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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Tramadol Duiven retard 100/150/200 mg modified release tablets I.C.C.B.V. Duiven

tramadol (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/539/001- 003/MR
Registration number in the Netherlands: RVG 30577-9

13 January 2011

Pharmacotherapeutic group:	analgesics, other opoids
ATC code:	N02AX02
Route of administration:	oral
Therapeutic indication:	moderate to severe pain
Prescription status:	prescription only
Date of first authorisation in NL:	22 March 2004
Concerned Member States:	Mutual recognition procedure with ES, IT, and PT
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 Tramadol Duiven retard 100, 150, and 200 mg modified release tablets, from I.C.C.B.V. The date of authorisation was on 22 March 2004 in the Netherlands. The product is indicated for the treatment of moderate to severe pain.

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

Tramadol is a centrally acting opioid analgesic. It is a non-selective, partial agonist of μ-, δ- and κ opioid receptors with a higher affinity for μ-receptors. Other mechanisms contributing to the analgesic effect are the inhibition of the neural noradrenaline reuptake, and an enhanced release of serotonin.
Tramadol has an antitussive action. Contrary to morphine tramadol does not suppress respiration in analgetic doses over a large range. The action on the cardiovascular system is minimal. The potency of tramadol is reported to be 1 / 10 to 1 / 6 of morphine.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Tramal retard 100, 150, and 200 mg (NL license RVG 22361-3) which have been registered in the Netherlans by Grünenthal B.V. since 1998 (original product). In addition, reference is made to Tramal 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 products Tramal long and Contramal, registered in France. 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 tramadol hydrochloride is described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is a white or almost white, crystalline powder; freely soluble in water and methanol, slightly soluble in acetone and petroleum ether. Tramadol hydrochloride is a centrally acting analgesic with opioïd agonist properties. The active substance is a racemate consisting of equal amounts of two enantiomers. Two geometric isomers are known: RS,SR-tramadol hydrochloride and RR,SS-tramadol hydrochloride. RR,SS-tramadol hydrochloride is the active isomer. No polymorphism has been observed. The applicant uses the ASMF procedure for one supplier. A Certificate of Suitability (CoS) is granted to the other two suppliers of the active substance.
The Active Substance Master File (ASMF) procedure is used for the active substance from one manufactuerer. 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

By two other manufacturers the CEP procedure is used. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitablity concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Manufacture
A five-step synthesis is presented for the EDMF procedure. 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 applicant based on the Ph. Eur. monograph. Additional specifications for residual solvents and particle size are laid down. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data of all suppliers, demonstrating compliance with the drug substance specification have been provided for.

Stability of drug substance
The granted CEP for one manufacturer mentions a retest period for the drug substance: 3 years, no storage conditions in double PE bags inside a fibre drum.
For the drug substance from the other suppliers stability data are present, justifying a retest period of 5 and 3 years respectively, no storage conditions.

Stability data on the active substance have been provided; 25°C/60%RH (3 batches – 36 months, 1 batch – 18 months, 2 batches – 9 months and 1 batch - 6 months) and 40°C/75%RH (7 batches - 6 months). The drug substance was adequately packed.
From another manufacturer stability data on the active substance have been provided; 25°C/60%RH (3 batches – 60 months, 1 batch – 36 months, 1 batches – 24 months and 1 batch - 12 months) and 40°C/75%RH (3 batches - 6 months). The drug substance was adequately packed.

Medicinal Product

Composition
The product is a modified release tablet. According to the SPC up to 400 mg daily can be used. The product is packaged in PVC/Al blister packs (white opaque or transparent) and in polypropylene bottles with polyethylene lid. This is a usual packaging for tablets.

The excipients are: Calcium hydrogen phosphate dihydrate (E341), Hydroxypropylcellulose (E463), Colloidal anhydrous silica (E551), and Magnesium stearate (E470b).

Pharmaceutical development
The three strengths are proportionally fully identical. The development of the product has been described, the choice of excipients is justified and their functions explained. The composition of the Application product is different to the composition of the innovator reference product, the tablets are considered equivalent with the innovator product with respect to dissolution profile. The excipients comply with Ph. Eur. Requirements.

Manufacturing process
The manufacturing process has been adequately described in a flow chart and a narrative. The tablets are prepared by direct compression. Sufficient details on the manufacture are present. The validation has been focussed on the blend before tabletting. Validation data for the three strengths have been submitted for batches produced at one manufacturing site (10 batches of the 100 mg strength, four batches of the 150 strength and five batches of the 200 mg strength). For another production site, validation data have been submitted for two production scale blends that were divided into three separate batches of the three strengths. The MAH committed to validate a third production scale blend divided over the three strengths in the future. Validation is considered adequate.

Quality control of medicinal product
The product specification for the tablets includes tests for appearance, mean weight, uniformity of dosage units, hardness, identity of drug substance, assay, impurities (TLC and HPLC), dissolution at 1, 2, 4, 6 and 8 hours, and microbial quality. Both release and shelf-life requirements are acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production sites have been provided, demonstrating compliance with the release specification.

Stability tests on the finished product
The tablets have been stored at 25°C/60% RH, 30ºC/60%RH and 40°C/75% RH in all packages. The conditions used in the stability studies are according to the ICH stability guideline. The MAH has used a bracketing/matrixing approach, as the three strengths are fully dose proportional. The tablets appear stable for at least 3 years without a special storage temperature. No significant differences have been observed for the three strengths in the three possible container/closure systems. If stored in open container, the surface texture changes somewhat, probably by water uptake, but no degradation have been observed for the tablets. An in-use stability of 6 months is considered acceptable.

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. Magnesium stearate is vegetable grade. A statement thereto is present.

II.2 Non clinical aspects

This product is a generic formulation of Tramal, 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 tramadol hydrochloride 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

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

For this generic application, the MAH submitted the following bioequivalence studies:

Study 1 - (ZLIP 3): Single dose, three-way study with the 200 mg dose. Each subject received Reference (fasted), Test(fasted), Test (fed) , in random order.
This study provided data regarding bioequivalence to the Innovator product as well as information of the stability under fed condition for the new generic product.

Study 2 - In this multiple-dose study the 200 mg prolonged-release test tablet was compared to Immediate Release Reference product Contramal 50 mg tablets. **This is considered as a supportive study, and therefore is not discussed in detail in this report.**

Study 3 - Single dose bioequivalence study with the 100 mg Test and Reference prolonged-release formulation, under fed conditions.

Study 4 - Multiple dose bioequivalence study with the 100 mg Test and Reference prolonged-release formulation, under fasted conditions.

Regulatory history
Tramadol HCl Duiven retard was registered in NL in 2004, based on the 200 mg studies only (Study 1 & 2). As no food effect was observed for the 200 mg test tablet, bioequivalence between test and reference product (Tramal Long, Grünental) was not further studied under fed conditions. For this Mutual Recoginition Procedure, the MAH however performed additional bioequivalence studies on the 100 mg dose under fed conditions, and a multiple dose study with the 100 mg strength under fasted conditions. Based on Study 1-4, the MAH applied for marketing authorization for this generic product.

The choice of the reference product
The choice of the reference products in the bioequivalence studies has been justified by comparison of dissolution results and compositions of reference products (if applicable) in different member states, except for Study 2.

The formula and preparation of the bioequivalence batches were identical to the formula proposed for marketing in all studies.

For all studies, the methods used for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Study 1- Single-dose bioequivalence and food-interaction study with the 200 mg dose

Test: Tramadol HCl Duiven retard 200 mg (I.C.C.B.V., the Netherlands)
Reference: Tramal long 200 mg tablet (Grünenthal, the Netherlands)

A three-way, single-dose, randomised, crossover bioequivalence study was carried out under fed and fasting conditions in 18 healthy volunteers, aged 19 to 38 years. For each subject there were 3 dosing periods, separated by a washout period of at least 7 days.
Each subject received a single dose (200 mg) of one of the 2 tramadol hydrochloride formulations. The tablets were orally administered with 200 ml of water after a 10 hour fasting period. At a different occasion, the test tablet was also administered 30 minutes after the consumption of a high fat content meal. The standardised high fat meal included: 1 pizza of 200 gram, Lebna (yoghurt) with olive oil, fool (Arabic beans) with olive oil, Arabic bread, and 200 ml of mineral water.
Blood samples were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 hours after administration of the products. One subject withdrew, because of adverse events (nausea). Data from 17 subjects were eligible for statistical analysis.

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

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of **tramadol** under **fasted and fed conditions**.

Treatment N=10	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test - fasting	4979 ± 2310	6301 ± 3202	404 ± 176	5.0 (2.0 – 8.0)	9.5 ± 3.9
Test - Fed	5053 ± 1637	6118 ± 2335	386 ± 105	6.0 (2.0 – 10.0)	7.8 ± 2.8
Reference	5188 ± 1874	6393 ± 2924	413 ± 141	5.0 (2.0 – 10.0)	8.4 ± 2.9
***Ratio (90% CI) test/ref**	0.96 (0.83-1.11)	0.95 (0.80 - 1.12)	0.94 (0.81 -1.09)	---	---
***Ratio (90% CI) fasting/fed**	1.00 (0.86-1.15)	1.01 (0.85 - 1.19)	1.00 (0.85 - 1.14)	---	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Conclusion bioequivalence study 1
The 90% confidence interval calculated for C_{max} and AUC are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters , it can be concluded that Tramadol HCl Duiven retard 200 mg and Tramal Long 200 mg, Grünenthal are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

There was no significant food effect. Only t_{max} was prolonged, but this did not result in differences in C_{max}.

Study 3 - Single-dose bioequivalence study under fed conditions with 100 mg dose

Test: Tramadol HCl Duiven retard 100 mg (I.C.C.B.V., the Netherlands)
Reference: Contramal L.P. 100 mg (Laboratoires Grünenthal, France)

A single-dose, randomised, two-way open-label, cross-over bioequivalence study was carried out with blinded bioanalysis under fed conditions in 16 healthy adult male and female volunteers (+4 alternates). Each subject received a single dose (100 mg) of one of the 2 tramadol hydrochloride formulations. The tablets were administered with 200 ml of water, 30 minutes after the consumption of a high-fat standardised meal (two slices of toast with butter (10 g), 2 eggs fried in butter, 2 strips of bacon (40 g), hash brown potatoes (120 g), and 240 mL of whole milk). There were 2 dosing periods, separated by a washout period of at least 6 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 18, 24, 30, 36 and 48 hours after administration of the products at day 1 and 7. Of the 20 randomised subjects, one subject was withdrawn from the study during the wash-out period because of a non-drug-related adverse event (tonsillitis). Nineteen subjects finished the study completely. One subject was considered an outlier based on pharmacokinetical and statistical grounds. In this oulier subject , the plasma exposure of tramadol and its metabolite was considerably lower after the reference product than after the test product. In addition, to keep the group-sequence balanced, two subjects were excluded, conform the protocol. Finally, the MAH considered the dataset of 16 subjects as decisive sample size, but also reported (balanced) data including the outlier (n=18).
However, the assessor did not agree that subjects are excluded for being a statistically outlier. It could not be excluded that differences between the Test and Reference product may cause outlying data. The assessor therefore recalculated bioequivalence parameters for all 19 subject who completed the study using ANOVA. As shown in table 6 and 7 below, the 90% CI of the Test and Reference ratio of C_{max}, AUC_{0-t} and AUC_{0-inf} were within acceptance criteria of 0.80-1.25, even if the “outlier” is included.

Table 6. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of **tramadol** under **fed conditions** (including the outlier)

Treatment N=19	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	2573.4 ± 1043.9	2613.8 ± 1105.4	197.6 ± 51.2	6 (2-8)
Reference	2422.5 ± 604.5	2454 ± 1029.5	189.5 ± 55.0	6 (2-8)
***Ratio (90% CI)**	1.09 (0.95 – 1.24)	1.09 (0.95 – 1.24)	1.06 (0.96 – 1.17)	---
CV (%)	24.2	24.2	17.7	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Table 7. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of **O-demethyl-tramadol** under **fed conditions** (including the outlier.

Treatment N=19	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	585.6 ± 171.2	600.2 ± 173.7	40.5 ± 14.1	7 (3-12)
Reference	582.5 ± 213.4	596.7 ± 213.0	41.4 ± 17.2	7 (2.5-10)
***Ratio (90% CI)**	103.66 (89.9 – 119.3)	104.08 (89.7 – 120.5)	100.4 (88.5 – 113.8)	---
CV (%)	24.8	26.1	22.6	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Conclusion bioequivalence study 3
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25 (with or without outlier). Based on the pharmacokinetic parameters of tramadol under fed conditions, it can be concluded that Tramadol HCl Duiven retard and Contramal L.P. are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance. Bioequivalence was also demonstrated when the sequence factor was not taken into account.

Study 4 - Multiple-dose bioequivalence study under fasting conditions with the 100 mg dose.

Test: Tramadol HCl Duiven retard 100 mg (I.C.C.B.V., the Netherlands)
Reference: Contramal L.P. 100 mg (Laboratoires Grünenthal, France)

A multiple-dose, randomised, two-way open-label, cross-over study bioequivalence study was carried out with blinded bioanalysis under fed conditions in 16 healthy male and female adult volunteers (+4 alternates). Each subject received 6-7 oral doses of 100 mg every 12 hours of either the test or reference tramadol tablet. The tablets were administered with 200 ml of water, under fasting conditions. For each subject there were 2 dosing periods, with overlapping wash-out and build-up period of 72 hours.

Blood samples were collected pre-dose and at 0.25, 0.5, 1.5, 3, 4, 5, 6, 8, 10, 12, hours following the first dose, just before drug administration at t =24, 36, 48, 60, 72 hours, and at t = 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 12 hours after the last dose. All twenty subjects were eligible for pharmacokinetic and statistical analyses.

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

Treatment N=20	**$AUC_{0\text{-}tau}$** ng.h/ml	**C_{max}** ng/ml	**C_{min}** ng/ml	**t_{max}** h	**PTF** %
Test	3004.6 ± 840.7	327.1 ± 89.9	152.8 ± 50.8	4 (2-6)	70.9 ± 11.5
Reference	2988.1 ± 885.0	331.0 ± 89.5	150.4 ± 46.0	5 (3-5.02)	73.7 ± 11.8
***Ratio (90% CI)**	1.01 (0.98 – 1.04)	98.5 (0.95 – 1.02)	1.01 (0.94 – 1.07)	---	0.96 (0.91 – 1.02)
CV (%)	5.7	6.1	11.7	---	9.8

$AUC_{0\text{-}\infty}$ area under the plasma concentration-time curve from time zero to infinity
$AUC_{0\text{-}t}$ area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
PTF pedotransfer functions
^{1} first maximum
^{2} second maximum

**ln-transformed values*

Table 9. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of **O-desmethyl-tramadol** under **fasted conditions**.

Treatment N=20	**$AUC_{0\text{-}tau}$** ng.h/ml	**C_{max}** ng/ml	**C_{min}** ng/ml	**t_{max}** h	**PTF** %
Test	678.0 ± 140.7	68.9 ± 14.2	40.8 ± 10.7	5 (3-9)	50.6 ± 13.6
Reference	670.5 ± 137.7	69.2 ± 13.4	39.7 ± 9.3	5 (3-6)	53.4 ± 13.8
***Ratio (90% CI)**	1.01 (0.98 – 1.05)	0.99 (96.0 – 1.03)	1.02 (0.94 – 1.10)	---	0.95 (0.88 – 1.02)
CV (%)	6.4	6.4	14.6	---	14.2

$AUC_{0\text{-}\infty}$ area under the plasma concentration-time curve from time zero to infinity
$AUC_{0\text{-}t}$ area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
PTF pedotransfer functions
^{1} first maximum
^{2} second maximum

**ln-transformed values*

Conclusion bioequivalence study 4
The 90% confidence intervals calculated for $AUC_{0\text{-}tau}$, C_{min} and C_{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 tramadol under fasted conditions, it can be concluded that Tramadol HCl Duiven retard and Contramal L.P. are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

CMD referral

During the procedure a major objection was raised by two of the Concerned Member States which resulted in a referral to the CMD. The following questions were raised:

1) **100 mg tablets:** For the 100 mg tablets both a single-dose study under fed conditions as well as a multiple dose study under fasting conditions have been performed. According to the *Note for Guidance on the investigation of bioavailability and bioequivalence* and the *Note for guidance on modified release oral and transdermal dosage forms: section II (pharmacokinetic and clinical evaluation)* modified release dosage forms should demonstrate bioequivalence in a single dose study under fasting conditions. The MAH was requested to argue why there is no need for a single dose bio-equivalence study with the 100 mg strength under fasting conditions.
2) **Study 3 (single dose, fed):** The MAH was asked to explain why including or excluding the statistical outlier from this study results in the same conclusion, namely that bio-equivalence has been demonstrated.
3) **200 mg tablets:** The MAH was asked to elaborate on why it is justified to eliminate two subjects from the results of this study and why the remaining 10 subjects are sufficient to demonstrate bio-equivalence (Study 2)
4) The MAH was asked to justify the relevance of this study comparing a prolonged release formulation with immediate release tablets (Study 2).
5) 150 mg tablets: the MAH was asked to justify why no studies had been submitted for the 150 mg strength tablets, and why data from the 100 and 200 mg studies can be extrapolated to the 150 mg tablets.

Question 1-4, regarding the studies with the 100 and 200 mg formulations, were considered as resolved by the CMD; as food had no significant effect on absorption, a bioequivalence study under fed conditions can be considered as valid. A fasted single –dose study is available for the 200 mg strength, and the data could be extrapolated to lower strengths, as the tablets have a dose proportional composition. They only differ in diameter. The tablets are *not* considered as a 'single-unit' formulations where bioequivalence should be demonstrated for each available strength separately, as (a) the prolonged release mechanism consists of swelling of the cellulose matrix and gradual disintegration/erosion by gastric movements, and (b) the tablets have no coating that could influence release mechanism. Absorption and elimination of tramadol is not dose dependent and exposure is linearly related to dose, making extrapolation from 200 to 100 mg dose feasible. The same arguments are applicable for the 150 mg dose.

Regarding the outlier, bioequivalence was shown with and without outlier in Study 3.
This generic product has been broadly marketed in Europe before the start of this Mutual Recognition Procedure. About 25 million tablets of all three strengths had been marketed in Europe without reporting of significant adverse events or conversion problems.

During the CMD meeting April 2007, one CMS proposed that the MAH could perform an *in-vitro in-vivo* correlation (iviv-c) analysis, in order to support a biowaiver of the 150 mg tablets to other strengths. This was supported by another CMS.

Following the Oral Explanation at the April 2007 CMD meeting and the post explanation discussion, the MAH committed to perform a formal IVIVC (*In Vitro In Vivo* Correlation) using the existing data package and to submit this to the RMS and CMS. However, due to lack of formulations with different release mechanism, the IVIV-C model provided could not properly validated. Therefore, the MAH performed another bioequivalence study with the 150 mg prolonged release dose, as a post-approval commitment by means of a type II variation (NL/H/0539/002/II/002). See annex II.

The explanation and arguments provided by the MAH were considered sufficient to resolve the initial concern.

Extrapolation of results
The 100 and 200 mg tablets are dose proportional with the 150 mg tablets. The results of the bioequivalence study performed with the 100 and 200 mg tablets therefore apply to the 150 mg strength.

The MEB has been assured that the bioequivalence studies have 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
A risk management plan is available, although this is not necessarry for this type of application. Routine pharmacovigilance activities are sufficient to identify actual or potential risks.

Product information

SPC
The SPC is identical to the SPC for the MRP procedure NL/H/538/01-03, for which I.C.C. B.V. is also the MAH in the Netherlands.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.

Test method
After reading the leaflet, the patient was asked for a first impression straight away: what is good and what is bad about this leaflet? Then the actual diagnostic test followed, using 14 standard practical questions (questions that could come about when using Tramadol retard). The questions were asked in random order. First it was determined how well and how rapidly the respondent is capable of finding the answer in the leaflet: the ability to find. Second, the interviewer recorded to what extent the respondent is capable of giving the correct answer: the ability to understand.
After the diagnostic test, an assessment of layout and content followed. To do so, the interviewers laid down 16 assessment criteria focusing on clarity, fonts and paper, readability, language, completeness and appearance.

Discussion
The test comprised two rounds. During the first round 10 respondents were questioned and observed. After that, an evaluation followed based on the results obtained. The results of the first round of testing were good. For all items at least 80% scored well on the diagnostic questions. Therefore no changes were made to the leaflet for the second test round. Another 10 respondents were questioned and observed during the second test round.

The test method is acceptable, although the questions that were asked were simple. Furthermore only one question to test the suitability was asked, which is limited. In both test rounds respondents found the leaflet in order with respect to layout. For all items at least 90% scored not good/not bad, good or very good.

Conclusion
The package leaflet has been tested in two rounds of 10 respondents (20 in total). The results have shown that the information most relevant to the patient can be found (97.5%) and understood (96.1%) in a good way. The recommendations made by the organisation performing the readability test as given below should be reviewed and implemented where appropriate by the MAH during the MRP procedure.

During the test some spontaneous remarks were made by respondents. According to the respondents there were two areas where the leaflet could be improved:
1. The advice to be careful combining tramadol with alcohol was found ambiguous. It was recommended to change the advice to "If you experience drowsiness after taking tramadol, do not drink alcohol".

2. The information regarding driving a car was considered to be clear. However, a clear advice is lacking, for instance "Do not drive a car or do other activities that need you to be alert, until you know how tramadol affects you."

Other spontaneous remarks made by respondents indicate that there are some areas where enhancements can be made to the leaflet:
1. Use during pregnancy is not allowed (section Pregnancy), however, it is not included as contraindication (Do not use X). At least one respondent found this confusing.
2. The use of medical terms was not helpful for some respondents. Two sections are mentioned: interactions and adverse effects.
3. The last paragraph in the section on adverse effects showed difficulty for at least one respondent. It is not clear whether this information is related to stopping treatment or whether this information contains adverse effects. If the information is related to stopping treatment, the two paragraphs could be combined. In the latter case, it is advised to move these adverse effects to the frequency category they belong in.

The recommendations made during the procedure have been reviewed by the MAH and have been implemented where appropriated.

The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Tramadol Duiven retard 100/150/200 mg modified release tablets have a proven chemical-pharmaceutical quality and are a generic form of Tramal retard tablets. Tramal 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, package leaflet and labelling are in the agreed templates and are in agreement with other tramadol containing products.

The Board followed the advice of the assessors. Tramadol Duiven retard tablets were authorised in the Netherlands on 22 March 2004

During the procedure, a concern was raised by two of the CMS's, with regard to the demonstration of bioequivalence of the test product and the reference product, which lead to a CMD referral.

In the CMD(h) - meeting of 24 April 2007, the RMS presented its view and the MAH's written response were discussed. The MAH made use of an oral hearing. Following the discussion all involved Member States could agree on a commitment from the MAH to submit *in vitro – in vivo* correlation data in addition to the available studies to demonstrate bioequivalence. However, due to lack of formulations with different release mechanism, the IVIV-C model provided could not properly validated. Therefore, the MAH performed another bioequivalence study with the 150 mg prolonged release dose, as a post-approval commitment by means of a type II variation (NL/H/0539/002/II/002). See annex II.

It was noted that this should not be taken as a precedent, but that only in this particular case (the product is marketed for several years in a number of member states) the lack of studies at the time of approval was accepted. In conclusion, the explanation and arguments provided by the MAH were considered sufficient to resolve the initial concern.

As a result of this the procedure was approved as of 3 May 2007, and therefore a marketing authorisation was granted.

The MAH proposed to submit the first PSUR with the renewal and thereafter every three years.

The first renewal procedure was started on 17 July 2008, and ended positively on 12 December 2008. See Annex I.

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

<u>Quality - medicinal product</u>

- The MAH committed to validate one batch of each strength manufactured at a specific manufacturing site.
- The MAH committed to investigate the effect of alcohol, *in vitro*, on release characteristics of the drug products. This commitment was fulfilled. See annex II.

Post-approval commitments resulting from CMD(h) referral:

- The MAH committed to perform a formal IVIVC (*In vitro-in vivo* correlation) using the existing data package and submit this to the RMS and CMS within 8 weeks of the formal acceptance of the commitment. (This commitment has been fulfilled, see annex II)

- The MAH committed not to market the product in Spain until the results if *in vivo-in vitro* correlation are submitted and approved

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
b.i.d.	Two times a day
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PTF	Pedotransfer Functions
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Renewal of the marketing authorization.	NL/H/539/001-003/R/001	Renewal	14-7-2008	12-12-2008	Approval	Y, Annex I
Additional BE study for the 150 mg strength under fasting conditions. (Post approval commitment)	NL/H/0539/002/II/001	II / Post-approval commitment	28-11-2009	27-1-2010	Approval	Y, Annex II
• Change in the specification parameters and/or limits of an excipient, tightening of specification limits. • Change in the specification parameters and/or limits of the finished product, deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter). • Change in test procedure for the finished product minor changes to an approved test procedure. • Submission of a new or updated Ph. Eur. certificate of suitability; - European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. - Updated certificate from an already approved manufacturer (3x) - European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient, - Updated certificate from an already approved manufacturer.	NL/H/539/001-003/IA/002/G	IA/G	19-7-2010	18-8-2010	Approval	N
To submit the interaction study of alcohol effect on tramadol prolonged release tablets *in – vitro.*	NL/H/539/001-003/IB/003	IB	18-10-2010	17-11-2010	Approval	Y, Annex III

Annex I – Renewal of the marketing authorization (variation NL/H/0539/001-003/R/-001)

I.1 Introduction

Tramadol HCL retard contains the active constituent tramadol, which is a centrally acting opioid analgesic indicated for the treatment of moderate to severe pain. The Netherlands acted as Reference Member State in six Mutual Recognition Procedures.

The MAH submitted the following documents in scope of the Renewal:

- PSUR, covering the period Augustus 2005-April 2008.
- Clinical Expert Statement, dated April 2008.

No changes to the SPC were proposed.

Of note, the PSUR concerns all tramadol containing products, including tramadol capsules, tablets and solution for injection, of the manufacturer. However, ICC only authorised the tablets via the mutual recognition procedure.

I.2 Data review

PSUR

World wide marketing authorisation status

At data lock point the tramadol HCL retard products were authorised in 23 countries worldwide and were actually on the market in 7 of them.

Assessor's comment: The MAH did not provide a clear overview of the worldwide marketing authorisation status of the tramadol HCL retard products. In the next PSUR the MAH should provide information on the license of the products and their marketing status per country. The MAH should also provide EU procedure numbers instead of national registration numbers. See Annex 5.2.2 in Volume 9A of The Rules Governing Medicinal Products in the European Union for an example of such an overview.

Update of regulatory authority or MAH actions taken for safety reasons

No actions have been taken for safety reasons during the period under review.

Changes to the Reference Safety Information

The SPC for Mabron Retard (MRP procedures NL/H/0539+0888-890+0892/01-03/MR) was provided as Reference Safety Information (RSI). No changes were made to the RSI in the period covered by the PSUR.

Patient exposure

Patient exposure was estimated for the period 2005 through 2008 using sales data and the WHO DDD (Defined Daily Dose) of 0.3 g/day, because more accurate data were not available. A total of 5.702.000 DDDs/year were calculated taking all formulations into account. Regarding the prolonged release tablets, a total of 17.655.166 DDDs/year could be calculated.

The patient exposure is based on the time period from August 2005 to April 2008 (time period covered by PSUR). It was noted that sales data for 2007 for at least the prolonged release tablets are considerably larger than for 2006.This was due to the launch of products on the new markets and increase in production of prolonged release tablets.

Adverse events

The MAH received one spontaneously reported case which was non-serious and listed. This was the only case included in the line listings.

Furthermore, the MAH mentioned that 36 case reports were identified in the literature. Most cases concern drug interactions (between tramadol and warfarin, tramadol and amitriptyline and tramadol and meperidine), overdose and dependence with or without fatal outcome. However, there was no comprehensive view of the exact numbers of cases due to overlapping information. The MAH assessed the interactions with warfarin and amitriptyline as listed in the SPC and the interaction with meperidine as unlisted. The MAH commented that the interaction between tramadol and meperidine will be closely monitored.
Upon the RMS's request, The MAH submitted complete line-listings for serious and non-serious case reports and for listed and unlisted case reports. Duplicates were excluded. There were 22 case reports from literature: 9 serious and unlisted, 12 non-serious and unlisted and 1 non-serious and listed. Most cases concern overdose, drug interactions and dependence.

From the remaining cases, 6 cases were serious and unlisted (including inappropriate secretion of antidiuretic hormone, hypersensitivity pneumonitis and hypoglycaemia), 3 were serious and listed, 3 non-serious unlisted, 1 was non-serious listed and 2 cases could not be assessed due to lack of information. The serious and unlisted adverse reactions will be closely monitored.

Studies
The MAH did not perform any safety study. Table 1 shows the studies for tramadol HCL prolonged release identified in the literature.

Table 1: Literature studies of tramadol HCL prolonged release

Topic	Number of studies	Safety issue identified	
Overdose	2	-unintentional tramadol overdose - seizures after tramadol intoxication	*Addressed under the heading Overdose and Abuse or Misuse.*
Children and Elderly	3	-myoclonic seizures by tramadol in juvenile myoclonic epilepsy - nonconvulsive status epilepticus association with tramadol treatment - adverse events of tramadol use in relief of cancer pain	*Addressed under the heading Special patient groups.*
Other topics	5	- Safety and efficacy of tramadol in idiopathic detrusor overactivity - Increased mortality in peptic ulcer disease after tramadol use - Incidence of adverse events, including diarrhoea, after tramadol in cancer patients - Increased risk on severe cutaneous reactions after tramadol - Adverse reactions of tramadol reported to Iranian Pharmacovigilance centre	*Addressed under the heading Efficacy related information.* *The MAH commented that all adverse reactions in these studies were included in the SPC. However, diarrhoea was not included in the currently approved SPC, as well as the masking effect of tramadol in case of symptoms of a perforated peptic ulcer in peptic ulcer disease.*

RMS's comments: The MAH should closely monitor peptic ulcer diseases and their outcome among tramadol users, and provide a detailed discussion on this topic in the next PSUR.

Lack of efficacy
The MAH did not identify any reports regarding lack of efficacy.

Late breaking information
There was no late breaking information.

Risk Management Plan
Safety information collected and analysed by the manufacturer did not trigger the design of any risk management programme for tramadol. Therefore, the MAH has no risk management programme.

Drug interactions
The MAH identified several cases of drug interactions from literature between tramadol and warfarin, tramadol and amitriptyline and tramadol and meperidine. However, there was no comprehensive view of the exact numbers of cases due to overlapping information. The interactions with warfarin and amitriptyline are listed in the SPC, the interaction with meperidine was unlisted. The MAH commented that the interaction between tramadol and meperidine will be closely monitored.
There were no literature studies on drug interactions identified.

During the renewal procedure the MAH submitted complete line-listings for each interaction case. There were 4 cases of drug-interactions. It concerns the drug-interactions with meperide, morphine, amitriptyline and an antidepressant not otherwise specified, respectively. In the last 3 cases the serotonin syndrome occurred, which was fatal in 1 case.
The risk of a serotonin syndrome is included in the current SPC and the MAH has agreed to update the SPCs regarding the interaction with warfarin. The MAH has committed to closely monitor the interaction with meperidine.

CMS comment: 11 cases of tramadol- warfarin interaction were reported by Australian Drug Reactions Advisory Committee: 2 cases were fatal. The innovator in Ireland has strengthened its warning regarding the interaction between tramadol and coumarin derivates (e.g. warfarin) due to reports of increased INR with major bleeding and ecchymoses in some patients. A similar wording should be included in the SmPC for tramadol products.

Interaction with ondansetron:

CMS comment: There are published studies suggesting an interaction between tramadol and the 5-HT3 antagonist ondansetron. These studies indicate that the analgesic effect of tramaol is in part mediated by inhibition of the re-uptake of norepinephrine and serotonin (5-HT) and enhancement of the release of serotonin. Pre- or post operative application of the antiemetic 5-HT3 antagonist increased the requirement of tramadol in patients with postoperative pain.
After literature research the assessor agrees with the CMS comment. The MAH should update section 4.5 of the SPCs by including the interaction with ondansetron.

Overdose
The MAH identified several literature cases of overdose. One literature study is presented regarding fatal unintentional intoxications with tramadol during the period 1995-2005 in Sweden. Two percent of 49,700 forensic death investigations could be ascribed to fatal unintentional intoxication with tramadol. The authors concluded that fatal toxicity occurs rarely, but that precaution is warranted in patients with a history of substance abuse.
There were 4 intentional overdose cases of which 3 cases had a fatal outcome. In 2 cases it concerns a multiple drug overdose: 1 (fatal) case of tramadol and amitriptyline overdose and 1 case of tramadol in combination with hydroxyzine, gabapentin and clonazepam. One case concerns a patient with liver failure and renal failure probable related to a tramadol overdose. The outcome was fatal. The risk of tramadol overdose and the accompanying symptoms are described in section 4.9 of the SPC. The MAH has committed to closely monitor overdoses with a fatal outcome.
In addition, there were 2 cases of long-term overdosing. In 1 case there was a regular intake of high doses of tramadol during 3 years, in association with mild cognitive impairment and the coadministration of mirtazapine, which may have caused a serotonergic-cholinergic imbalance. One other case developed

memory disturbances and confusion on high doses of tramadol (450 mg/d) over the years.

Dependence
The MAH identified several literature cases of dependence.
There were 3 cases of dependence with withdrawal symptoms, of which 2 cases were related to long-term use of high doses of tramadol: 1 case used 1,200 mg/d and 1 case 1,000 mg/d.
The MAH has been requested in the assessment report, dated 30 June 2008, to include "Dependence may occur." in section 4.8 of the SPC, which is in line with the RSI and the information included in the SPC of the Dutch innovator product Tramal.

Abuse or misuse
One study addresses the common occurrence of seizures in younger patients, who were long term users or who used tramadol in combination with alcohol.
In line with the warning in section 4.4 of the RSI, the MAH should include in section 4.4 of the SPC that tramadol HCL retard should not be used in combination with alcohol.

Special patient groups (elderly, paediatric, etc.)
Children
One literature study was presented addressing myoclonic seizures induced by tramadol in patients with juvenile myoclonic epilepsy. No proper assessment could be done due to a lack of information. However, no action is necessary, because a warning for the use of tramadol in patients with epilepsy is included in section 4.4 of the SPC.

Elderly
Two studies from literature address the use by elderly. The first study was a case-control study showing a relationship between tramadol use and non-convulsive status epileptics. The second study addresses the incidence of adverse reactions in cancer pain in old age. All observed adverse reactions were included in section 4.8 of the SPC.

Pregnancy and lactation
There were no literature studies addressing the safety and efficacy of tramadol HCL prolonged release.

Long-term treatment
The MAH did not address any study regarding long-term treatment.

Conclusions of the MAH
The MAH concluded that there are no important safety issues or concerns with tramadol when used appropriately and that it continues to have a positive risk/benefit profile. The MAH considers no amendments of the SPC to be nessecary.

I.3 Clinical Expert Statement
The MAH states that the clinical data available for tramadol continue to support the clinical efficacy and safety of tramadol prolonged release tablets. The MAH concludes that there are no safety concerns with tramadol when used appropriately and that it continues to have a positive risk/benefit profile. Considering the favourable risk benefit profile, the MAH concludes that the marketing authorisation should be renewed.

I.4 Product information

1.4.1 SPC
No changes to the SPC were proposed. The proposed SPC is identical for all procedures.

1.4.2 PIL
No changes to the PIL were proposed.

1.4.3 Labelling

No changes to the labelling were proposed.

I.5 GMP declaration / manufacturing authorisation

GMP active substance

The MAH has provided a statement on GMP for the active substance manufacturers signed by the qualified person from the manufacturers responsible for the finished product and for batch release for all active substance manufacturers.

Manufacturing licenses

For this renewal the RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. 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.

I.6 Post approval commitments

The MAH has provided a Chronological list of follow up measures.

II Conclusions

Renewal may be granted for unlimited validity provided that the following issues are resolved.

- Section 4.8 of the SPC should be updated as indated.
- The PIL and labeling should be updated accordingly, if applicable.

In view of the EU PSUR synchronisation project, the MAH will follow the harmonised birth date for tramadol with its allocated data lock point of August 2009 (see http://www.hma.eu/uploads/media/draft_DLP_old_substances_20080422_alphabetic_order.pdf). Therefore, the next PSUR will have a data lock point of August 2009. Note that the PSUR should be submitted within 60 days after data lock point.

Annex II – Post approval commitment / type II variation NL/H/0539/002/II/001

I RECOMMENDATION

Based on the review of the data the RMS considers that the variation application NL/H/0539/02/II/001 for Tramadol HCl Duiven Retard 150 mg for the following proposed changes

to submit a new single dose bioequivalence study for Tramadol HCl SR tablets 150 mg/tab, under fasting conditions

is approvable.

II EXECUTIVE SUMMARY

II.1 Scope of the variation

The MR procedure NL/H/0539/01-03/MR for Tramadol HCl Duiven Retard 100, 150 and 200 mg was referred to CMD(h). One of the referral issues (CMD(h) April 2007) was that no BE studies were performed with the 150 mg strength.

In the guideline for modified release products it is indeed required that BE studies are performed for every strength of a single-unit tablet. The marketing authorisation in the RMS was based on 4 bioequivalence studies with the 100 and 200 mg strengths, and bioequivalence was shown under different conditions (single or multiple dose, fed or fasted). The RMS proposed to excempt the 150 mg study, as the different tablet strengths have a dose-proportional composition, tramadol displays linear kinetics, and the absorption of tramadol is fast and complete once dissolved. The 100-150-200 displayed similar dissolution profile. No significant differences were therefore expected for the 150 mg strengths. Moreover, whether the Tramadol controlled release tablets are single-unit tablets is a matter of debate, as the tablets consist of a simple matrix without any coating.

During the CMD(h) meeting April 2007, it was proposed that the MAH could perform an *in-vitro in-vivo* correlation (iviv-c) analysis, in order to support a biowaiver of the 150 mg tablets to other strengths. The MAH performed the requested analyses by two methods. However, due to lack of formulations with different release mechanism, the IVIV-C model provided could not properly validated. Therefore, the MAH performed another bioequivalence study with the 150 mg prolonged release dose, as a post-approval commitment by means of this type II variation.

This study and its results are discussed below.

II.2 Clinical aspects

Clinical study report

Single-dose bioequivalence study with the 150 mg dose, under fasted conditions.

Test: Tramadol HCL 150 mg prolonged release tablets (I.C.C.B.V., the Netherlands)
Reference: Tramal retard 150 mg tablets, (Grunenthal B.V., the Netherlands)

The Marketing Authorisation Holder submitted data of a single-dose, randomized, two-period, crossover bioequivalence study on tramadol preparations Tramadol HCl 150 mg prolonged-release tablets (Farmaceutisch Anatytisch Laboratorium (FAL) Duiven BY. The Netherlands) versus Tramal retard 150 mg tablets (Grünenthal BV, the Netherlands) in healthy volunteers under fasting conditions, performed in 2009.A washout period between doses at least 6 days was applied. Study drugs were administered with 200 ml of water under fasting conditions (at least 10 hours).

Blood samples (6 ml each) were collected at time 0 (pre-dose), and at 0.25, 0.50, 1.00, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 14.0, 18.0, 24.0, 30.0, 36.0, and 48.0 hours upon drug administration in each study period. Plasma concentrations of tramadol and O-desmethyl tramadol were determined.
In this study 26 healthy subjects including males (11 subjects) and female (15 subjects), aged 18 - 52 years, participated. All volunteers completed both periods of the study.

Analytical methods
For determination of tramadol and the main metabolite 0-desmethyl tramadol an achiral HPLC-MS/MS method was used. The lower limits of quantitation for tramadol and 0-desmethyl tramadol were 1.0 µg/ml and 0.9 µg/ml, respectively. The analytical method is well described and the validation report was provided. The accuracy, precision, selectivity and long –term stability were well estimated. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable

The report is of good quality. The study was conducted according the GLP/GCP rules. The study design is considered acceptable taken into account that Tramal can be taken regardless of food and the apparent half-life of 7 hours of tramadol**.**

Results

Safety
The tolerance of the products studied was comparable. Twenty-three adverse events probably related (six cases of weariness, three cases of vomiting, three cases of nausea, one case of dizziness and one case of tiredness), possibly related (two cases of dizziness, one case of tiredness, one case of tremor, one case of headache, one case of nausea, and one case of weariness), unlikely related (one case of dizziness), and conditionally related (one case of backache) occurred in twelve subjects. No adverse event was assessed as a serious adverse event, an unexpected adverse drug reaction or other clinical significant adverse event.

Table 10. Pharmacokinetic parameters of tramadol: non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment N = 26	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**MRT h**	**$t_{1/2}$** h
Test	4067 ± 1310	4157 ± 1372	274 ± 64	5.0 2.5 – 8.0	13.3 ± 2.66	7.4 ± 1.9
Reference	4177 ± 1126	4233 ± 1178	292 ± 54	5.0 2.0 – 10.0	12.5 ± 2.14	6.6 ± 1.2
***Ratio (90% CI)**	0.96 0.90 – 1.03	0.97 0.90 – 1.03	0.93 0.87 – 0.99	---	1.05 1.00 – 1.11	---
CV (%)	14.3%	14.3%	13.1%	---	11.1%	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
T_{max} time for maximum concentration
MRT mean residence time
$T_{1/2}$ half-life

**ln-transformed values*

Table 11. Pharmacokinetic parameters of O-desmethyl tramadol: non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment N = 26	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h	MRT h	$t_{1/2}$ h
Test	1009 ± 338	1033 ± 336	61.6 ± 23.5	6.0 2.5 – 10.0	14.5 ± 2.7	7.22 ± 2.13
Reference	1040 ± 335	1058 ± 333	65.9 ± 25.0	6.0 2.5 – 10.0	13.7 ± 1.95	6.45 ± 1.16
***Ratio (90% CI)**	0.97 0.92 – 1.03	0.98 0.93 – 1.03	0.95 0.90 – 1.01	---	1.05 1.00 – 1.10	---
CV (%)	11.2%	10.9%	12.5%	---	10.3%	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
T_{max} time for maximum concentration
MRT mean residence time
$T_{1/2}$ half-life

**ln-transformed values*

The following conclusions could be drawn:
The pharmacokinetic variables after treatment with test and reference product are comparable. The 90% confidence intervals of the pharmacokinetic variables of interest are well within the predefined acceptance criteria of 0.80 – 1.25. Both products were well tolerated. Bioequivalence was adequately shown for the 150 mg dose. These data confirmed that biowaiver to the 150 mg strength was justified.

III OVERALL CONCLUSION

The submitted study shows that the 150 mg tablet formulation of Tramadol HCl Duiven is bioequivalent with the reference product Tramal retard 150 mg from Grunnenthal, the Netherlands. The commitment can therefore be considered fulfilled.

Annex III – Post-approval commitment - submission of interaction study of alcohol effect on tramadol prolonged release tablets *in - vitro*

I RECOMMENDATION

Based on the review of the data on quality, the RMS considered that the type IB variation regarding *in-vitro* alcohol testing, for Tramadol Retard tablets, in the treatment of chronic pain, is approvable. As no relevant interaction with alcohol was observed *in-vitro*, no update of the SPC is required. (See Section V).

II EXECUTIVE SUMMARY

II.1 Problem statement

The Marketing Authorization Holder (MAH) answers to the objection raised by one of the Authorities during MRP regarding possible dose-dumping by interaction of the alcohol effect on tramadol prolonged release tablets *in-vitro*.The objection is cited below.

" *In EU NfG on modified release oral and transdermal dosage forms it is mentioned that the risk of unexpected release characteristics (dose dumping) should be studied. As former cases (with prolonged release morphine products) has shown possible dose dumping risk problems, when the excipient(s) responsible for the prolonged release mechanism of the Drug Product, is(are) soluble in ethanol, we would like you to evaluate the risk when using the product applied for. As you may be aware, there are no official pharmacopoeial or EU guideline tests to check any possible adverse effects alcohol may have on the release of tramadol from your product. We would however like to suggest that you obtain* in- vitro *profiles using 0.1N HCl with varying concentrations of ethanol up to 40% (e. g. 10%, 20%,40%) and compare with the profile obtained using pure 0.1N HCl. Our reasoning is that although the total ethanol concentrations in the stomach may not reach 40%, there may theoretically be " pockets" of higher ethanol concentrations in areas of the stomach to which your product may be exposed. We suggest that the profiles obtained at the various ethanol concentrations be compared against that obtained in pure 0.1N HCl by calculation of a similarity factor (see NfG on the Investigation of Bioavailability and Bioequivalence CPMP/ EWP/ QWP/ 1401/ 98 – Appendix II). Where profiles differ, we would like you to address potential in vivo concentrations from a patient safety viewpoint."*

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

The MAH has examined the effects of alcohol on the dissolution profile of the tablets. Dissolution media 0.1N HCl with 10%, 20% and 40% v/v ethanol were used covering more than the practical alcohol concentrations that might be found in the stomach of patients. All three strengths tablets were tested. The analytical procedure was the routine quality control procedure: basket, 100 rpm, 900 mL volume, detectin by UV (271 nm), sampling after 1, 2, 4, 6 and 8 hours. The analytical procedure was validated, agreed. The dissolution profiles for the 100mg and 150 mg strength were essentially similar, irrespective of the alcohol percentage and all within specification. For the 200 mg strength, the results at 6 and 8 hours points were slightly out of specification for the medium 0.1N HCl with 40% v/v ethanol. However, the values were slighty lower than required and dose dumping is out of the question.

IV BENEFIT RISK ASSESSMENT

Alcohol had no significant effect on the rate of dissolution of the active substance from the formulation *in-vitro* and was within specification limits (see figures Quality section).
Although there is no significant effect of alcohol on dissolution, pharmacodynamic interaction may still occur between alcohol and tramadol. In the SPC, it is therefore recommended that Tramadol retard

should not be used in combination with alcohol in section 4.4, 4.5 and 4.7. There is no need to update this wording.

V OVERALL CONCLUSION

The variation regarding the submission of interaction study of alcohol effect on tramadol prolonged release tablets *in – vitro* can be approved. As no relevant interaction with alcohol was observed *in-vitro*, no update of the SPC is required.

Abbreviations used in Annexes

DDD	Defined Daily Dose
MRT	Mean Residence Time