

## 1. NAME OF THE MEDICINAL PRODUCT

**Tiapridal 100 mg tablets**

**Tiapridal drops of solution for internal use**

**Tiapridal solution for injection**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

## 3. PHARMACEUTICAL FORM

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

### 4.2 Posology and method of administration

### 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Concomitant Prolactin-dependent tumours, e.g. pituitary gland prolactinoma and breast cancer.
- Pheochromocytoma
- Association with levodopa or other dopaminergic medicines (see section 4.5).

### 4.4 Special warnings and precautions for use

As with other neuroleptics, Neuroleptic Malignant Syndrome, a potentially fatal complication, which is characterised by hyperthermia, muscle rigidity and autonomic dysfunction may occur. In case of hyperthermia of undiagnosed origin, tiapride should be discontinued.

Neuroleptic agents may reduce the seizure threshold in epilepsy, although this has not been evaluated with tiapride. Therefore, patients with a history of epilepsy should be closely monitored during tiapride treatment.

In patients with renal impairment the dose has to be reduced (see section 4.2).

Tiapride should not be used in patients with Parkinson's disease, with the exception of special circumstances.

Because tiapride can have an increased sedative effect in elderly patients, caution should be exercised.

#### Prolongation of the QT interval

Tiapride may induce a prolongation of the QT interval. This effect is known to potentiate the risk of serious ventricular arrhythmias such as torsades de pointes (see Adverse reactions). Before any administration, and if possible according to the patient's clinical status, it is recommended to monitor factors which could favour the occurrence of this rhythm disorder, such as for example:

- bradycardia less than 55 bpm,
- electrolyte imbalance in particular hypokalaemia,
- congenital prolongation of the QT interval,
- on-going treatment with a medication likely to produce pronounced bradycardia (< 55 bpm), electrolyte imbalance, decreased intracardiac conduction, or prolongation of the QT interval (see section Interactions).

Tiapride should be prescribed with caution in patients presenting with risk factors which may predispose to prolongation of the QT interval.

### Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with tiapride and preventive measures undertaken.

### Increased Mortality in Elderly people with dementia

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death in clinical trials with atypical antipsychotics were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

### Stroke

In randomized clinical trials versus placebo performed in a population of elderly patients with dementia and treated with certain atypical antipsychotic drugs, a 3-fold increase of the risk of cerebrovascular events has been observed. The mechanism of such risk increase is not known. An increase in the risk with other antipsychotic drugs or other populations of patients cannot be excluded. Tiapride should be used with caution in patients with stroke risk factors.

### Children

In children, tiapride has not been thoroughly investigated. Therefore, caution should be exercised when prescribing to children (see section 4.2).

## **4.5 Interaction with other medicinal products and other forms of interaction**

### **Combinations which are contra-indicated:**

Dopaminergic agonists, excluding patients with Parkinson's disease (cabergoline, quinagolide), due to reciprocal antagonism between dopaminergic agonists and neuroleptics.

### **Combinations which are not recommended:**

+ **Medications which can induce torsades de pointes:** Class Ia (quinidine, hydroquinidine, disopyramide), and class III antiarrhythmic agents (amiodarone, sotalol, dofetilide, ibutilide), certain neuroleptics (sultopride, pipothiazine, sertindole, veralipide, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, pimozide, haloperidol, droperidol, fluphenazine, pipamperone, flupentixol, zuclopentixol), some antiparasitic drugs (halofantrine, lumefrantrine, pentamidine), other medications: IV erythromycin, IV spiramycin, moxifloxacin, bepridil, cisapride, diphemanil,, mizolastine, IV vincamine.

Increased risk of ventricular arrhythmias, especially torsades de pointes.

If possible, discontinue the medication that can induce torsades de pointes, except for anti-infective agents. If combination therapy cannot be avoided, check the QT interval before starting treatment and monitor ECG.

**+ Alcohol**

Alcohol may enhance the sedative effect of neuroleptics.

The alteration of the vigilance can make dangerous the driving of vehicles and the use of machines.

Avoid drinking alcohol and taking medicines containing alcohol.

**+ Levodopa**

Reciprocal antagonism of the effects of levodopa and neuroleptics.

Use minimal effective doses of each of both drugs in patients with Parkinson's disease.

**+ Dopaminergic agonists except levodopa** (amantadine, apomorphine, bromocriptine, entacapone, lisuride, pergolide, priribedil, pramipexole, ropinirole, selegiline) in patients with Parkinson's disease.

Reciprocal antagonism of the effects of the dopaminergic agonist and neuroleptics.

The dopaminergic agonist can induce or accentuate psychotic disorders.

When neuroleptic therapy cannot be avoided in patients with Parkinson's disease treated with dopaminergic agonists, these agents must be tapered off and discontinued (sudden withdrawal of dopaminergic agonists can induce neuroleptic malignant syndrome).

**+ Methadone**

Enhanced risk of ventricular arrhythmia, in particular torsades de pointes.

**Combinations which require precautions for use:**

**+ Bradycardia-inducing agents** (in particular class Ia antiarrhythmia agents, beta-blockers, some class II antiarrhythmia agents, some calcium antagonists, cardiac glycosides, pilocarpine, cholinesterase-inhibitors):

Increased risk of ventricular arrhythmias, especially torsades de pointes.

Clinical and electrocardiographic monitoring.

**+ Beta-blockers in heart failure (bisoprolol, carvedilol, metoprolol, nebivolol)**

Enhanced risk of ventricular arrhythmia, in particular torsades de pointes. Clinical monitoring and ECG monitoring are necessary.

**+ Potassium-lowering agents** (potassium-lowering diuretics, stimulant laxatives, IV amphotericin B, glucocorticoids, cosyntropin)

Increased risk of ventricular arrhythmias, especially torsades de pointes.

Correct any hypokalaemia before starting treatment with amisulpride and ensure clinical, electrolyte and electrocardiographic monitoring.

**Its concomitant administration has to be taken into account:**

**+ Antihypertensives (all):**

Antihypertensive effect and increased risk of orthostatic hypotension (additive effect).

**+ Other central nervous system depressants:**

Narcotics (analgesics, antitussives and opioid replacement therapy); barbiturates; benzodiazepines; other non-benzodiazepine anxiolytics; hypnotics; neuroleptics; sedative antidepressants (amitriptyline, doxepine, mianserin, mirtazapine, trimipramine); sedative H1 antihistamines; centrally-acting antihypertensives; other drugs: baclofen, thalidomide, pizotifène.

Increase of central depression. Impaired alertness may make the driving of vehicles and the use of machines dangerous.

**+ Beta-blockers (except esmolol, sotalol and beta-blockers used in heart failure)**

Vasodilator effect and risk of hypotension, in particular postural hypotension (additive effect).

## + Nitrate derivatives and related compounds

### 4.6 Pregnancy and lactation

#### **Pregnancy**

If drug therapy is needed to maintain a good mental balance and to avoid decompensation, it must be instituted or continued at effective dose throughout the pregnancy.

There are limited amount of data from the use of tiapride in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

Injectable neuroleptics used in emergency situations can cause maternal hypotension.

In neonates born to mothers receiving prolonged high-dose neuroleptic treatment, extrapyramidal syndromes (hypertonia, tremor) have been described in rare cases. Tiapride used in late pregnancy, could theoretically induce, particularly at high doses:

- atropinic manifestations increased by concomitant use of antiparkinsonism corrector : tachycardia, hyperexcitability, abdominal distention, delayed meconium
- sedation.

Accordingly, the use of tiapride may be considered regardless of the term of pregnancy. The monitoring of the newborn will consider the effects mentioned above.

#### **Breast-feeding**

It is not known whether tiapride is excreted in breast milk. Breast-feeding during treatment with tiapride is not recommended.

#### **Fertility**

A decrease in fertility was observed in animals treated with tiapride.

In humans, because of the interaction with dopamine receptors, tiapride may cause hyperprolactinemia which can be associated with amenorrhea, anovulation, and impaired fertility (cf 4.8 Endocrine disorders).

### 4.7 Effects on ability to drive and use machines

Even when used as recommended, tiapride may cause sedation so that the ability to drive vehicles or operate machinery can be impaired (see section 4.8).

### 4.8 Undesirable effects

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Undesirable effects are indicated in accordance with the following incidences: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

#### **Data of clinical studies**

During controlled clinical studies the following adverse effects were reported. It should be noted that in some instances it can be difficult to differentiate adverse events from symptoms of the underlying disease.

#### **Endocrine disorders:**

This may result in galactorrhea and amenorrhea (linked to hyperprolactinemia), breast enlargement and breast pain, and impotence

*Common : hyperprolactinemia\**

#### **General disorders and administration site conditions:**

*Common:* Asthenia/fatigue

*Uncommon:* Weight increase

#### **Nervous system disorders:**

*Common:* Dizziness/vertigo, headache.

Parkinsonism and symptoms related symptoms: tremor, hypertonia, hypokinesia, hypersalivation. These symptoms are generally reversible upon administration of antiparkinsonian medicines.

*Uncommon:* Akathisia, dystonia (spasm, torticollis, oculogyric crisis, and trismus). These symptoms are generally reversible upon administration of antiparkinsonian medicines.

*Rare:* Acute dyskinesia. This symptom is generally reversible upon administration of antiparkinsonian medicines.

#### **Psychiatric disorders:**

*Common:* drowsiness/sleepiness, insomnia, agitation, impassivity.

#### **Reproductive system and breast disorders:**

*Uncommon :* Galactorrhea, amenorrhea, breast enlargement, breast pain, impotence

#### **Post marketing data**

In addition to the above, cases of the following adverse reactions have been reported (spontaneous reporting only):

#### **Cardiac disorders:**

*Not known:*QT interval prolongation, ventricular arrhythmias such as torsades de pointes, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest and sudden death (see section 4.4 ' Special warnings and precautions for use').

#### **Vascular disorders**

Not known: Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs, Hypotension, usually orthostatic

#### **Nervous system disorders:**

*Not known:* Tardive dyskinesia (characterized by rhythmic, involuntary movements primarily of the tongue and/ or the face) have been reported, as with all neuroleptics, after a neuroleptic administration of more than 3 months. Antiparkinson treatment is ineffective, and it may even lead to aggravation of the symptoms.

As in case of all antipsychotic agents, neuroleptic malignant syndrome may occur (see section 4.4), that is a complication with a potentially fatal outcome.

*\* Hyperprolactinemia may in some cases induce galactorrhea, amenorrhea, gynecomastia, menstrual disorders or erectile dysfunction.*

## **4.9 Overdose**

### **Signs and symptoms:**

Experience regarding the overdose of tiapride is limited. Drowsiness, sedation, coma, hypotension and extrapyramidal symptoms may be observed.

### **Treatment:**

Hemodialysis should not be used in overdose to remove the active substance, because tiapride is moderately dialysed.

There is no specific antidote to tiapride. Appropriate supportive measures (monitoring vital and cardiac functions) should therefore be instituted.

In case of severe extrapyramidal symptoms, anticholinergic medicines should be administered.