APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

PINOMAZ 100 mg CR controlled release film coated tablet

PINOMAZ 200 mg CR controlled release film coated tablets

PINOMAZ 400 mg CR controlled release film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PINOMAZ 100 mg CR: Each controlled release film coated tablet contains carbamazepine 100 mg.

PINOMAZ 200 mg CR: Each controlled release film tablet contains carbamazepine 200 mg.

PINOMAZ 400 mg CR: Each controlled release film tablet contains carbamazepine 400 mg.

PINOMAZ CR is sugar and sodium free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Controlled release film coated tablet.

100 mg: Peach coloured, round shaped, biconvex film coated tablets with ‘CR 100’ debossed on one side and plain on the other side.

200 mg: Peach coloured, round shaped, biconvex film coated tablets with ‘CR 200’ debossed on one side and plain on the other side.

400 mg: Peach coloured, round shaped, biconvex film coated tablets with 'CR 400' debossed on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PINOMAZ CR is indicated in:

- epilepsy with motor and psychic manifestations:
    - psychomotor or temporal-lobe epilepsy
    - generalized tonic-clonic seizure
    - mixed forms of seizures
    - complex or simple partial seizures (with or without loss of consciousness) with or without secondary generalisation
- acute mania and maintenance treatment of bipolar affective disorders to prevent or attenuate recurrence
- idiopathic trigeminal neuralgia
- idiopathic glossopharyngeal neuralgia.

PINOMAZ CR is suitable for both monotherapy and combination therapy.

Note: PINOMAZ CR is not usually effective in absences (petit mal) and myoclonic seizures (see section 4.4).

4.2 Posology and method of administration

Posology

As a result of the slow, controlled release of the active substance from the CR tablets, these are to be taken in a twice daily dosage regimen.

Dosage should be as low as is consistent with a satisfactory effect. Blood plasma levels can be used to help establish the optimum dose. In the treatment of epilepsy, the dose of PINOMAZ CR usually requires total plasma-carbamazepine concentrations of about 4 to 12 µg/mL (17 to 50 µmol/L).

When transferring a patient from another anticonvulsant medicine to PINOMAZ CR, the dosage of the initial anticonvulsant should be reduced gradually.

Clinical experience indicates that, in some patients, when switching from conventional tablets to CR tablets, the dosage of the CR tablets may need to be increased.
Due to interactions and different anti-epileptic medicine pharmacokinetics, the dosage of PINOMAZ CR should be selected with caution in elderly patients.

Epilepsy

PINOMAZ CR should be prescribed as monotherapy where possible.
Treatment should be initiated with a low daily dose, gradually increasing the dosage until an optimal effect is achieved.
Determination of plasma levels may help in establishing the optimum dosage.

When PINOMAZ CR is added to existing anti-epileptic therapy, this should be done gradually while maintaining, or if necessary, adapting the dosage of the other anti-epileptic(s). (See section 4.5).

Dosage in adults

The initial dose of carbamazepine is 100 mg to 200 mg once or twice daily, followed by a slow increase until usually at a level of 400 mg twice or three times a day, the best response is obtained. In some instances, 1600 mg in 3 to 4 divided doses may be necessary.

Dosage in children:

For children aged 4 years or less, a starting dose of 20-60mg/day, increasing by 20-60mg every second day, has been recommended. For children over the age of 4 years, therapy may begin with 100mg/day, increasing at weekly intervals by 100mg.

Maintenance dosage:

10 to 20 mg /kg per day daily in several divided doses.

Age up to 1 year: 200 mg per day

1 to 5 years: 200 – 400 mg per day

6 to 10 years: 400 – 600 mg per day

11 to 15 years: 600 – 1000 mg per day

>15 years of age: 800 - 1200 mg/day (same as daily dose in adults)

Trigeminal neuralgia

The initial dosage of 200 - 400 mg should be increased daily until freedom from pain is achieved (normally at 200 mg 3 - 4 times daily, however, in some instances it may necessitate 1600 mg daily). The dosage should then be gradually reduced to the lowest possible maintenance level.

In elderly and particularly sensitive patients (see section 4.4) an initial dosage of 100 mg twice a day is recommended.

Acute mania and maintenance treatment of (bipolar) affective disorders

Dosage range

Approximately 400 - 1600 mg daily, the usual dosage being 400 - 600 mg daily given in 2 - 3 divided doses. In acute mania, the dosage should be increased rather quickly, whereas small dosage increments are recommended for maintenance therapy of bipolar disorders in order to ensure optimal tolerability.

Method of administration

Oral use.

PINOMAZ CR may be taken with or without food. Tablets are to be swallowed whole with a liquid.

Missed dose:

Doctors should advise patients who forget to take PINOMAZ CR to take a dose as soon as possible, however, if it is close to the time for the next dose, skip the missed dose, and continue with the normal dose regimen. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

PINOMAZ CR is contraindicated in the following patients:

- hypersensitivity to carbamazepine, structurally related medicines, (e.g. tricyclic

antidepressants) or to any of the excipients of PINOMAZ CR

- patients with atrioventricular block
- patients with a history of bone-marrow depression
- patients with a history of porphyria (e.g. acute intermittent porphyria, variegate porphyria)
- in combination with monoamine-oxidase inhibitors (MAOIs) or within 2 weeks of discontinuation of MAOIs (see section 4.5)
- the active substance of PINOMAZ CR passes into the breast milk (about 25 - 60 % of plasma concentration). Mothers taking PINOMAZ CR should not breastfeed their infants
- history of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) (see section 4.4).

4.4 Special warnings and precautions for use

Patients should be made aware of early toxic signs and symptoms of a potential dermatological problem, as well as symptoms of haematological or hepatic reactions. If reactions such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric haemorrhage appear, the patient should be advised to consult the medical practitioner immediately. Medical supervision during treatment is essential.

Haematological effects

Aplastic anaemia and agranulocytosis have been reported and transient or persistent decreased platelet or white blood cell count may occur. In the majority of cases these

effects prove transient. Complete pre-treatment blood counts including platelets and possibly reticulocytes and serum iron should be obtained as baseline and periodically thereafter. If, during the course of therapy, a patient exhibits low or decreased white blood cell or platelet counts both the patient and the complete blood count should be monitored closely.

Patients and their relatives should be made aware of early toxic signs and symptoms indicative of a potential haematological problem, as well as symptoms of dermatological or hepatic reactions. If reactions such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric haemorrhage appear, the patient should be advised to consult the medical practitioner immediately.

If the white blood cell or platelet count is definitely low or decreased during treatment, the patient and the complete blood count should be closely monitored (see Section 4.8). However, treatment with PINOMAZ CR should be discontinued if the patient develops leucopenia which is severe, progressive or accompanied by clinical manifestations, e.g. fever or sore throat. PINOMAZ CR should also be discontinued if any evidence of significant bone marrow depression appears.

Serious dermatological reactions

Serious dermatologic reactions including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have been reported with PINOMAZ CR. Patients with serious dermatological reactions may require hospitalisation, as these conditions may be life-threatening and may be fatal. Most of these cases appear in the first few months of therapy. If signs and symptoms suggestive of severe skin reactions (e.g., SJS or TEN) appear, PINOMAZ CR should be withdrawn at once and alternative therapy should be considered (see section 4.3).

Immune-mediated adverse drug reactions (ADR)

There is growing evidence of the role of different Human Leukocyte Antigen (HLA) alleles in predisposing patients to immune-mediated adverse reactions.

HLA-A*3101 allele

Human Leukocyte Antigen (HLA)-A*3101 may be a risk factor for the development of cutaneous adverse drug reactions such as SJS, TEN, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP) and maculopapular rash.

Retrospective genome-wide studies in Japanese and Northern European populations reported association between severe skin reactions (SJS, TEN, DRESS, AGEP and maculopapular rash) associated with carbamazepine use and the presence of the HLA-A*3101 allele in these patients.
The frequency of the HLA-A*3101 allele varies widely between ethnic populations, with a frequency between 5 - 15 %.
A prevalence of 10 -15 % has been estimated in some ethnic groups.

Testing for the presence of HLA-A*3101 allele should be considered in patients with ancestry in genetically at-risk populations (for example, patients of the Japanese and Caucasian populations, patients who belong to the indigenous populations of the Americas, Hispanic populations, people of southern India, and people of Arabic descent), prior to initiating treatment with PINOMAZ CR.

The use of PINOMAZ CR should be avoided in patients who are found to be positive for HLA-A*3101. Screening is generally not recommended for any current PINOMAZ CR users, as the risk of SJS/TEN, AGEP, DRESS and maculopapular rash is largely confined to the first few months of therapy, regardless of HLA-A*3101 status.

HLA-B *1502 allele - in Han Chinese, Thai and other Asian populations

Retrospective studies in patients of Han Chinese ancestry found a strong correlation between SJS/TEN skin reactions associated with carbamazepine (as in PINOMAZ CR) and the presence in these patients of the HLA-B*1502 allele.

The frequency of HLA-B*1502 allele ranges from:

- 2 to 12 % in Han Chinese populations
- 8 % in Thai populations
- above 15 % in the Philippines and some Malaysian populations
- about 2 % and 6 % have been reported in Korea and India, respectively.

Higher reporting rates of SJS (rare rather than very rare) are reported in some countries in Asia (e.g. Taiwan, Malaysia and the Philippines).

The prevalence of the HLA-B*1502 allele is negligible in Caucasian, African, indigenous people of the Americas, and Hispanic populations sampled and in Japanese (<1 %).

The allele frequencies listed above, represent the percentage of chromosomes in the specified population that carry the allele of interest (i.e. the percentage of patients who carry a copy of the allele on at least one of their two chromosomes - the "carrier frequency") is nearly twice as high as the allele frequency. Therefore, the percentage of patients who may be at risk is nearly twice the allele frequency.

Testing for the presence of HLA-B *1502 allele should be considered in patients with ancestry in genetically at-risk populations, prior to initiating treatment with PINOMAZ CR.

The use of PINOMAZ CR should be avoided in tested patients who are found to be positive for HLA-B*1502. HLA-B*1502 may be a risk factor for the development of SJS/TEN in Chinese patients taking other anti-epileptic medicines associated with SJS/TEN. Consideration should therefore be given to avoiding use of other medicines associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally acceptable. Screening is not generally recommended in patients from populations in which the prevalence of HLA-B*1502 is low.
Screening is generally not recommended for any current PINOMAZ CR users, as the risk of SJS/TEN is largely confined to the first few months of therapy, regardless of HLA-B*1502 status. The identification of subjects carrying the HLA-B*1502 allele and the avoidance of PINOMAZ therapy in these subjects has been shown to decrease the incidence of carbamazepine-induced SJS/TEN.

Genetic screening results must never substitute for appropriate clinical vigilance and patient management. Many Asian patients positive for HLA-B*1502 and treated with PINOMAZ CR will not develop SJS/TEN and patients negative for HLA-B*1502 of any ethnicity, can still develop SJS/TEN. Similarly, many patients positive for HLA-A*3101 and treated with PINOMAZ CR may not develop severe cutaneous side-effects and patients negative for this allele can still develop them.

The role of other possible factors in the development of, and morbidity from, these severe cutaneous side-effects, such as other anti-epileptic medicines dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

Information for the healthcare professionals

When testing for the presence of the HLA-B*1502 allele, high resolution "HLA-B*1502 genotyping" is recommended. The test is positive if either one or two HLA-B*1502 alleles are detected and negative if no HLA-B*1502 alleles are detected.

Similarly, if testing for presence of the HLA-A*3101 allele should be performed, high-resolution "HLA-A*3101 genotyping" respectively is recommended. The test is positive if either one or two HLA-A*3101 alleles are detected and negative if no HLA-A*3101 alleles are detected.

Other dermatologic reactions

Skin reactions, e.g. macular or maculopapular exanthema, can also occur. However, since it may be difficult to differentiate the early signs of more serious skin reactions from less severe skin reactions, the patient should be kept under close surveillance with consideration given to immediately withdrawing PINOMAZ CR.

The HLA-A*3101 allele has been found to be associated with less severe adverse cutaneous reactions from PINOMAZ CR, such as anticonvulsant hypersensitivity syndrome or non-serious rash (maculopapular eruption). However the HLA-B*1502 allele has not been found to predict the risk of these aforementioned skin reactions.

Hypersensitivity

Hypersensitivity reactions including DRESS, a delayed multi-organ hypersensitivity disorder with fever, rash, vasculitis, lymphadenopathy, pseudo-lymphoma, arthralgia, leukopenia, eosinophilia, hepatosplenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), that may occur in various combinations, may be triggered by PINOMAZ CR therapy. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon) (see section 4.8).

The HLA-A*3101 allele has been found to be associated with the occurrence of hypersensitivity syndrome, including maculopapular rash.

Patients who have exhibited hypersensitivity reactions to carbamazepine (as in PINOMAZ CR) may experience hypersensitivity reactions with oxcarbazepine.

Cross-hypersensitivity can occur between carbamazepine and aromatic antiepileptic drugs (e.g. phenytoin, primidone and phenobarbital).

If signs and symptoms of hypersensitivity reactions occur, PINOMAZ CR should be withdrawn immediately.

Seizures

PINOMAZ CR therapy should be undertaken with caution in patients with mixed seizures, which includes absences, either typical or atypical. In all these conditions, PINOMAZ CR may exacerbate seizures. In the event of exacerbation of seizures, PINOMAZ CR should be discontinued.

Hepatic function

Liver function tests should also be performed before commencing treatment and periodically thereafter, particularly in patients with a history of liver disease and in elderly patients.

If allergic skin reactions occur, if the platelet count diminishes, if tests reveal deterioration in liver function, or if any serious adverse symptoms develop, PINOMAZ CR should be discontinued.

Some liver function tests in patients receiving carbamazepine may be found to be abnormal, particularly gamma glutamyl transferase. This is probably due to hepatic enzyme induction. Enzyme induction may also produce modest elevations in alkaline phosphatase. These enhancements of hepatic metabolising capacity are not an indication for the withdrawal of carbamazepine.

Severe hepatic reactions to carbamazepine occur very rarely. The development of signs and symptoms of liver dysfunction or active liver disease should be urgently evaluated and treatment with PINOMAZ CR suspended pending the outcome of the evaluation.

Renal function

Baseline and periodic complete urine analysis and blood urea determinations are recommended.

PINOMAZ CR should be prescribed only after a critical benefit-risk appraisal and under close monitoring in patients with a history of cardiac, hepatic, or renal damage, adverse haematological reactions to other medicines, or interrupted courses of therapy with PINOMAZ CR.

Hyponatraemia

Hyponatraemia is known to occur with carbamazepine (as in PINOMAZ CR). In patients with pre-existing renal conditions associated with low sodium or in patients treated concomitantly with sodium-lowering medicines (e.g., diuretics, medicines associated with inappropriate ADH secretion), serum sodium levels should be measured prior to initiating PINOMAZ CR therapy. Thereafter, serum sodium levels should be measured after approximately two weeks and then at monthly intervals for the first three months during therapy, or according to clinical need. These risk factors may apply especially to elderly patients. If hyponatraemia is observed, water restriction is an important counter-measurement if clinically indicated.

Hypothyroidism

Carbamazepine, (as in PINOMAZ CR), may reduce serum concentrations of thyroid hormones through enzyme induction, requiring an increase in dose of thyroid replacement therapy in patients with hypothyroidism. Hence thyroid function monitoring is suggested to adjust the dosage of thyroid replacement therapy.

Anticholinergic effects

Carbamazepine has shown mild anticholinergic activity. Patients with increased intra-ocular pressure and urinary retention should therefore be closely observed during PINOMAZ CR therapy (see section 4.8).

Other

Medical supervision during treatment is essential.

Long-term therapy with PINOMAZ CR has been associated with abnormalities of liver function and jaundice.

Psychiatric effects

Latent psychosis may be activated and in elderly patients the possibility of confusion or agitation exists.

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic medicines such as PINOMAZ CR in several indications. A meta-analysis of randomised placebo-controlled trials of antiepileptic medicines has shown an increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known. Therefore, patients should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered.

Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Endocrinological effects

Breakthrough bleeding has been reported in women taking hormonal contraceptives and the reliability of hormonal contraceptives may be adversely affected by PINOMAZ CR. Women of childbearing age should be advised to consider using alternative forms of birth control while taking PINOMAZ CR.

Patients taking PINOMAZ CR and requiring hormonal contraception should receive a preparation containing not less than 50µg estrogen or use of some alternative nonhormonal method of contraception should be considered.

Women of childbearing potential

Carbamazepine may cause foetal harm when administered to a pregnant woman.

Prenatal exposure to carbamazepine may increase the risks for major congenital malformations and other adverse development outcomes (see Section 4.6).

Carbamazepine should not be used in women of childbearing potential unless the benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options.

Women of childbearing potential should be fully informed of the potential risk to the foetus if they take carbamazepine during pregnancy.

Before the initiation of treatment with carbamazepine in a woman of childbearing potential, pregnancy testing should be considered.

Women of childbearing potential should use highly effective contraception during treatment and for at least two weeks after stopping treatment. Due to enzyme induction, carbamazepine may result in a failure of the therapeutic effect of hormonal contraceptives, therefore, women of childbearing potential should be counselled regarding the use of other effective contraceptive methods (see Sections 4.5 and 4.6).

Women of childbearing potential should be counselled regarding the need to consult their doctor as soon as they are planning a pregnancy to discuss switching to alternative treatments prior to conception and before contraception is discontinued (see Section 4.6).

Women of childbearing potential should be counselled to contact the doctor immediately if they become pregnant or think they might be pregnant and are taking carbamazepine.

Women of child-bearing potential should be warned that the concurrent use of PINOMAZ CR with hormonal contraceptives may render this type of contraceptive ineffective (see sections 4.5 and 4.6). Alternative non-hormonal forms of contraception are recommended when using PINOMAZ CR.

Dose reduction and withdrawal effects

Tolerance may develop to some of the untoward effects of PINOMAZ CR. These effects can be minimised by gradual increase in dosage and adjustment to the lowest effective maintenance dosage.

Abrupt withdrawal of PINOMAZ CR may precipitate seizures, therefore, withdrawal should be gradual over a 6-month period. If treatment with PINOMAZ CR is withdrawn abruptly, the change-over to other anti-epileptic medication should be started under cover of a suitable medicine (e.g., diazepam or phenytoin).

Monitoring of plasma levels

Although correlations between dosages and plasma levels of carbamazepine, and between plasma levels and clinical efficacy or tolerability are rather tenuous, monitoring of the plasma levels may be useful in the following conditions:

dramatic increase in seizure frequency/verification of patient compliance; during pregnancy; when treating children or adolescents; in suspected absorption disorders; in suspected toxicity when more than one drug is being used (see 4.5 Interaction with other medicinal products and other forms of interaction).

Falls

Therapy with PINOMAZ CR has been associated with ataxia, dizziness, somnolence, hypotension, confusional state, sedation (see section 4.8) which may lead to falls and, consequently fractures or other injuries. For patients with diseases, conditions, or medicines that could exacerbate these effects, complete risk assessment of fall should be considered recurrently for patients on long-term PINOMAZ CR therapy.

Interactions

Co-administration of inhibitors of CYP3A4 or inhibitors of epoxide hydrolase with PINOMAZ CR can induce adverse reactions (increase of carbamazepine or carbamazepine-10,11 epoxide plasma concentrations, respectively). The dosage of PINOMAZ CR should be adjusted accordingly and/or the plasma levels monitored.

Co-administration of CYP3A4 inducers with PINOMAZ CR may decrease carbamazepine plasma concentrations and its therapeutic effect, while discontinuation of a CYP3A4 inducer may increase carbamazepine plasma concentrations. The dosage of PINOMAZ CR may have to-be adjusted.

PINOMAZ CR is a potent inducer of CYP3A4 and other phase I and phase II enzyme systems in the liver and may therefore reduce plasma concentrations of co-medications mainly metabolized by CYP3A4 by induction of their metabolism (see section 4.5).

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per 200 mg or 400 mg, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicines and other forms of interaction

Cytochrome P4503A (CYP3A4) is the main enzyme catalysing formation of the active metabolite carbamazepine-10,11-epoxide.

Co-administration of inhibitors of CYP3A4 may result in increased plasma concentrations, which could induce adverse reactions.

Co-administration of CYP 3A4 inducers may increase the rate of PINOMAZ CR metabolism, thus leading to a potential decrease in carbamazepine serum level and potential decrease in the therapeutic effect.

Similarly, discontinuation of a CYP3A4 inducer may decrease the rate of metabolism of carbamazepine, leading to an increase in carbamazepine plasma levels.

PINOMAZ CR is a potent inducer of CYP3A4 and other phase I and phase II enzyme systems in the liver and may therefore reduce plasma concentrations of co-medications mainly metabolised by CYP3A4 by induction of their metabolism.

Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine-10,11-epoxide. Co-administration of inhibitors of human microsomal epoxide hydrolase may result in increased carbamazepine-10,11-epoxide plasma concentrations. Such inhibitors are valproic acid, valpromide, valnoctamide and progabide

Medicines that may raise carbamazepine plasma levels

Since raised plasma carbamazepine levels may result in adverse reactions (e.g., dizziness, drowsiness, ataxia, diplopia), the dosage of PINOMAZ CR should be adjusted accordingly and/or the plasma levels monitored when used concomitantly with the substances described below:

Analgesics, anti-inflammatory medicines: ibuprofen, dextropropoxyphene

Androgens: danazol

Antibiotics: macrolide antibiotics (e.g. erythromycin, troleandomycin, josamycin, clarithromycin) and ciprofloxacin

Antidepressants: desipramine, fluoxetine, fluvoxamine, nefazodone, paroxetine, trazadone, viloxazine

Antiepileptics: stiripentol, vigabatrin

Antifungals: azoles (e.g. itraconazole, ketoconazole, fluconazole, voriconazole). Alternative anticonvulsants may be recommended in patients treated with voriconazole or itraconazole

Antihistamines: loratadine, terfenadine

Antipsychotics: olanzapine

Antituberculosis: isoniazid

Antivirals: protease inhibitors for HIV treatment (e.g. ritonavir)

Carbonic anhydrase inhibitors: acetazolamide

Cardiovascular medicines: diltiazem, verapamil

Gastrointestinal medicines: cimetidine, omeprazole

Muscle relaxants: oxybutynin, dantrolene

Platelet aggregation inhibitors: ticlopidine

Other interactions: nicotinamide (only in high dosage), grapefruit juice.

Medicines that may raise the active metabolite carbamazepine-10,11-epoxide plasma levels

Since raised plasma carbamazepine-10,11-epoxide levels may result in adverse reactions (e.g., dizziness, drowsiness, ataxia, diplopia), the dosage of PINOMAZ CR should be adjusted accordingly and/or the plasma levels monitored when used concomitantly with the substances described below:

Loxapine, quetiapine, primidone, progabide, valproic acid, valnoctamide, valpromide, brivaracetam.

Medicines that may decrease carbamazepine and/or carbamarepine-10, 11-epoxide plasma levels

The dose of PINOMAZ CR may have to be adjusted when used concomitantly with the substances described below:

Antiepileptics: felbamate, methsuximide, oxcarbazepine, phenobarbitone, phensuximide, phenytoin (to avoid phenytoin intoxication and sub-therapeutic concentrations of carbamazepine it is recommended to adjust the plasma concentration of phenytoin to 13 µg/ml before adding PINOMAZ CR to the treatment), primidone and, although the data are partly contradictory, possibly also clonazepam

Antineoplastics: cisplatin or doxorubicin

Antituberculosis: rifampicin

Bronchodilators or anti-asthma medicines: theophylline, aminophylline

Dermatological medicines: isotretinoin

Other interactions: herbal preparations containing St John's Wort (*Hypericum perforatum*).

Effect of PINOMAZ CR on plasma levels of concomitant medicines

PINOMAZ CR may lower the plasma level or diminish - or even abolish - the activity of certain medicines. The dosage of the following medicines may have to be adjusted to clinical requirements:

Analgesics, anti-inflammatory medicine: buprenorphine, methadone, paracetamol (long-term administration of carbamazepine and paracetamol (acetaminophen) may be associated with hepatotoxicity), tramadol

Antibiotics: doxycycline, rifabutin

Anticoagulants: oral anticoagulants (e.g. warfarin, rivaroxaban and others e.g. dabigatran, apixaban, endoxaban)

Antidepressants: bupropion, citalopram, mianserin, nefazodone, trazodone, tricyclic antidepressants (e.g. imipramine, amitriptyline, nortriptyline, clomipramine). The use of PINOMAZ CR is contraindicated in combination with monoamine oxidase inhibitors (MAOIs); before administering PINOMAZ CR, MAOIs should be discontinued for a minimum of 2 weeks or longer, if the clinical situation permits (see section 4.3)

Antiemetics: aprepitant

Antiepileptics: clobazam, clonazepam, ethosuximide, felbamate, lamotrigine, eslicarbazepine, primidone, tiagabine, topiramate, valproic acid, zonisamide. There have been reports at an increase in plasma mephenytoin levels. To avoid phenytoin intoxication and sub-therapeutic concentrations of carbamazepine, it is recommended to adjust the plasma concentration of phenytoin to 13 µg/mL before adding PINOMAZ CR to the treatment

Antifungals: itraconazole, voriconazole. Alternative anticonvulsants may be recommended in patients treated with voriconazole or itraconazole

Anthelmintics: praziquantel, albendazole

Antineoplastics: imatinib, cyclophosphamide, lapatinib, temsirolimus

Antipsychotics: clozapine, haloperidol and bromperidol, quetiapine, risperidone, ziprasidone, olanzapine, aripiprazole, paliperidone

Anxiolytics: alprazolam, midazolam

Bronchodilators or anti-asthma medicines: theophylline

Contraceptives: hormonal contraceptives (alternative contraceptive methods should be considered)

Cardiovascular medicines: calcium channel blockers (dihydropyridine group) e.g. felodipine, digoxin, simvastatin, atorvastatin, lovastatin, cerivastatin, ivabradine

Corticosteroids: corticosteroids (e.g. prednisolone, dexamethasone)

Medicines used in erectile dysfunction: tadalafil

Immunosuppressants: ciclosporin, everolimus, tacrolimus, sirolimus

Thyroid medicine: levothyroxine.

The level of serum folic acid should be observed during anticonvulsant therapy since PINOMAZ CR may enhance the metabolism of folic acid.

Combinations that require specific consideration

Concomitant use of PINOMAZ CR and levetiracetam has been reported to increase carbamazepine-induced toxicity.

Concomitant use of PINOMAZ CR and isoniazid has been reported to increase isoniazid-induced hepatotoxicity.

Combined use of PINOMAZ CR and lithium, or metoclopramide on the one hand, and PINOMAZ CR and neuroleptics (haloperidol, thioridazine) on the other, may lead to increased neurological adverse reactions (with the latter combination even in the presence of therapeutic plasma levels).

Concomitant medication with PINOMAZ CR and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatraemia.

PINOMAZ CR may antagonise the effects of non-depolarising muscle relaxants (e.g., pancuronium); their dosage may need to be raised, and patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected.

PINOMAZ CR may reduce the patient's alcohol tolerance; it is therefore advisable to abstain from alcohol during treatment.

Concomitant use of PINOMAZ CR with direct acting oral anti-coagulants (rivaroxaban, dabigatran, apixaban and edoxaban) may lead to reduced plasma concentrations of direct acting oral anticoagulants, which carries the risk of thrombosis. Therefore, if concomitant use is necessary, close monitoring of signs and symptoms of thrombosis is recommended.

Interference with serological testing

PINOMAZ CR may result in false positive perphenazine concentrations in HPLC analysis due to interference.

Carbamazepine and the 10,11-epoxide metabolite may result in false positive tricyclic antidepressant concentration in fluorescence polarised immunoassay method.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

If women receiving PINOMAZ CR either become pregnant or plan to become pregnant or should the need of initiating treatment with PINOMAZ CR arises during pregnancy, the medicine's expected benefits must be carefully weighed against its possible hazards, particularly in the first 3 months of pregnancy.

In women of childbearing potential, PINOMAZ CR should, wherever possible, be prescribed as monotherapy, due to the incidence of congenital abnormalities in the offspring of women treated with a combination of antiepileptic medicines being greater than in those of mothers receiving the individual medicines as monotherapy. The risk of malformations following exposure to carbamazepine as polytherapy may vary depending on the specific medicines used and may be higher in polytherapy combinations that include valproate.

Minimum effective doses should be given, and monitoring of plasma levels is recommended. The plasma concentration could be maintained in the lower side of the therapeutic range (4 to 12 µg/mL) provided seizure control is maintained. There is evidence to suggest that the risk of malformation with PINOMAZ CR may be dose-dependent, i.e., at a dose <400 mg per day, the rates of malformation were lower than with higher doses of carbamazepine.

Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.

During pregnancy, an effective antiepileptic treatment should not be interrupted, since aggravation of the illness is detrimental to both the mother and the foetus.

Women of childbearing potential should use effective contraception during treatment with PINOMAZ CR and for 2 weeks after the last dose. Due to enzyme induction, PINOMAZ

CR may result in a failure of the therapeutic effect of oral contraceptive medicine containing estrogen and/or progesterone. Therefore, women of child-bearing potential should be advised to use alternative contraceptive methods while on treatment with PINOMAZ CR.

Pregnancy

Safety of PINOMAZ CR in pregnancy has not been demonstrated.

Patients should consult their doctor for guidance on the use of PINOMAZ CR during pregnancy.

Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.

Offspring of epileptic mothers are known to be more prone to developmental disorders, including malformations. There are reports of developmental disorders and malformations, including spina bifida and hypospadias in association with PINOMAZ CR.

Monitoring and prevention

Folic acid deficiency is known to occur in pregnancy. Anti-epileptic medicines have been reported to aggravate folic acid deficiency, which in turn may contribute to the increased incidence of birth defects in the offspring of treated epileptic women.

Folic acid supplementation has therefore been recommended before and during pregnancy.

In the neonate

Vitamin K, given to the mother during the last weeks of pregnancy, as well as to the neonate, is recommended in order to prevent bleeding disorders in the offspring.

Cases of neonatal seizures and/or respiratory depression associated with maternal PINOMAZ CR and other concomitant anticonvulsant medicine use have been reported. Cases of neonatal vomiting, diarrhoea and/r decreased feeding have also been reported in association with maternal PINOMAZ CR use. These reactions may represent a neonatal withdrawal syndrome.

Women with manic depressive (bipolar) disorders have an increased risk to relapse during pregnancy and/or the post-partum period.

Breastfeeding

Carbamazepine passes into breast milk (about 25 to 60 % of plasma concentrations). Mothers taking PINOMAZ CR should not breastfeed their infants (see section 4.3).

Fertility

There have been reports of impaired male fertility and/or abnormal spermatogenesis.

4.7 Effects on ability to drive and use machines

The patient's ability to react may already be impaired by the diagnosed medical condition, resulting in seizures. Additional adverse reactions when taking PINOMAZ CR include dizziness, drowsiness, ataxia, diplopia, impaired accommodation and blurred vision, especially at the start of treatment or in connection with dose adjustments.

Patients should therefore exercise due caution when driving a vehicle or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

The most frequently observed side-effects at the start of treatment or when initial dosage is too high or when treating elderly patients are dizziness, headache, drowsiness, ataxia, fatigue, diplopia, gastrointestinal disturbances (nausea and vomiting), as well as allergic skin reactions, especially at initiation of therapy, initial dose being too high or in the elderly.

Dose-related adverse reactions may abate within a few days, either spontaneously or after a transient dosage reduction. The occurrence of central nervous system (CNS) adverse reactions may be a manifestation of relative overdosage or significant fluctuation in plasma levels. In such cases it is advisable to monitor the plasma levels.

Tabulated summary of adverse reactions

The frequencies of adverse events are ranked according to the following:

Frequent = (≥ 1/100 to < 1/10).

Less frequent = Infrequent (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (<1/10,000).

Frequency not known = cannot be estimated from the available data.

System Organ Class	Frequency	Side effects
Infections and infestations	Frequency unknown	Reactivation of Human herpes virus 6 infection*

Blood and lymphatic system disorders	Frequent Less frequent Frequency unknown	Leucopenia, thrombocytopenia, eosinophilia Leucocytosis, lymphadenopathy, pure red cell aplasia, agranulocytosis, anaemia, aplastic anaemia, pancytopenia, megaloblastic anaemia, reticulocytosis, haemolytic anaemia, bone marrow depression Bone marrow failure
Immune system disorders	Less frequent Frequency unknown	Delayed multi-organ hypersensitivity disorder with fever, rashes, vasculitis, lymphadenopathy, pseudo-lymphoma, leukopenia, eosinophilia, arthralgia, hepatosplenomegaly and abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), occurring in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon), anaphylactic reaction, angioedema, hypogammaglobinaemia Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)
Endocrine disorders	Frequent Less frequent	Oedema, fluid retention, weight increase, hyponatraemia and blood osmolarity decreased due to an antidiuretic hormone (ADH)-like effect leading in rare cases to water intoxication accompanied by lethargy, vomiting, headache,confusion, neurological disorders Galactorrhoea, gynaecomastia
Metabolism and nutrition disorders	Less frequent	Folate deficiency, decreased appetite, porphyria acute (acute intermittent porphyria and variegate porphyria), porphyria non-acute (porphyria cutanea tarda), hyperammonaemia
Psychiatric disorders	Less frequent	Hallucinations (visual or auditory), depression, aggression, agitation, restlessness, confusional state, activation of psychosis

Nervous system disorders	Frequent Less frequent Frequency unknown	Dizziness, ataxia, somnolence, headache Abnormal involuntary movements (e.g. tremor, asterixis, dystonia, tics), nystagmus, dyskinesia, speech disorders (e.g. dysarthria, slurred speech), choreoathetosis, peripheral neuropathy, paraesthesia, paresis, neuroleptic malignant syndrome, aseptic meningitis with myoclonus and peripheral eosinophilia, dysgeusia Sedation, memory impairment
Eye disorders	Frequent Less frequent	Accommodation disorders (e.g. blurred vision), diplopia Lenticular opacities, conjunctivitis
Ear and labyrinth disorders	Less frequent	Hearing disorders, e.g., tinnitus, hyperacusis, hypoacusis, change in pitch perception
Cardiac disorders	Less frequent	Cardiac conduction disorders, dysrhythmia, atrioventricular block with syncope, bradycardia, congestive cardiac failure, aggravation of coronary artery disease
Vascular disorders	Less frequent	Hypertension or hypotension, circulatory collapse, embolism (e.g. pulmonary embolism), thrombophlebitis
Respiratory, thoracic and mediastinal disorders	Less frequent	Pulmonary hypersensitivity characterized e g. by fever, dyspnoea, pneumonitis or pneumonia
Gastrointestinal disorders	Frequent Less frequent Frequency unknown	Nausea, vomiting, dry mouth Diarrhoea, constipation, abdominal pain, pancreatitis, glossitis, stomatitis Colitis
Hepatobiliary disorders	Less frequent	Hepatitis of cholestatic, parenchymal (hepatocellular) or mixed type, vanishing bile duct syndrome, jaundice, hepatic failure, granulomatous liver disease

Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency unknown	Allergic dermatitis, urticaria which may be severe Exfoliative, dermatitis, systemic lupus erythematosus, pruritus, Stevens-Johnson syndrome, Toxic Epidermal Necrolysis (TEN), photosensitivity reaction, erythema multiforme, erythema nodosum, pigmentation disorder, purpura, acne, hyperhidrosis, alopecia, hirsutism Acute Generalised Exanthematous Pustulosis (AGEP), lichenoid keratosis, onychoradasis
Musculoskeletal, connective tissue and bone disorders	Less frequent Frequency unknown	Muscular weakness, bone metabolism disorders (decrease in plasma calcium and blood 25-hydroxy-cholecalciferol) leading to osteomalacia/osteoporosis, arthralgia, myalgia, spasms Fracture
Renal and urinary disorders	Less frequent	Tubulointerstitial nephritis, renal failure, renal impairment (e.g., albuminuria, haematuria, oliguria, and increased blood urea/azotaemia, urinary retention, urinary frequency
Reproductive system and breast disorders	Less frequent	Sexual dysfunction/erectile dysfunction, abnormal spermatogenesis (with decreased sperm count and/or motility)
General disorders and administrative site conditions	Frequent	Fatigue

Investigations	Frequent Less frequent Frequency unknown	Gamma-glutamyl transferase increased (due to hepatic enzyme induction), usually not clinically relevant blood alkaline phosphatase increased Transaminases increased ,intraocular pressure increased, blood cholesterol increased, high density lipoprotein increased, blood triglycerides increased, thyroid function test abnormal, decreased L-Thyroxin (free thyroxine, thyroxine, tri-iodothyronine) and increased blood thyroid stimulating hormone, usually without clinical manifestations, blood prolactin increased Bone density decreased
Injury and poisoning	Frequency unknown	Fall (associated with PINOMAZ CR treatment induced ataxia, dizziness, somnolence, hypotension, confusional state, sedation) (see section 4.4)

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 professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

The presenting signs and symptoms of overdosage usually involve the central nervous, cardiovascular, and respiratory systems.

Central nervous system: CNS depression, disorientation, somnolence, agitation, hallucination, coma, blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia, initially hyperreflexia, later hyporeflexia, convulsions, psychomotor disturbances, myoclonus, hypothermia, mydriasis.

Respiratory system: Respiratory depression, pulmonary oedema.

Cardiovascular system: Tachycardia, hypotension, hypertension, conduction disturbances with widening of QRS complex, syncope in association with cardiac arrest.

Gastrointestinal system: Vomiting, delayed gastric emptying, reduced bowel motility.

Musculoskeletal system: Cases of rhabdomyolysis have been reported in association with carbamazepine toxicity.

Renal function: Retention of urine, oliguria or anuria, fluid retention, water intoxication due to an ADH-like effect.

Laboratory findings: Hyponatraemia, metabolic acidosis, hyperglycaemia, increased muscle creatinine phosphokinase.

Management of overdose:

No specific antidote. Management should initially be guided by the patient's clinical condition; admission to hospital. Measurement of the plasma level to confirm PINOMAZ CR poisoning and to ascertain the size of the overdose.

Administration of activated charcoal. Delay in evacuating the stomach may result in delayed absorption, leading to relapse during recovery from intoxication. Supportive medical care in an intensive care unit with cardiac monitoring and careful correction of electrolyte imbalance.

Special recommendations

Charcoal haemoperfusion has been recommended. Haemodialysis is the effective treatment modality in the management of PINOMAZ CR overdose.

Relapse and aggravation of symptomatology on the 2nd and 3rd day after overdose, due to delayed absorption, should be anticipated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-epileptic, neurotropic and psychotropic agent.

ATC code: N03A F01.

Pharmacological classification: A 2.5 Anticonvulsants, including anti-epileptics.

Mechanism of action

Carbamazepine possesses both anticonvulsant and psychotropic properties.

5.2 Pharmacokinetic properties

Absorption

Carbamazepine is absorbed relatively slowly from the tablet. The sustained release tablets yield a mean peak plasma concentration of the carbamazepine within 24 hours. The controlled release tablets provide more stable plasma concentrations throughout the day, thereby allowing twice daily dosage.

Distribution

Carbamazepine is 70 - 80 % bound to plasma proteins. The concentration of carbamazepine in the saliva reflects the unbound fraction in the plasma (20 to 30 %).

Biotransformation

Carbamazepine is metabolised the liver, where the epoxide pathway of biotransformation is the most important one, yielding the 10, 11-transdiol derivative and its glucuronide as the main metabolites. Cytochrome P450 is responsible for the formation of carbamazepine-10, 11-epoxide from carbamazepine, while the microsomal epoxide epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine-10,11 epoxide.

The steady-state plasma concentrations of carbamazepine considered as in the 'therapeutic range', vary considerably inter individually. for the majority of patients a range between 4 - 12 µg/mL corresponding to 17 - 50 µmol/L has been reported.

Elimination

The elimination halt-life of carbamazepine is approximately 36 hours after a single oral dose, whereas alter repeated administration, which leads to auto induction of hepatic enzymes, it averages only 16 to 24 hours, depending on the duration of the medication. In patients receiving concomitant treatment with other enzyme inducing anti-epileptic medicine, half-life values averaging 9 to 10 hours have been found.
Only 2 to 3 % of the dose is excreted in the urine in unchanged form. The primary metabolite is the pharmacologically active carbarmazepine-10,11 -epoxide.

Pharmacokinetics in special patient groups

Paediatric population

Owing to enhanced carbamazepine elimination, children may require higher doses of carbamazepine (in mg/kg) than adults.

Elderly patients (65 years or above)

There is no indication of altered pharmacokinetics of carbamazepine in elderly patients as compared with young adults.

Patients with hepatic or renal impairment

No data are available on the pharmacokinetics of carbamazepine in patients with impaired hepatic or renal function.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:

Colloidal Silicon Dioxide

Croscarmellose Sodium

Ethyl Acrylate and Methyl methacrylate Copolymer Dispersion/ Polyacrylate Dispersion

Ethyl Cellulose Aqueous Dispersion

Hydroxy Propyl Methyl Cellulose

Magnesium stearate

Microcrystalline Cellulose

Talc

Coating:

Instacoat Universal Peach:

Hypromellose 2910

Polyethylene Glycol 400 & 6000

Red Iron Oxide

Talc

Titanium dioxide

Yellow Iron Oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C. Keep HDPE bottle tightly closed.

6.5 Nature and contents of container

100 mg: 100 or 1000 tablets will be packed in HPDE bottles with a polypropylene Child resistant (100's) or Continuous thread (1000's) closure.

200 mg: 100 or 1000 tablets will be packed in HPDE bottles with a polypropylene Child resistant (100's) or Continuous thread (1000's) closure.

400 mg: 100 or 1000 tablets will be packed in HPDE bottles with a polypropylene Child resistant (100's) or Continuous thread (1000's) closure.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBERS

Pinomaz 100 mg CR: A59/2.5/0338

Pinomaz 200 mg CR: A59/2.5/0339

Pinomaz 400 mg CR: A59/2.5/0340

9. DATE OF FIRST AUTHORISATION

28 July 2026