PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Tiapride Ratiopharm 100 mg tablets
Ratiopharm GmbH, Germany

tiapride (as hydrochloride)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states. It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation. This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB’s knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/664/001/MR
Registration number in the Netherlands: RVG 32520

Date of first publication: 12 October 2009
Last revision: 14 March 2011

Pharmacotherapeutic group: antipsychotics, benzamide
ATC code: N05AL03
Route of administration: oral
Therapeutic indication: neuroleptic-induced tardive dyskinesia, mainly oro-bucco-lingual type
Prescription status: prescription only
Date of first authorisation in NL: 15 June 2005
Concerned Member States: Mutual recognition procedure with DE, SK, CZ, and HU (withdrawn in HU on 27 October 2005).
Application type/legal basis: Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.
I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Tiapride Ratiopharm 100 mg tablets, from Ratiopharm GmbH. The date of authorisation was on 20 June 2005 in the Netherlands. The product is indicated for the treatment of neuroleptic-induced tardive dyskinesia, mainly oro-bucco-lingual type.

A comprehensive description of the indications and posology is given in the SPC.

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.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Tiapridal (NL license RVG 07613) which has been registered in the Netherlands by Sanofi-Aventis Netherlands B.V. since 1981 (original product). In addition, reference is made to Tiapridal and Tiapridex authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Tiapridex 100 mg tablets, registered in Germany. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted.
II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The drug substance tiapride hydrochloride is described in the European Pharmacopoeia (Ph.Eur*.). The drug substance is a white or almost white, crystalline powder; very soluble in water, soluble in methanol and slightly soluble in anhydrous ethanol.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacture
An overview of the manufacturing process has been provided for both active substance manufacturers. The manufacturing process has been adequately described. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification has been established in-house by the MAH based on the Ph.Eur. monograph. Additional specifications for residual solvents are laid down. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data of 2 pilot-scale and 1 full-scaled batch have been provided for one ASM. For the other manufacturer, batch analytical data of 3 full-scaled batches have been provided. The data demonstrate compliance with the drug substance specification.

Stability of drug substance
Stability data on the active substance have been provided by the DMF holders. For one manufacturer, batches were stored at 25°C/60%RH (2 batches - 48 months and 1 batch 24 months), 40°C/75%RH (3 batches - 6 months) and 1 batch, stored at 15-25°C (60 months). For the other manufacturer, stability data have been provided for batches stored at 15-25°C (5 batches - 60 months and 1 batch – 36 months) and 40°C/75%RH (3 batches - 6 months). The batches were stored in the packaging of the DMF holder. A retest period of 3 years and no special storage conditions, in the proposed packaging materials has been granted.

* Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.
**Medicinal Product**

**Composition**
The product is an immediate release tablet. One tablet contains: 111.1 mg tiapride hydrochloride, equivalent to 100 mg tiapride.

The product is packaged in PVC/Aluminium blisters. The aluminium contains a PVC/PVAC 5 µm heat seal coating. The blisters are packaged in cardboard boxes. This is a usual packaging for tablets.

The excipients are: Mannitol (E421), microcrystalline cellulose (E460), magnesium stearate (E470b), povidone K30 (E1201), silicone dioxide (E551).

**Pharmaceutical development**
The development of the product has been described, the choice of excipients is justified and their functions explained. The composition of the test product is qualitatively similar to the composition of the innovator reference product. The tablets are considered bioequivalent with the innovator product based upon the closely similar composition and the results of in-vitro studies.

**Dissolution**
Dissolution profiles of the product at issue as well as various EU innovator products (DE, AT, FR, EL) have been established and show similarity. After 45 minutes more than 60%, after 60 minutes more than 70% and after 90 minutes more than 85% is dissolved.

**Excipients**
The excipients comply with Ph. Eur. requirements.

**Manufacturing process**
The manufacturing process has been adequately described in a flow chart and a narrative. A conventional wet granulation process is used.

The manufacturing process was validated with three pilot batches. Although the MAH made a commitment to provide process validation results of the first three production scaled batches, it is not considered necessary that these data will be added to the dossier in due course, since a standard manufacturing process is used for which no problems are expected during scaling up. However, the results of production scaled validation should be held at the disposal of the Inspectorate.

**Quality control of drug product**
The product specification includes tests for appearance, average weight, uniformity of weight, hardness, friability, loss on drying, disintegration time, dissolution, identification, assay, uniformity of content, degradation, residual solvents and microbiological purity. Based on the stability data, the shelf-life requirements are widened for hardness and dissolution. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 6 pilot scaled batches, demonstrating compliance with the release specification. The MAH has committed to provide the analytical results of production-scaled batches as soon as available.

**Stability of the finished product**
Stability data on the product has been provided for 3 pilot scaled batches stored at 25°C/60% RH (36 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the intended PVC/Al blisters. At 25°C, 30°C and at 40°C the products show increase in hardness of the tablets, but remain within specification during the test periods.

Based on the presented data, a shelf-life of 3 years and no special storage condition, is acceptable in view of the available stability data. The MAH has committed to submit the stability results of production-scaled batches in due course.
Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded. A statement is present that magnesium stearate is from vegetable origin.

II.2 Non clinical aspects

This product is a generic formulation of Tiapridal, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of tiapride released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Tiapride is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Tiapride Ratiopharm 100 mg tablets (Ratiopharm GmbH, Germany) is compared with the pharmacokinetic profile of the German reference product Tiapridex 100 mg tablets (Synthelabo Arzneimittel GmbH, Germany).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results of reference products in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study
A single-dose, randomised, two-way cross-over bioequivalence study was carried out under fasted conditions in 28 healthy male volunteers, aged 18-55 years. Each subject received a single dose (100 mg) of one of the 2 tiapride formulations. The tablet was orally administered with 240 ml water after a 10 h fasting period. For each subject there were 2 dosing periods, separated by a washout period of 7 days. Blood samples were collected predose and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours after administration of the products.

Two subjects did not complete the study due to study protocol violation. Twenty-six subjects were therefore eligible for pharmacokinetic analysis.

The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The long term stability data are covering the storage period of the plasma samples.

Tiapride tablets should preferably be taken with a little liquid after meals. From the literature it is known that food does not interact with the absorption of tiapride. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.
**Results**

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, \(t_{\text{max}}\) (median, range)) of tiapride under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>(\text{AUC}_{0-t}) ng.h/ml</th>
<th>(\text{AUC}_{0-\infty}) ng.h/ml</th>
<th>(C_{\text{max}}) ng/ml</th>
<th>(t_{\text{max}}) h</th>
<th>(t_{1/2}) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>3708 ± 664</td>
<td>3830 ± 703</td>
<td>611 ± 152</td>
<td>1.67</td>
<td>3.7 ± 0.7</td>
</tr>
<tr>
<td>Reference</td>
<td>3674 ± 629</td>
<td>3763 ± 665</td>
<td>632 ± 173</td>
<td>1.67 (0.50 – 4.0)</td>
<td>3.7 ± 0.8</td>
</tr>
<tr>
<td><em>Ratio (90% CI)</em></td>
<td>1.01 (0.98 – 1.03)</td>
<td>1.01 (0.98 – 1.03)</td>
<td>0.97 (0.90 – 1.05)</td>
<td>---</td>
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<tr>
<td>CV (%)</td>
<td>5.1</td>
<td>4.7</td>
<td>15.9</td>
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</tr>
</tbody>
</table>

*In-transformed values

The 90% confidence intervals calculated for \(\text{AUC}_{0-t}\), \(\text{AUC}_{0-\infty}\) and \(C_{\text{max}}\) are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of tiapride under fasted conditions, it can be concluded that Tiapride Ratiopharm 100 mg and the reference product Tiapridex 100 mg are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

**Risk management plan**

Tiapride was first approved in 1981, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of tiapride can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

**Product information**

**SPC**

The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the innovator product Tiapridal marketed by Sanofi-Aventis.

**Readability test**

At the time of the start of the MRP (31 August 2005) a readability test was not required. Therefore, no readability test was performed by the MAH.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Tiapride Ratiopharm 100 mg tablets have a proven chemical-pharmaceutical quality and are a generic form of Tiapridal. Tiapridal is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the innovator product. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other tiapride containing products.

The Board followed the advice of the assessors. Tiapride Ratiopharm was authorised in the Netherlands on 15 June 2005.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Tiapride Ratiopharm 100 mg with the reference product, and has therefore granted a marketing authorisation. The mutual recognition procedure was finished on 29 November 2005.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from 29 November 2005 to 29 November 2008.

The date for the first renewal will be: 29 November 2010.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product
- The MAH has committed to provide the analytical results of production-scaled batches as soon as available.
- The MAH has committed to submit the stability results of production-scaled batches in due course.
List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
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<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
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<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
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<tr>
<td>BP</td>
<td>British Pharmacopoeia</td>
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<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum plasma concentration</td>
</tr>
<tr>
<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
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<tr>
<td>EDMF</td>
<td>European Drug Master File</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<tr>
<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
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<tr>
<td>OTC</td>
<td>Over The Counter (to be supplied without prescription)</td>
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<tr>
<td>PAR</td>
<td>Public Assessment Report</td>
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<tr>
<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
</tr>
<tr>
<td>PIL</td>
<td>Package Leaflet</td>
</tr>
<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>t&lt;sub&gt;½&lt;/sub&gt;</td>
<td>Half-life</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Time for maximum concentration</td>
</tr>
<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
</tr>
<tr>
<td>USP</td>
<td>Pharmacopoeia in the United States</td>
</tr>
</tbody>
</table>
### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal of the marketing authorization in Hungary on 27 October 2005.</td>
<td>NL/H/0664/001/MR</td>
<td>Withdrawal</td>
<td>---</td>
<td>27-10-2005</td>
<td>---</td>
<td>N</td>
</tr>
<tr>
<td>Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. Solid pharmaceutical forms, e.g. tablets and capsules.</td>
<td>NL/H/0664/001/IA/001</td>
<td>IA</td>
<td>6-1-2006</td>
<td>20-1-2006</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a site where batch control/testing takes place.</td>
<td>NL/H/0664/001/IA/002</td>
<td>IA</td>
<td>6-1-2006</td>
<td>20-1-2006</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>Change in test procedure of the finished product. Other changes to a test procedure, including replacement or addition of a test procedure.</td>
<td>NL/H/0664/001/IB/003</td>
<td>IB</td>
<td>4-4-2006</td>
<td>4-5-2006</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>Request for change in the product information following a PhVWP/ CMD(h) decision: - Implementation of warning on risk of venous thromboembolism. - Implementation of warnings on increased mortality in elderly people with dementia for all conventional antipsychotics following CHMP art. 5(3) referral.</td>
<td>NL/H/0664/001/II/004</td>
<td>II</td>
<td>5-1-2010</td>
<td>22-3-2010</td>
<td>Approval</td>
<td>N</td>
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