Public Assessment Report

Decentralised Procedure

MANEO 100 MG, 150 MG AND 200 MG PROLONGED-RELEASE TABLETS

TRAMADOL HYDROCHLORIDE

UK/H/4160/001-003/DC

UK Licence No: PL 17871/0104-6

JENSON PHARMACEUTICAL SERVICES LIMITED
On 6th September 2012, the UK granted Jenson Pharmaceutical Services Limited Marketing Authorisations (licences) for Maneo 100 mg, 150 mg and 200 mg Prolonged-release tablets.

Maneo 100 mg, 150 mg and 200 mg Prolonged-release tablets contain the active ingredient, tramadol hydrochloride, which belongs to a group of medicines called opioids. Opioids act on the central nervous system and relieve pain by acting on specific nerve cells of the spinal cord and brain.

Maneo 100 mg, 150 mg and 200 mg Prolonged-release tablets are used for the treatment of moderate to severe pain in adults and children over 12 years of age.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Maneo 100 mg, 150 mg and 200 mg Prolonged-release tablets outweigh the risks; hence these Marketing Authorisations have been granted.
# TABLE OF CONTENTS

Module 1: Information about procedure  
Page 4

Module 2: Summary of Product Characteristics  
Page 5

Module 3: Product Information Leaflets  
Page 5

Module 4: Labelling  
Page 6

Module 5: Scientific Discussion  
Page 12

1 Introduction  
2 Quality aspects  
3 Non-clinical aspects  
4 Clinical aspects  
5 Overall conclusions

Module 6: Steps taken after initial procedure  
Not applicable
# Module 1

| Product Names                      | Maneo 100 mg Prolonged-release tablets  
|                                  | Maneo 150 mg Prolonged-release tablets  
<table>
<thead>
<tr>
<th></th>
<th>Maneo 200 mg Prolonged-release tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Application</td>
<td>Generic application, Article 10(1)</td>
</tr>
<tr>
<td>Active Substance</td>
<td>Tramadol hydrochloride</td>
</tr>
<tr>
<td>Form</td>
<td>Prolonged-release tablets</td>
</tr>
</tbody>
</table>
| Strengths                         | 100 mg                                  
|                                  | 150 mg                                  
|                                  | 200 mg                                  |
| MA Holder                         | Jenson Pharmaceutical Services Limited  
|                                  | Carradine House, 237 Regents Park Road,  
|                                  | London, N3 3LF United Kingdom           |
| Reference Member State (RMS)      | United Kingdom (UK)                    |
| Concerned Member States (CMS)     | Austria (AT), Belgium (BE), the Czech Republic (CZ), Germany (DE), Denmark (DK), Spain (ES), Finland (FI), France (FR), Italy (IT), the Netherlands (NL), Norway (NO), Portugal (PT), Sweden (SE) and the Slovak Republic (SK). |
| Procedure Numbers                 | UK/H/4160/001/DC                       
|                                  | UK/H/4160/002/DC                       
|                                  | UK/H/4160/003/DC                       |
| End of Procedure                  | Day 210: 4th July 2012                  |
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

Please note that there is no mock-up available for these products. The marketing authorisation holder has stated that it is not currently intending to market the products and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK labelling for review to the regulatory authority before marketing the products. The labelling text for PL 17871/0104 is shown below as an example.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Maneo 100 mg Prolonged-release tablets
tramadol hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg of tramadol hydrochloride

3. LIST OF EXCIPIENTS

Also contains: Lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release tablets

10 Prolonged-release tablets.
20 Prolonged-release tablets.
28 Prolonged-release tablets.
30 Prolonged-release tablets.
50 Prolonged-release tablets.
56 Prolonged-release tablets.
60 Prolonged-release tablets.
90 Prolonged-release tablets.
100 Prolonged-release tablets.
500 Prolonged-release tablets.
1000 Prolonged-release tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

No special storage conditions required.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER

Jenson Pharmaceutical Services Limited
Carradine House, 237 Regents Park Road, London, N3 3LF
United Kingdom

12. MARKETING AUTHORIZATION NUMBER (S)

PL 17871/0104

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Manco 100mg tablets
| PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING |
| HDPE BOTTLE WITH POLYPROPYLENE SCREW CLOSURE - DISPENSING PACKAGE |

| 1. NAME OF THE MEDICINAL PRODUCT |
| Maneo 100 mg Prolonged-release tablets |
| tramadol hydrochloride |

| 2. STATEMENT OF ACTIVE SUBSTANCE(S) |
| Each tablet contains 100 mg of tramadol hydrochloride |

| 3. LIST OF EXCIPIENTS |
| Also contains: Lactose. See leaflet for further information. |

| 4. PHARMACEUTICAL FORM AND CONTENTS |
| Dispensing Package |
| Prolonged-release tablets |
| 500 prolonged-release tablets. |
| 1000 prolonged-release tablets. |

| 5. METHOD AND ROUTE(S) OF ADMINISTRATION |
| For oral use. Read the package leaflet before use. |

| 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN |
| Keep out of the sight and reach of children. |

| 7. OTHER SPECIAL WARNING(S), IF NECESSARY |

| 8. EXPIRY DATE |
| EXP: |

| 9. SPECIAL STORAGE CONDITIONS |
| No special storage conditions required. |

| 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE |

| 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER |
| Jenson Pharmaceutical Services Limited |
12. MARKETING AUTHORISATION NUMBER(S)

PL 17871/0104

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Maneo 100mg tablets
PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING
HDPE BOTTLE WITH POLYPROPYLENE CHILD RESISTANT CLOSURE

1. **NAME OF THE MEDICINAL PRODUCT**

Maneo 100 mg Prolonged-release tablets
tramadol hydrochloride

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 100 mg of tramadol hydrochloride

3. **LIST OF EXCIPIENTS**

Also contains: Lactose. See leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

Prolonged-release tablets

100 prolonged-release tablets.

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

For oral use. Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP:

9. **SPECIAL STORAGE CONDITIONS**

No special storage conditions required.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Limited
Carradine House, 237 Regents Park Road, London, N3 3LF
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 17871/0104

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Maneo 100 mg tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Al/OPA/PVC & PVC/PE/PVDC BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Maneo 100 mg Prolonged-release tablets tramadol hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Limited
Carradine House, 237 Regents Park Road, London, N3 3LF
United Kingdom

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. OTHER

Not applicable
Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Austria, Belgium, the Czech Republic, Germany, Denmark, Spain, Finland, France, Italy, the Netherlands, Norway, Portugal, Sweden, the Slovak Republic and the UK considered that the applications for Maneo 100 mg, 150 mg and 200 mg Prolonged-release tablets (PL 17871/0104-6; UK/H/4160/001-3/DC) could be approved.

Maneo 100 mg, 150 mg and 200 mg Prolonged-release tablets are prescription only medicines (POM) and are indicated for the treatment of moderate to severe pain.

These applications for Maneo 100 mg, 150 mg and 200 mg Prolonged-release tablets were submitted according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Tramal long 100 mg, 150 mg and 200 mg Retardtabletten, authorised in Germany to Grünenthal GmbH on 22nd May 1996. The UK reference products are Zydol SR 100 mg, 150 mg and 200 mg Prolonged-release tablets, originally authorised to Monsato PLC on 1st January 1996 (PL 08821/0003-1). These licences underwent a change of ownership to Grunenthal Limited on 1st December 2004 (PL 21727/0003-5).

Tramadol is a synthetic, centrally acting analgesic agent with 2 distinct but complementary mechanisms of action. It acts as an opioid agonist with selectivity for the µ-receptor and also binds weakly to κ- and δ-receptors. Tramadol is indicated for treatment of moderate to severe pain in doses of maximum 200 mg twice daily.

No new non-clinical studies have been performed which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies, with the exception of the bioequivalence studies, have been performed, which is acceptable given that the applications were for products that are intended to be generic medicinal products of reference products that have been licensed for over 10 years. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
### II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Maneo 100 mg Prolonged-release tablets  
Maneo 150 mg Prolonged-release tablets  
Maneo 200 mg Prolonged-release tablets |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Tramadol hydrochloride</td>
</tr>
</tbody>
</table>
| Pharmacotherapeutic classification (ATC code)     | Other opioids  
ATC code: N 02 AX 02                                                             |
| Pharmaceutical form and strength(s)              | 100 mg Prolonged-release tablets  
150 mg Prolonged-release tablets  
200 mg Prolonged-release tablets |
| Reference numbers for the Decentralised Procedure | UK/H/4160/001/DC  
UK/H/4160/002/DC  
UK/H/4160/003/DC |
| Reference Member State                           | United Kingdom (UK)                                                             |
| Member States concerned                          | Austria (AT), Belgium (BE), the Czech Republic (CZ), Germany (DE), Denmark (DK), Spain (ES), Finland (FI), France (FR), Italy (IT), the Netherlands (NL), Norway (NO), Portugal (PT), Sweden (SE) and the Slovak Republic (SK). |
| Marketing Authorisation Number(s)                | PL 17871/0104  
PL 17871/0105  
PL 17871/0106 |
| Name and address of the authorisation holder      | Jenson Pharmaceutical Services Limited  
Carradine House,  
237 Regents Park Road,  
London,  
N3 3LF  
United Kingdom |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Tramadol hydrochloride

Chemical name: (1RS,2RS)-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride

Structural formula:

![Structural formula of Tramadol hydrochloride]

Molecular formula: C_{16}H_{25}ClNO_{2}

Appearance: White crystalline powder

Solubility: freely soluble in water and in methanol but only very slightly soluble in acetone

Molecular weight: 299.8

The tramadol hydrochloride used in the product complies with the European Pharmacopoeia monograph for tramadol hydrochloride.

All aspects of the manufacture of the active substance from its starting materials are controlled by a Certificate of Suitability.

All potential known impurities have been identified and characterised.

An appropriate specification with suitable test methods and limits is provided for the active substance. The methods of testing and limits for residual solvents are in compliance with current guidelines. Suitable Certificates of Analysis have been provided for all reference and impurity standards used. Batch analysis data are provided and comply with the proposed specification.

The container closure system and stability of the active substance are all as specified by the Certificate of Suitability. This is satisfactory.
P. Medicinal Product

Other Ingredients

Other ingredients in the tablet cores consist of pharmaceutical excipients microcrystalline cellulose, hypromellose, colloidal ahydrous silica, magnesium stearate.

The ingredients in the film-coating are hypromellose (E464), lactose monohydrate, talc (E553 b), macrogol, propylene glycol (E1520) and titanium dioxide (E171).

The 150 mg strength has the additional excipients iron oxide red (E172), iron oxide brown (E172) and lake quinoline yellow (E104).

The 200 mg strength has the additional excipients iron oxide red (E172) and lake quinoline yellow (E104).

With the exception of the excipients iron oxide red (E172), iron oxide brown (E172) and lake quinoline yellow (E104), all excipients in the tablet cores comply with their respective European Pharmacopoeia monographs.

Iron oxide brown (E172) and lake quinoline yellow (E104) comply with in-house specifications. Iron oxide red (E172) complies with the National Formulary (NF) monograph. All comply with EU Directives concerning the use of colouring agents.

None of the excipients used contain material of animal or human origin. Confirmation has been provided that the magnesium stearate used is of vegetable origin.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to produce safe, efficacious products containing tramadol hydrochloride that could be considered generic medicinal products of Tramal long 100 mg, 150 mg and 200 mg Prolonged-release tablets.

The applicant has provided suitable product development sections. 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.

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 batches of each strength have been provided and are satisfactory. The applicant has committed to perform process validation on future commercial-scale batches.

Finished Product Specification

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.
Container-Closure System
The products are packaged in:

i) High-density polyethylene (HDPE) bottles with polypropylene (PP) child-resistant closures containing 100 prolonged-release tablets.

ii) HDPE bottles with polypropylene screw-cap closures containing 500 and 1000 prolonged-release tablets (Dispensing package).

iii) Blisters composed of aluminium (Al), oriented polyamide (OPA), polyvinyl chloride (PVC), polyethylene (PE) and polyvinylidene chloride (PVDC) in cardboard cartons containing 10, 20, 28, 30, 50, 56, 60, 90 and 100 prolonged-release tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with the relevant EU directives and EU legislation regarding contact with food.

Stability of the 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 2 years with no special storage instructions.

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are pharmaceutically acceptable.

User testing results have been submitted for the PIL for this product. The results indicate that the PIL is in accordance with Article 59 of Council Directive 2001/83/EC, as amended and is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Quality Overall Summary
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
From a quality point of view, it is recommended that Marketing Authorisations are granted for these applications.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of tramadol hydrochloride 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.

Non-Clinical Overview
The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

Impurities
The drug substance is in compliance with the European Pharmacopoeia and has a certificate of suitability so impurities are controlled satisfactorily. Based on the drug products maximum daily dose, the proposed limits for known and unknown impurities are set according to the requirements of ICHQ3B(R2) - Impurities in New Drug Products.

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

Conclusion
From a non-clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
III.3 CLINICAL ASPECTS
Clinical Pharmacology

With the exception of the following bioequivalence studies, no new pharmacokinetic or pharmacodynamic data were submitted with these applications and none were required. To support the application, data has been provided for five bioequivalence studies (single dose fasting 100/150/200 mg; single dose fed 100 mg; steady state fasting 100 mg).

Pharmacokinetics

Bioequivalence study 1

A randomised, open-label, two-period, two-treatment, two-sequence, single-dose crossover bioequivalence study to compare the pharmacokinetics of the test product Maneo 100 mg Prolonged-release tablets versus the reference product Tramal long 100 mg Retardtabletten (Grüenthal GmbH, Germany) in healthy subjects under fasting conditions.

Blood samples were taken pre- and up to 48 hours post dose. The washout period between each treatment period was at least 12 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for tramadol hydrochloride are presented below as non-transformed values for geometric means:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC$_{0-t}$ (ng/ml/h)</th>
<th>AUC$_{0-\infty}$ (ng/ml/h)</th>
<th>C$_{max}$ (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (T)</td>
<td>4053.153</td>
<td>4154.216</td>
<td>252.251</td>
</tr>
<tr>
<td>Reference (R)</td>
<td>3769.319</td>
<td>3863.3187</td>
<td>227.843</td>
</tr>
</tbody>
</table>

*T/R Ratio *(90 % CI)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC$_{0-t}$ (ng/ml/h)</th>
<th>AUC$_{0-\infty}$ (ng/ml/h)</th>
<th>C$_{max}$ (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (T)</td>
<td>(108.69)</td>
<td>(108.71)</td>
<td>(110.90)</td>
</tr>
<tr>
<td>Reference (R)</td>
<td>(100.85 – 117.13)</td>
<td>(100.84 – 117.19)</td>
<td>(110.39 – 117.83)</td>
</tr>
</tbody>
</table>

AUC$_{0-t}$ area under the plasma concentration-time curve from time zero to t hours
AUC$_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C$_{max}$ maximum plasma concentration

The results for the primary variables indicated that the 90 % confidence intervals test/reference ratio of geometric means for AUC$_{0-t}$ and C$_{max}$ for tramadol hydrochloride lie within acceptable limits (80-125 %). Thus, bioequivalence has been shown between the test and reference products in this study.

Bioequivalence study 2

A randomised, open-label, two-period, two-treatment, two-sequence, single-dose crossover bioequivalence study to compare the pharmacokinetics of the test product Maneo 100 mg Prolonged-release tablets versus the reference product Tramal long 100 mg Retardtabletten (Grüenthal GmbH, Germany) in healthy subjects under fed conditions.
Blood samples were taken pre- and up to 48 hours post dose. The washout period between each treatment period was at least 11 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for tramadol hydrochloride are presented below as non-transformed values for geometric means:

<table>
<thead>
<tr>
<th>Tramadol</th>
<th>Treatment</th>
<th>AUC₀₋ₜ (ng/ml/h)</th>
<th>AUC₀₋∞ (ng/ml/h)</th>
<th>Cₚₐₓ (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (T)</td>
<td>4281.731</td>
<td>4367.234</td>
<td>286.112</td>
<td></td>
</tr>
<tr>
<td>Reference (R)</td>
<td>4189.020</td>
<td>4280.127</td>
<td>273.460</td>
<td></td>
</tr>
<tr>
<td>*T/R Ratio</td>
<td>103.62</td>
<td>103.46</td>
<td>105.99</td>
<td></td>
</tr>
<tr>
<td>*(90 % CI)</td>
<td>(99.13 – 108.30)</td>
<td>(98.89 – 108.24)</td>
<td>(101.50 – 110.68)</td>
<td></td>
</tr>
</tbody>
</table>

* ln-transformed values

The results for the primary variables indicated that the 90 % confidence intervals test/reference ratio of geometric means for AUC₀₋ₜ and Cₚₐₓ for tramadol hydrochloride lie within acceptable limits (80-125 %). Thus, bioequivalence has been shown between the test and reference products in this study.

**Bioequivalence study 3**

A randomised, open-label, two-period, two-treatment, two-sequence, steady state crossover bioequivalence study to compare the pharmacokinetics of the test product Maneo 100 mg Prolonged-release tablets versus the reference product Tramal long 100 mg Retardtabletten (Grüenthal GmbH, Germany) in healthy subjects under fasting conditions.

Blood samples were taken pre- and up to 24 hours post dose. The washout period between each treatment period was at least 13 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for tramadol hydrochloride are presented below as non-transformed values for geometric means:

<table>
<thead>
<tr>
<th>Tramadol</th>
<th>Treatment</th>
<th>AUCₜ₋ss (ng/ml/h)</th>
<th>Cₚₐₓ₋ss (ng/ml)</th>
<th>Cₘᵢₙ₋ss (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (T)</td>
<td>4822.000</td>
<td>317.089</td>
<td>85.502</td>
<td></td>
</tr>
<tr>
<td>Reference (R)</td>
<td>4706.451</td>
<td>301.321</td>
<td>88.216</td>
<td></td>
</tr>
<tr>
<td>*T/R Ratio</td>
<td>102.79</td>
<td>105.08</td>
<td>99.41</td>
<td></td>
</tr>
<tr>
<td>*(90 % CI)</td>
<td>(99.77 – 105.91)</td>
<td>(101.70 – 108.56)</td>
<td>(93.20 – 106.03)</td>
<td></td>
</tr>
</tbody>
</table>

* ln-transformed values

The results for the primary variables indicated that the 90 % confidence intervals test/reference ratio of geometric means for AUC₀₋ₜ and Cₚₐₓ for tramadol hydrochloride lie within acceptable limits (80-125 %). Thus, bioequivalence has been shown between the test and reference products in this study.
**Bioequivalence study 4**

An open-label, balanced, randomised, two-treatment, two-period, two-sequence, crossover, single-dose, bioequivalence study to compare the pharmacokinetics of the test product Maneo 150 mg Prolonged-release tablets versus the reference product Tramal long 150 mg Retardtabletten (Grünenthal GmbH, Germany) in healthy subjects under fasting conditions.

Blood samples were taken pre- and up to 48 hours post dose. The washout period between each treatment period was 17 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for tramadol hydrochloride are presented below as non-transformed values for geometric means:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} (ng/ml/h)</th>
<th>AUC_{0-∞} (ng/ml/h)</th>
<th>C_max (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (T)</td>
<td>4416.36</td>
<td>4497.86</td>
<td>273.66</td>
</tr>
<tr>
<td>Reference (R)</td>
<td>4526.00</td>
<td>4616.70</td>
<td>298.91</td>
</tr>
<tr>
<td>*T/R Ratio</td>
<td>97.58</td>
<td>97.43</td>
<td>91.55</td>
</tr>
<tr>
<td>*(90 % CI)</td>
<td>(94.18 – 101.10)</td>
<td>(93.99 – 100.99)</td>
<td>(87.57 – 95.72)</td>
</tr>
</tbody>
</table>

* ln-transformed values

The results for the primary variables indicated that the 90 % confidence intervals test/reference ratio of geometric means for AUC_{0-1} and C_max for tramadol hydrochloride lie within acceptable limits (80-125 %). Thus, bioequivalence has been shown between the test and reference products in this study.

**Bioequivalence study 5**

An open-label, balanced, randomised, two-treatment, two-period, two-sequence, crossover, single-dose, bioequivalence study to compare the pharmacokinetics of the test product Maneo 200 mg Prolonged-release tablets versus the reference product Tramal long 200 mg Retardtabletten (Grünenthal GmbH, Germany) in healthy subjects under fasting conditions.

Blood samples were taken pre- and up to 48 hours post dose. The washout period between each treatment period was 14 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.
Results for tramadol hydrochloride are presented below as non-transformed values for geometric means:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC₀₋ₜ (ng/ml/h)</th>
<th>AUC₀₋∞ (ng/ml/h)</th>
<th>Cₘₐₓ (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (T)</td>
<td>7285.68</td>
<td>7446.73</td>
<td>430.46</td>
</tr>
<tr>
<td>Reference (R)</td>
<td>7290.23</td>
<td>7432.79</td>
<td>474.65</td>
</tr>
<tr>
<td>*T/R Ratio</td>
<td>99.94</td>
<td>100.19</td>
<td>90.69</td>
</tr>
<tr>
<td>*(90 % CI)</td>
<td>(97.34 – 102.61)</td>
<td>(97.54 – 102.91)</td>
<td>(86.33 – 95.27)</td>
</tr>
</tbody>
</table>

* In-transformed values

The results for the primary variables indicated that the 90 % confidence intervals test/reference ratio of geometric means for AUC₀₋ₜ and Cₘₐₓ for tramadol hydrochloride lie within acceptable limits (80-125 %). Thus, bioequivalence has been shown between the test and reference products in this study.

Bioequivalence has been shown in steady state, fasted and fed studies with the lowest dose, of 100 mg. The results of the final studies show bioequivalence of the test and reference products at the 150 mg and 200 mg strengths, in the fasted state after single dose only. This is satisfactory as the pharmacokinetics of tramadol are linear over the product range and there is little effect of food on the pharmacokinetic profile.

As the product range meet all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) for a biowaiver for the other strengths, the results and conclusions of the bioequivalence studies in the steady and fed state on the 100 mg strength can be extrapolated to Maneo 150 mg and 200 mg Prolonged-release tablets.

**Efficacy**

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

**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.

**The Pharmacovigilance System and Risk Management Plan**

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant 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.
Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are clinically satisfactory and consistent with those for the reference products, where appropriate.

Clinical Overview
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA Forms
The MAA forms are clinically satisfactory.

Conclusions
From a clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Maneo 100 mg, 150 mg and 200 mg Prolonged-release tablets 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 in fasted studies between the applicant’s Maneo 150 mg and 200 mg Prolonged-release tablets and the reference product Tramal long 150 mg and 200 mg Retardtabletten.

Bioequivalence has been demonstrated in steady state, fed and fasted between the applicant’s Maneo 100 mg Prolonged-release tablets and the reference product Tramal long 100 mg Retardtabletten. The bioequivalence study results and conclusions from the steady state and fed studies can be extrapolated to Maneo 150 mg and 200 mg Prolonged-release tablets.

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

The SmPCs, PIL 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 tramadol hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk ratio is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>