SUMMARY OF PRODUCT CHARACTERISTICS
Tiacob

1. NAME OF THE MEDICINAL PRODUCT
Tiacob 200 mg, tablets

2. QUALITATIVE AND QUANTIATIVE COMPOSITION
1 tablet contains: 222.2 mg tiapride hydrochloride, equivalent to 200 mg tiapride
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablet

White, round tablets with a breakline on both sides.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
For the treatment of neuroleptic-induced tardive dyskinesia, mainly oro-bucco-lingual type.

4.2 Posology and method of administration
Adults should take 100 – 200 mg tiapride three times daily, depending on the severity of the disease and the body weight of the individual . The proposed daily dose for the claimed indication is 300 – 600 mg tiapride.
The effect of treatment may not be apparent until after a period of 4-6 weeks of treatment.
Tiacob tablets should preferably be taken with a little liquid after meals.

Tiapride is not intended for treatment in children.

Dosage in renal impairment

Creatinine clearance:	50-80 ml/min = 75 %	of the
	10-50 ml/min = 50 %	normal
	less than 10 ml/min = 25 %	daily dose

4.3 Contraindications
- Hypersensitivity to tiapride hydrochloride or to any of the excipients.
- Prolactin-dependent tumours: pituitary prolactinomas and breast cancer;
- Phaeochromocytoma;
- Concomitant treatment with levodopa (see section 4.5).
- Neuroleptic malignant syndrome (see section 4.4)

4.4 Special warnings and precautions for use
Tiapride should be administered with particular caution in the following cases:
- The occurrence of neuroleptic malignant syndrome is described very rarely, characterised by high fever, muscular rigidity, autonomic instability, altered consciousness

and raised CPK values. Following the development of such symptoms, particularly the development of hyperthermia, tiapride should be discontinued.

Tiapride belongs to the benzamide type neuroleptics, which all share certain rare unwanted effects, predominantly hyperprolactinemia and QT-interval prolongation.

New researches indicate that increased prolactine levels may be associated with an increased risk of breast cancer.

Notwithstanding, due to a lack of epidemiologic studies, a final conclusion on hyperprolactinemia as an independent risk factor of breast cancer can so far not be drawn.

According to clinical experience tiapride should be prescribed with caution to patients with manifest cardiovascular diseases e.g. organic heart failure or proneness to atrial fibrillation, because of the risk of QT-intervall prolongation or torsades de pointes, which rarely can be provoked by QT-prolongation. Alternative treatments should be considered for these patients. Otherwise the lowest effective dose should be chosen and the patient should be monitored carefully.

- As tiapride is predominantly excreted via the kidneys, in patients with impaired renal function (renal failure) the dose should be reduced by the physician, while in patients with severely impaired renal function tiapride should be discontinued on medical advice (see section 4.2).
- Tiapride can decrease the cerebral seizure threshold. Patients with a known history of epilepsy should be monitored carefully.
- Parkinson's disease

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

4.5 Interactions with other medicinal products and other forms of interaction

Tiapride potentiates the action of other central depressants. These include morphine derivatives, barbiturates, benzodiazepines, anxiolytics, most H1-antihistamines and also centrally acting antihypertensives such as clonidine and analogues.
The action of neuroleptics can be potentiated by tiapride.
Alcohol potentiates the sedative action of tiapride. The use of alcoholic drinks and the consumption of alcohol-containing preparations should be avoided.
Anticholinergics such as biperiden can attenuate the action of tiapride.
Co-administration of levodopa and tiapride is contra-indicated as these drugs exhibit a mutually antagonistic effect (see section 4.3).

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of tiapride in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. The long-term use of antipsychotics prior to parturition is known to cause extrapyramidal disorders and withdrawal reactions in the new-born infant. Tiapride should not be used during pregnancy unless clearly necessary.

Lactation
It is not known whether tiapride is excreted in human breast milk. The excretion of tiapride in milk has not been studied in animals. Based on the lack of data and the potential pharmacological effects on the newborn child, breastfeeding should be discontinued.

Fertility
There are no human data on the effect of tiapride on fertility. Experience with benzamides in schizophrenic patients suggests that increases in prolactin level may cause a reversible impairment of fertility. In animals, adverse reactions of tiapride on fertility have been observed (see section 5.3).

4.7 Effect on ability to drive and use machines
Tiapride has minor or moderate influence on the ability to drive and use machines.

Even when used correctly, tiapride can affect the reaction time to such an extent that the ability to drive or use machines is impaired. This applies to an increased extent in combination with alcohol.

4.8 Undesirable effects
The following frequency estimates are used in assessing the undesirable effects:

Very common:	(>1/10)
Common:	(>1/100, <1/10)
Uncommon:	(>1/1,000, <1/100)
Rare:	(>1/10,000, <1/1,000
Very rare:	(<1/10,000) including isolated cases

Endocrine disorders
Uncommon: raised prolactin levels in the blood which can be the cause of breast pain, breast enlargement and milk production (gynaecomastia, galactorrhoea), cycle disorders (dysmenorrhoea, amenorrhoea) in women, and orgasm and potency disorders in men. These disorders generally regress within a short time after discontinuation of tiapride.

Psychiatric disorders
Common: agitation, apathy and insomnia.

Nervous system disorders
Common: dizziness, headache. At the beginning of treatment: extrapyramidal symptoms as in Parkinson's syndrome (tremor, rigidity, hypokinesia and increased salivation). These symptoms generally regress after administration of an anticholinergic (e.g. biperiden).
Uncommon: early dyskinesia (spastic torticollis, oculogyric crises, lockjaw) and akathisia generally regress after administration of an anticholinergic (e.g. biperiden).
Very rare: after prolonged treatment (more than 3 months), the occurrence of tardive dyskinesia, characterised by rhythmic involuntary movements predominantly of the tongue and/or facial muscles, cannot be excluded. Antiparkinsonian agents should not be used in this case as they do not work or may exacerbate the symptoms.
Very rare: neuroleptic malignant syndrome (see section 4.4).

Vascular disorders
Common: orthostatic hypotension

General disorders
Common: asthenia (rapidly becoming tired/weakness), tiredness and drowsiness.
Uncommon: weight gain.

4.9 Overdose
Experience with overdose of tiapride is limited. Drowsiness, sedation, coma, hypotension and extrapyramidal symptoms have been observed.
In the case of an acute overdose, the possibility of multiple drug use should be considered. After an oral overdose, therapy to reduce absorption can be administered (gastric lavage in the case of a potentially severe intoxication and, if shortly after ingestion, administration of activated charcoal in combination with a laxative).
Because tiapride is moderately dialysed, haemodialysis should not be administered to eliminate the active substance.
There is no specific antidote to tiapride. Appropriate supportive measures should be administered, and careful evaluation of the vital functions and cardiac monitoring should be performed until the patient has recovered.
In the case of severe extrapyramidal symptoms, anticholinergics should be administered.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Benzamide-antipsychotics
ATC code: NO5AL3

Tiapride is an atypical neuroleptic which exhibits selectivity in in-vitro studies for D2 and D3 dopamine subtype receptors without any affinity for subtype receptors of the principal central neurotransmitters (including serotonin, noradrenaline and histamine). These properties have been confirmed in neurochemical and behavioural studies in which antidopaminergic properties have been demonstrated in the absence of sedation, catalepsy and cognitive impairment.

5.2 Pharmacokinetic properties
Tiapride is rapidly absorbed. Maximal concentration of the active substance are reached as early as within one hour.

The absolute bioavailability of the tablets is 80%.

Tiapride is mostly eliminated in the first 24 hour urine. Tiapride is mainly eliminated as the parent compound, although two metabolites have been identified. These are the N-oxide and the N-monodesethyl derivatives of the active substance.
The elimination half-life is about 3 hours.

5.3 Preclinical safety data

An increased incidence of breast tumours was observed in rats. This was probably due to hyperprolactinaemia as a consequence of the pharmacological action of the substance. This is probably a species-specific effect and does not constitute any particular risk to humans in therapeutic use. Other abnormalities seen in experimental animals were associated with the known pharmacological action.

A tiapride-induced reduced fertility was observed in rats due to a suppression of the estrous cycle in females and a reduced libido in males. These effects are related to the pharmacological effect of tiapride on prolactin secretion. In studies on reproductive toxicity no signs of teratogenicity were observed, however, embryotoxic effects occurred. In a study on peri-postnatal toxicity toxic effects in the offspring were seen following high doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Microcrystalline cellulose (E460)
Magnesium stearate (E470b)
Povidone K30 (E1201)
Silicone dioxide (E551)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and content of containers

PVC/Aluminium blister pack
Pack of 10 tablets
Pack of 20 tablets
Pack of 50 tablets
Pack of 60 tablets
Pack of 100 tablets
Hospital pack: 500 (10 x 50 tablets)
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

HEXAL AG

Industriestrasse 25
83607 Holzkirchen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

33533

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

23.11.2006