Dit kan met ander reaksies soos buiveranderings, angs en rusteloosheid gepaard gaan.

Aangesien die risiko van die onttrekkingsverskynsel/terugslageffek verskynsel groter is na skielike staking van behandeling, word dit aanbeveel dat die dosis geleidelik verminder sal word.

Duur van behandeling: Die duur van die behandeling moet so kort as moontlik wees (sien Dosis), maar moet nie langer as 8 - 12 weke wees, insluitende die afskaalproses nie. Verlenging langer as hierdie periodes moet nie plaasvind sonder her-evaluering van die situasie nie. Dit kan nuttig wees om die pasiënt tydens die aanvang van die behandeling in te lig dat die behandeling net 'n beperkte tydperk sal wees en om presies te verduidelik hoe die dosering progressief verminder sal word. Verder is dit belangrik dat die pasiënt bewus sal wees van die moontlikheid van die terugslageffek, daardeur die angstigheid oor sulke simptome sal verminder indien hulle sou voorkom tydens staking van die produk.

Versigtigheid is by ouer en verswakte pasiënte, wat meer vatbaar vir newe-effekte is, nodig. Versigtigheid is ook nodig by pasiënte met belemmerde lewer- of nierfunksies.
Sedasie of respiratoriese en kardiovaskulêre onderdrukking kan deur ander medikasie met sentrale senustelselonderdrukkende eienskappe, versterk word; dit sluit alkohol, antidepressante, antihistamiene, algemene narkosemiddels, ander hipnotika, of sedeermiddels, neuroleptika en opioïede analgetika, in.

Interaksies
ZOPAX (alprasolam) lewer additiewe sentrale senustelselonderdrukkende effekte wanneer dit gelyktydig met middels soos barbiturate, alkohol of ander sentrale senustelselonderdrukkers toegedien word. Pasiënte moet gewaarsku word aangaande die additiewe effek van alkohol.

Dit is gerapporteer dat vastetoestand van die plasmakonsentrasie van imipramien en desipramien onderskeidelik 'n gemiddelde verhoging van 31% en 20% toon met die gelyktydige toediening van **ZOPAX** (alprasolam). Farmakokinetiese interaksie van **ZOPAX** is ook met ander geneesmiddels gerapporteer. Die opruiming van **ZOPAX** kan deur die gelyktydige toediening van simetidien of makroliedantibiotika vertraag word.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN:

Sien "Newe-effekte en Spesiale Voorsorgmaatreëls".
Oordosering kan tot sentrale senustelselonderdrukking en koma lei.
Behandeling is simptomaties en ondersteunend.
Die teenmiddel flumasenil kan toegedien word.

IDENTIFIKASIE:

Ligte blou, ronde, plat, afgeskuinsde, glad aan eenkant met sentrale breeklyn aan die ander kant.

AANBIEDING:

Stulpverpakking van 10 tablette verpak in 5 x 10's.

BERGINGSAANWYSINGS:

Berg benede 30°C en beskerm teen lig.
HOU BUITE BEREIK VAN KINDERS.

REGISTRASIENOMMER:

30/2.6/0357

NAAM EN BESIGHEIDSADRES VAN DIE APPLIKANT:

Cipla-Medpro (Pty) Ltd
Rosen Heights
Rosen Park
BELLVILLE
7530

DATUM VAN PUBLIKASIE VAN HIERDIE VOUBILJET: