Public Assessment Report

Scientific discussion

Tolterodinetartraat Aurobindo SR 2 mg and 4 mg prolonged-release capsules, hard

(tolterodine L-tartrate)

NL/H/4306/001-002/DC

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This module reflects the scientific discussion for the approval of Tolterodinetartraat Aurobindo SR 2 mg and 4 mg, prolonged-release capsules, hard. The procedure was finalised on 20 June 2012. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Tolterodinetartraat Aurobindo SR 2 mg and 4 mg, prolonged-release capsules, hard, from Aurobindo Pharma B.V.

The product is indicated for symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Detrusitol film-coated tablets, 1 mg, which has been registered in Sweden by Pfizer AB since 5 September 1997. In the Netherlands, Detrusitol SR 2 mg and 4 mg, prolonged-release capsules, hard, has been registered since 4 September 2001 by procedure SE/H/0139/003.

The concerned member state (CMS) involved in this procedure was Spain.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Tolterodinetartraat Aurobindo SR is a prolonged-release capsule, hard.

And contains as active substance 2 mg or 4 mg of tolterodine tartrate.

The capsules are packed in:
Blister packs made of polyvinyl chloride (PVC), polyethylene (PE), polyvinylidene chloride (PVDC) and aluminium foil.
White opaque bottles made of high-density polyethylene (HDPE) with a screw cap.

The excipients are:
Capsule content - lactose monohydrate, cellulose microcrystalline, poly (vinyl acetate), povidone, silica, sodium laurilsulfate, docusate sodium, magnesium stearate (E470b) and hydroxypropylmethylcellulose.
Capsule itself – indigo carmine (E132), titanium dioxide (E171) and gelatin.
Capsule coating – ethylcellulose, triethyl citrate, methacrylic acid – ethyl acrylate copolymer and 1,2-propylene glycol.

II.2 Drug Substance

The active substance is tolterodine L-tartrate, which is not subject of a European Pharmacopoeia (Ph.Eur.) monograph. It is a white or almost white powder. Tolterodine L-tartrate is soluble in methanol, slightly soluble in ethanol and water. It has one chiral centre and exhibits enantiomerism. The drug substance is the L-isomer. Tolterodine L-tartrate does not exhibit polymorphism.

Manufacturing process
Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

Quality control of drug substance
An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Stability of drug substance
Stability studies have been performed with the active substance and no significant changes of the parameters were observed. On the basis of the results, a suitable re-test period could be approved.

II.3 Medicinal Product

Pharmaceutical development
The objective of the development programme was to produce safe, efficacious products containing tolterodine L-tartrate that could considered generic medicinal products of Detrusitol XL 2 mg and 4 mg prolonged-release capsules, hard.

The MAH has provided suitable product development sessions. Valid justifications for the use and amounts of each excipient have been provided.

Comparative dissolution and impurity profiles have been provided for the proposed and reference products.

The reference product used in the bioequivalence studies was Detrusitol Retard 4 mg prolonged-release capsules, sourced from Italy. This product is considered to be pharmaceutically equivalent to the UK reference product.

Manufacturing process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. Process validation data on production-scale batches of each strength have been provided and are satisfactory. The MAH has committed to perform process validation on future commercial batches.

Control of excipients
With the exception of quinolone yellow (E104), all excipients comply with their respective Ph.Eur. Monographs. Quinolone yellow complies with specifications wet by the United Nations (UN) Food and Agriculture Organisation (FAO).
These specifications are acceptable.

Quality control of drug product
The finished product specifications are acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for any working standards used.

Stability of drug product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 24 months and an in-use shelf life of 200 days for the HDPE bottle pack only. The storage instructions are ‘Do not store above 25°C’.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
With the exception of lactose monohydrate and gelatin, non of the excipients used contain material of animal or human origin. Transmissible spongiform encephalopathy (TSE) Certificates of Suitability have been provided for gelatin. A declaration has been provided that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption. Confirmation has been provided that the magnesium stearate used is of vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

From a quality point of view, it is recommended that Marketing Authorisations are granted for these applications.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamics, pharmacokinetics and toxicological properties of tolterodine tartrate are well-known. No new non-clinical studies have been performed which is acceptable given that the products contain a widely-used , well-known active substance. The provided overview based on literature is satisfactory.

III.2 Pharmacology

Not applicable for this product type.

III.1 Pharmacokinetics

Not applicable for this product type.

III.1 Toxicology

Not applicable for this product type.

Residual solvents and impurities
Based on the maximum dose, the proposed limits for impurities within the drug substance and drug product all comply with ICH Q3A (R2) and ICH Q3B(R2), respectively. The proposed limit for heavy metals within the drug substance is acceptable.

III.2 Ecotoxicity/environmental risk assessment (ERA)

A satisfactory justification has been provided for the absence of an Environmental Risk Assessment.

III.3 Discussion on the non-clinical aspects

From a non-clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.

IV. CLINICAL ASPECTS

IV.1 Introduction

Clinical Pharmacology
Data from three clinical studies have been provided to support the applications and prove bioequivalence. Two standard single bioequivalence studies in the fed and fasting states and a multiple dose study were carried out.

IV.2 Pharmacokinetics

Bioequivalence study 1
A multiple-dose, two-stage, crossover comparative bioavailability study to compare the pharmacokinetics of the test product Tolterodinetartraat Aurobindo SR 4 mg prolonged-release

capsules versus the reference product Detrusitol Retard 4 mg prolonged-release capsules in healthy subjects in a steady state.

Blood samples were taken pre- and up to 24 hours post dose. The washout period between each treatment period was seven days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for tolterodine and its metabolite, 5 hydroxymethyl tolterodine are presented below as log-transformed values for geometric means:

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tolterodine.

Treatment	AUC_{0-t} pg.h/ml	C_{min} pg/ml	C_{max} pg/ml
Test	21330.0	425.6	1801.5
Reference	20153.3	398.9	1714.2
T/R Ratio (95% CI)	1.06 (0.99 – 1.13)	1.07 (0.95 – 1.20)	1.05 (0.96 – 1.15)
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{min} minimum plasma concentration C_{max} maximum plasma concentration			

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 5-hydroxymethyl tolterodine.

Treatment	AUC_{0-t} pg.h/ml	C_{min} pg/ml	C_{max} pg/ml
Test	25503.1	617.5	1933.7
Reference	24396.6	591.2	1873.3
T/R Ratio (95% CI)	1.05 (1.00 – 1.10)	1.04 (0.96 – 1.14)	1.03 (0.96 – 1.11)
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{min} minimum plasma concentration C_{max} maximum plasma concentration			

The criteria for bioequivalence was based on 95% confidence interval, which is acceptable as a two-stage approach has been applied to demonstrate bioequivalence.

The results for the primary variables indicated that the 95% confidence intervals test/reference ration of geometric means for AUC_{0-t}, C_{min} and C_{max} for tolterodine and its metabolite, 5 hydroxymethyl tolterodine lie within acceptable limits (80-125%). Thus, bioequivalence has been shown between the test and reference products in this study.

Bioequivalence study 2

A multiple-dose, two-stage, crossover comparative bioavailability study to compare the pharmacokinetics of the test product Tolterodinetartraat Aurobindo SR 4 mg prolonged-release capsules versus the reference product Detrusitol Retard 4 mg prolonged-release capsules in healthy subjects in a fed state.

Blood samples were taken pre-and up to 60 hours post dose. The washout period between each treatment period was 7 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for tolterodine and its metabolite, 5 hydroxymethyl tolterodine are presented below as log-transformed values for geometric means.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tolterodine.

Treatment	AUC_{0-t} pg.h/ml	C_{min} pg/ml	C_{max} pg/ml
Test	25502.5	34414.8	1566.2
Reference	23164.1	31937.7	1584.0
T/R Ratio (90% CI)	1.10 (0.99 – 1.22)	1.08 (0.97 – 1.20)	0.99 (0.84 – 1.17)
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{min} minimum plasma concentration C_{max} maximum plasma concentration			

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tolterodine.

Treatment	AUC_{0-t} pg.h/ml	C_{min} pg/ml	C_{max} pg/ml
Test	25502.5	34414.8	1566.2
Reference	23164.1	31937.7	1584.0
T/R Ratio (95% CI)	1.10 (0.97 – 1.24)	1.08 (0.94 – 1.23)	0.98 (0.81 – 1.21)
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{min} minimum plasma concentration C_{max} maximum plasma concentration			

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 5-hydroxymethyl tolterodine.

Treatment	AUC_{0-t} pg.h/ml	C_{min} pg/ml	C_{max} pg/ml
Test	30027.1	31163.2	1684.1
Reference	28699.9	30017.5	1704.7
T/R Ratio (90% CI)	1.05 (0.97 – 1.12)	1.04 (0.97 – 1.11))	0.99 (0.87 – 1.12)
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{min} minimum plasma concentration C_{max} maximum plasma concentration			

Table 6. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 5-hydroxymethyl tolterodine.

Treatment	AUC_{0-t} pg.h/ml	C_{min} pg/ml	C_{max} pg/ml
Test	30027.1	31163.2	1684.1
Reference	28699.9	30017.5	1704.7
T/R Ratio (95% CI)	1.05 (0.96 – 1.14)	1.04 (0.95 – 1.13)	0.99 (0.85 – 1.15)
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{min} minimum plasma concentration C_{max} maximum plasma concentration			

Results have been provided for the 90% and 95% confidence interval for AUC_{0-t}, C_{min} and C_{max} for tolterodine and its metabolite, 5 hydroxymethyl tolterodine.

The results for the primary variables indicated that the 90% and 95% confidence intervals test/reference ratio of geometric means for AUC_{0-t}, C_{min} and C_{max} for tolterodine and its metabolite, 5 hydroxymethyl tolterodine lie within acceptable limits (80-125%). Thus, bioequivalence has been shown between the test and reference products in this study.

Bioequivalence study 3

A single-dose, two-stage, crossover comparative bioavailability study to compare the pharmacokinetics of the test product Tolterodinetartraat Aurobindo SR 4 mg prolonged-release capsules versus the reference product Detrusitol Retard 4 mg prolonged-release capsules in healthy subjects in a fasted state.

Blood samples were taken pre-and up to 60 hours post dose. The washout period between each treatment period was 7 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for tolterodine and its metabolite, 5 hydroxymethyl tolterodine are presented below as log-transformed values for geometric means.

Table 7. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tolterodine.

Treatment	AUC_{0-t} pg.h/ml	C_{min} pg/ml	C_{max} pg/ml
Test	19596.8	24395.2	1402.5
Reference	18040.9	22115.0	1346.9
T/R Ratio (90% CI)	1.09 (1.00 – 1.18)	1.10 (1.02 – 1.20)	1.04 (0.95 – 1.15)
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{min}** minimum plasma concentration **C_{max}** maximum plasma concentration			

Table 8. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tolterodine.

Treatment	AUC_{0-t} pg.h/ml	C_{min} pg/ml	C_{max} pg/ml
Test	19596.8	24395.2	1402.5
Reference	18040.9	22115.0	1346.9
T/R Ratio (95% CI)	1.09 (0.99 – 1.19)	1.10 (1.00 – 1.22)	1.04 (0.93 – 1.17)
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{min}** minimum plasma concentration **C_{max}** maximum plasma concentration			

Table 9. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 5-hydroxymethyl tolterodine.

Treatment	AUC_{0-t} pg.h/ml	C_{min} pg/ml	C_{max} pg/ml
Test	27965.9	29173.5	1.666.2

Reference	26923.8	28343.0	1735.7
T/R Ratio (90% CI)	1.04 (0.98 – 1.10)	1.03 (0.97 – 1.09))	0.96 (0.89 – 1.03)
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{min}** minimum plasma concentration **C_{max}** maximum plasma concentration			

Table 10. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 5-hydroxymethyl tolterodine.

Treatment	AUC_{0-t} pg.h/ml	C_{min} pg/ml	C_{max} pg/ml
Test	27965.9	29173.5	1666.2
Reference	26923.8	28343.0	1735.7
T/R Ratio (95% CI)	1.04 (0.97 – 1.11)	1.03 (0.96 – 1.10)	0.96 (0.88 – 1.04)
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{min}** minimum plasma concentration **C_{max}** maximum plasma concentration			

Results have been provided for the 90% and 95% confidence interval for AUC_{0-t}, C_{min} and C_{max} for tolterodine and its metabolite, 5 hydroxymethyl tolterodine.

The results for the primary variables indicated that the 90% and 95% confidence intervals test/reference ratio of geometric means for AUC_{0-t}, C_{min} and C_{max} for tolterodine and its metabolite, 5 hydroxymethyl tolterodine lie within acceptable limits (80-125%). Thus, bioequivalence has been shown between the test and reference products in this study.

As the product range meets all the criteria as specified in the Noted for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) for a biowaiver for the other strength, the results and conclusions of the bioequivalence studies on the 4 mg strength can be extrapolated to Tolterodinetartraat Aurobindo 2 mg prolonged-release capsules, hard.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy

No new efficacy data were submitted with these generic applications and none were required.

IV.5 Clinical safety

With the exception of the data submitted during the bioequivalence studies, no new safety data were submitted with these generic applications and none were required. No new or unexpected safety concerns were raised during the bioequivalence studies.

IV.6 Pharmacovigilance System and Risk Management Plan

The RMS considers that the pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A satisfactory justification has been provided for the absence of a Risk Management Plan.

IV.7 Discussion on the clinical aspects

From a clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Article 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

The results show that the package leaflet meets the criteria for readability, as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The important quality characteristics of Tolterodinetartraat Aurobindo SR 2 mg and 4 mg prolonged-release capsules, hard are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

Non-clinical
No new non-clinical data were submitted and none are required for applications of this type.

Clinical
Bioequivalence has been demonstrated between the MAH's Tolterodinetartraat Aurobindo SR 4 mg prolonged-release capsules, hard and the reference product Detrusitol Retard 4 mg prolonged-release capsules. These bioequivalence study results and conclusions can be extrapolated to Tolterodinetartraat Aurobindo SR 2 mg prolonged-release capsules, hard.

No new or unexpected safety concerns arose from the bioequivalence studies.

The SmPCs, PLs and labelling are satisfactory and consistent with those for the reference products, where appropriate.

Benefit-risk assessment
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with tolterodine tartrate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk ration is, therefore, considered to be positive.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse