PUBLIC ASSESSMENT REPORT

Mutual Recognition Procedure

Module 5
Scientific discussion during the initial procedure

Fenta Regiomedica Matrix
25 / 50 / 75 and 100 µg/h transdermal patch
Fentapatch Matrix
25 / 50 / 75 and 100 µg/h transdermal patch
Fentamedica Matrix
12,5 / 25 / 50 / 75 and 100 µg/h transdermal patch

Fentanyl

DE/H/0763/01-04 / MR

DE/H/0764/01-04 / MR

DE/H/0765/01-05 / MR

Marketing authorisation holder in

the Reference Member State, Germany :

Regiomedica GmbH, Germany

Date: 22.12.2006

Module 5

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PUBLIC ASSESSMENT REPORT

This assessment report is published by BfArM following Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to BfArM and its fellow organisations in all concerned EU member states.

It reflects the scientific conclusion reached by BfArM 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 BfArM.

To the best of the BfArM`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: DE/H/0763/01-04/MR , DE/H/0764/01-04/MR , DE/H/0765/01-05/MR
Registration number in Germany: 62180.00.00, 62181.00.00, 62182.00.00, 62183.00.00, 62185.00.00, 62186.00.00, 62187.00.00, 62188.00.00, 62189.00.00, 62190.00.00, 62191.00.00, 62192.00.00, 62193.00.00

Pharmacotherapeutic group: opioid analgesic for systemic use - Fentanyl
ATC code: N02AB03
Route of administration: transdermal
Therapeutic indication: treatment of severe chronic opioid sensitive pain
Prescription status: prescription only
Date of first authorisation (national): 12.04.2006
For product information for healthcare professionals and users, including information on pack sizes and presentations, see modules 2, 3 and 4.

1. INTRODUCTION

The Mutual Recognition Procedure (MRP) started on September 21, 2006 and was positively ended on December 22, 2006.

The application has been submitted according to Directive 2001/83/EEC, Article 10(2)(b) as a generic product in reference to the original product Durogesic, which has been registered in Germany by Janssen-Cilag since 31 January 1995.
In addition, reference is also made to Durogesic authorisations in the individual Member States (reference product). The reference product used for bioequivalence studies is Durogesic 25 µg/h patch, registered by Janssen-Cilag in Germany.
Based on the review of the quality, safety and efficacy data, BfArM has granted a marketing authorisation (MA) for Fentanyl Regiomedica transdermal patches, from Regiomedica/Germany on 04.04.2006 for the treatment of: "severe chronic opioid sensitive pain"

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

The marketing authorisation is granted based on article 10 (2)(b) of Directive 2001/83/EC, as amended. It concerns a generic application claiming essential similarity with the innovator product

This type of application refers to information that is contained in 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 applications, 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 applicant has submitted bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the originator Durogesic 25 µg/h patch, registered in Germany.
A bioequivalence study is the widely accepted means of demonstrating that use of different excipients and different methods of manufacture has no influence on efficacy and safety.
A generic product can be used instead of its innovator 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 applicant with respect to these products.
Fentanyl is a prescription only medicine.

The present public assessment report for the Mutual Recognition Procedure (MRP) includes the information of the original dossier as well as additional information provided in response to the questions raised by the CMS in the course MRP.

2. QUALITY ASPECTS

2.1 Introduction

Fentanyl Regiomedica 12.5/25/50/75/100 Mikrogramm/h are transdermal matrix patches for three day application in the treatment of severe chronic opioid sensitive pain.
The German Marketing Authorisation for this product was granted in November 2006.

Fentanyl is a well known opioid analgesic.
It is marketed in several dosage forms and strengths world wide since many years.
The chemical-pharmaceutical documentation and Expert Report are of sufficient quality in view of the present European regulatory requirements.

2.2 Drug substance

The active substance is fentanyl, an established active substance described in the European Pharmacopoeia (Ph.Eur.).
The specifications in the ASMFs were satisfactory and met the requirements of Ph.Eur.. The impurities/degradation products were classified and analysed appropriately. The potential impurities/degradation products were limited according to the monograph of the Ph.Eur.. An adequate re-test period has been defined.

2.3 Medicinal product

The marketing authorisation holder is requesting a Mutual Recognition Procedure for their finished product Fentanyl TDS 12,5µg/h - 100 µg/h with Germany acting as Reference Member state.

The ingredients and the manufacturing process of the drug product are considered suitable to produce a pharmaceutical product of the proposed quality.

As required in Directive 2001/83/EC, the documentation provides an adequate synopsis of the method of preparation, mentioning the various stages of production, the in-process controls and batch formula.

The manufacturing process demonstrated the consistency of the specifications. The process has been validated adequately by investigating the critical manufacturing steps.

The excipients are appropriately controlled, using either in-house testing or, in case of the Durotak-adhesive, an own DMF. Satisfactory supplier Certificates and Certificates of Analysis are supplied.

The description of the analytical methods used to analyse the drug substance and drug product are adequate, the validation results are plausible.
The stability data presently available justify the claimed shelf-life of 24 months for the package proposed for marketing.

2.4 Discussion on chemical, pharmaceutical and biological aspects

The quality of the drug substance fentanyl complies with the specifications and requirements described in the monograph of the Ph Eur.

The quality of the medicinal products is satisfactory. The claimed shelf life of 24 months is justified by the stability data presently available.

On quality grounds, the grant of marketing authorisation is justified.

3. NON-CLINICAL ASPECTS

3.1 Introduction

Fentanyl is a centrally acting analgesic available in transdermal and parenteral formulations in Germany since many years.. The proposed formulations of Fentanyl Regiomedica are transdermal Matrixpatches.

3.2 Toxicology

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

3.3 Discussion on the non-clinical aspects

From the pharmacological/toxicological point of view, the grant of marketing authorisation is justified.

4 Clinical aspects

4.1 Introduction

The indication sought "treatment of severe chronic opioid sensitive pain" as well as the dosage recommendations are consistent with those of other fentanyl products and are appropriate for this dosage form which is intended for three day dosing.

The content of the SPC approved during the national procedure is in accordance with that accepted for the reference product Durogesic by Janssen-Cilag, Germany.
The SPC is also in agreement with the MRP-approved SPCs from other procedures.

Fentanyl is a well-known active substance with established efficacy and tolerability as an analgesic for approved indication.

This generic application is based on bioequivalence data referring to the German originator product Durogesic by Janssen-Cilag, Germany.

Three pilot studies and two pivotal bioavailability studies (one single dose bioequivalence trial and one multiple dose bioequivalence trial) were carried out:

The patch with the lowest release-rate of fentanyl (25 µg/h) was compared to the reference product Durogesic 25 µg/h patch (Janssen-Cilag).

Data obtained by studies conducted with one dose strength can be extrapolated to the other proposed patches releasing 50, 75 and 100 µg fentanyl per hour.

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

Based on the pharmacokinetic parameters of the active substance the applicant has demonstrated that Fentanyl 25 µg/h transdermal patches (Regiomedica GmbH Germany) and Durogesic 25 µg/h transdermal patches (Janssen Cilag GmbH, Germany) are bioequivalent after single and multiple transdermal administration.

4.2 Pharmacokinetics

The pharmacokinetic properties of fentanyl have been widely studied since first authorisation and are well characterised in literature.
Following administration of Fentanyl transdermal patch, fentanyl is continuously absorbed through the skin over a period of 72 hours. Due to the polymer matrix and the diffusion of fentanyl through the skin layers, the release rate remains relatively constant. Following initial administration, serum concentrations of fentanyl increase gradually and generally stabilise 12 to 24 hours after administration and then remain relatively constant for the rest of the 72-hour period. The serum concentrations reached are proportional to the size of the fentanyl patch. Following repeated administration, each of 72 hours duration, serum concentrations reach steady state, which is maintained following further administration of patches of the same size. After removal of the fentanyl patch, serum fentanyl concentrations fall slowly with a half-life of approximately 17 hours (range 13–

22 hours). The continuous absorption of fentanyl from the skin depot leads to a slower elimination from the body than following intravenous infusion. Elderly, cachectic patients may have a reduced clearance and subsequently a prolonged terminal half-life of fentanyl. The substance is mainly metabolised in the liver. Following single administration of a fentanyl patch in patients with cirrhosis of the liver, there were no changes to the pharmacokinetic parameters, although the serum concentrations of these patients tended to be higher. Approximately 75% of the absorbed substance is mainly eliminated in the form of metabolites and less than 10% as unchanged drug in the urine. Approximately 9% of the dose is excreted in mainly metabolised form in the faeces. An estimated 13–21% of fentanyl is present in the plasma as unbound fractions.
The patch is a pharmaceutical form for the systemic administration of fentanyl, by means of which, at a constant release rate, sufficiently high serum levels of fentanyl are reached for 72 hours following one administration. The product consists of a transdermal therapeutic system (TTS).

According to the various sizes of the active surface areas of the systems, which range from 5,25 / 10,5 / 21 / 31,5 and 42 cm2 with an identical fentanyl fraction approximately 12,5 / 25 / 50 / 75 or 100 µg fentanyl per hour, respectively, are released into the skin

Pharmakokinetic Studies

Pivotal studies

SCO 5167, 2004-03-TTS-4

- Single-dose replicate design study (Fentanyl TTS patch size 10,5 cm^2)

"An open, randomised, single-dose, four-period, two-sequence, two formulation replicate design study to assess the relative bioavailability of fentanyl from two different transdermal systems in healthy subjects."

- Objective:
- to assess the relative bioavailability of fentanyl Test and from Reference
- compare safety, tolerability and patch adhesion of both patches

- Study design:

randomised four-period crossover replicate design, monocentric, single-dose, bioequivalence study

- Subjects:

healthy Caucasian men, all of them randomized and analysed, age 21-43 years, non-smokers with BMI > 18 kg/m2 and < 27 kg/m2 were recruited.

- Test and Reference products:

Test product : Fentanyl TTS matrix patch 25 µg/h (10.5 cm^2) Batch No.: FTY0014TTS/2
transdermal patch with matrix delivery system, developed by Hexal AG, Germany, approval intended by Regiomedica GmbH, Germany

***Reference product**: Durogesic 25 µg/h (10 cm^2)*
Transdermal patch with reservoir delivery system, Janssen-Cilag GmbH, Germany

- Method:

The two formulations were administered in two sequences (given on day 2 of each period, and each 25 µ/h patch was applied for 72 hours) and four periods separated by a wash –out phase of at least 7 days.

- Endpoints:

-primary endpoints: 90% confidence intervals for $AUC_{0\text{-}tZ(\text{last measured})}$ and C_{max}
inter- and intrasubject variances

subject-by-formulation interaction ratio

-secondary endpoints: t_{max}, safety and tolerability of test and reference; patch adhesion

$AUC_{0-72,}$ $AUC_{0-\infty}$ and $t_{1/2,}$

- Statistical methods:

Pharmacokinetic parameters

90% confidence intervals served as interval estimates and were determined by parametric analysis (ANOVA) and nonparametric analysis (Wilcoxon-Mann-Whitney tests). Bioequivalence was accepted when the parametric confidence intervals did not exceed the limits of 80 and 125% for the ratio of $AUC_{0-tlast}$-and the limits of 70 and 143% for the ratio of C_{max}-values. The decision procedure based on 90 % confidence intervals corresponded to the two one-sided t-tests procedure on the significance level $\alpha = 0.05$.

- Results:

Results for target parameters and statistical analysis are given in Table 1 and Table 2

Table 1: PK parameters after single-dose application of test and reference patch,

	Fentanyl TTS		**Durogesic®**	
	$AUC_{0-tlast}$ [h*pg/ml]	**C_{max}** [pg/ml]	**$AUC_{0-tlast}$** [h*pg/ml]	**C_{max}** [pg/ml]
geometric mean	29637.1	481.46	27256.9	449.99

Extent of bioavailability was almost identical for both investigational products while C_{max} is slightly higher for reference compared to test.

Table 2: Point estimates and 90% confidence intervals for test / reference ratios

	Point estimate [%]	**90% confidence interval [%]**	**CV_{ANOVA}[%]**
$AUC_{0\text{-}tlast}$	108.51	96.39 – 122.15	0.883
$AUC_{0\text{-}72}$	107.11	95.69 119.89	0.928
C_{max}	106.75	94.23 – 120.94	0.985

Confidence intervals calculated for the comparison of test and reference confirm bioequivalence of both investigational products.

The intrasubject standard deviation of the log-transformed $AUC_{0\text{-}tlast}$ was 0.16 for the test formulation and 0.11 for the reference formulation.

- Patch adhesion

The mean detachment of the test patch rose in a1(test) treatment to 0.8% / a2(test) to 3% at 72 hours after application

and

The mean detachment of the reference patch rose in b1(reference) treatment to 8.1% / b2 (reference) to 11.6% at 72 hours after application.

The patch adhesion properties of the test patch were significantly better than those of the reference b.

- Safety

88 adverse events (AE`s) were reported by 17 subjects treated in the study, 50 of these events during test treatment and 38 events during reference treatment.

The majority of 80 (AE`s) were classified with a suspected relationship to the study treatments: 47 events during the test treatment and 33 events during the reference treatment.

The adverse events most frequently observed were dizziness ,nausea , vomiting , headache tiredness , drowsiness , itching general / itching at extremities and sweating .

The intensity of the AE`s was rated as mild in 59 cases and as moderate 29 cases.
None was rated as severe.

In 10 AE`s (nausea, vomiting, headache) corrective treatment was necessary. In one AE (hypertension) the subject was withdrawn from the study.

All of these AE´s are well known side effects after administration of fentanyl containing products.

No clinically relevant changes in body temperature and laboratory parameters were observed.

- Dermal tolerability

115 adverse events (irritation of the skin - all with full recovery) were reported in this study (64 cases after Test treatment and 52 after Reference treatment).

In general it can be stated that both treatments were well tolerated.

SCO 5167, 2004-02-TTS-3

- *Multiple-dose study (Fentanyl TTS patch size 10,5 cm^2)*

"A single-centre, open, randomised, cross-over study to assess the bioequivalence of fentanyl from two different transdermal systems after multiple doses, in healthy male subjects."
Objective:

- to assess the bioequivalence of fentanyl from Test and from Reference after multiple dosing
- compare safety, tolerability and patch adhesion of both patches

- Study design:

randomised cross-over of Test and Reference

- Subjects:

healthy Caucasian men, all of them randomized and analysed,
age 18-45 years,
non-smokers
BMI > 18 kg/m2 and < 27 kg/m2

- Test and Reference products:

Test product : Fentanyl TTS matrix patch 25 µg/h (10.5 cm^2) Batch No.: FTY0014TTS/1
transdermal patch with matrix delivery system, developed by Hexal AG, Germany, approval intended by Regiomedica GmbH, Germany

Reference product: Durogesic 25 µg/h (10 cm2)
Transdermal patch with reservoir delivery system, Janssen-Cilag GmbH, Germany

- Method:

Three 25 µ/h patches were applied for 72 hours each, given on day 2 of each period.
Treatmnet periods were separated by a wash – out phase of at least 7 days.

- Endpoints:

-primary endpoints: 90% confidence intervals for $AUC_{0\text{-}tZ(last\ measured)}$ and $C_{maxSS,}$ $C_{minSS,}$

- Statistical methods:

Pharmacokinetic parameters
90% confidence intervals served as interval estimates and were determined by
parametric analysis (ANOVA) and nonparametric analysis (Wilcoxon-Mann-Whitney tests).
Bioequivalence was accepted when the parametric confidence intervals did not exceed the limits of 80 and 125% for the ratio of $AUC_{0\text{-}tlast}$, and the limits of 70 and 143% for the ratio of $C_{maxSS.}$ The limit for the ratio of C_{minSS} should be above 70%.

- Results:

Results for target parameters and statistical analysis are given in Table 1 and Table 2

Table 1: PK parameters after single-dose application of test and reference patch,

	Fentanyl TTS		**Durogesic®**	
	$AUC_{0\text{-}tlast}$ [h*pg/ml]	**C_{max}** [pg/ml]	**$AUC_{0\text{-}tlast}$** [h*pg/ml]	**C_{max}** [pg/ml]
geometric mean	29637.1	481.46	27256.9	449.99

Extent of bioavailability was almost identical for both investigational products while C_{max} is slightly higher for reference compared to test.

Table 2: Point estimates and 90% confidence intervals for test / reference ratios

	Point estimate [%]	**90% confidence interval [%]**	**CV_{ANOVA}[%]**
$AUC_{0\text{-}tlast}$	109.2	99.7 - 119.5	15.2
C_{maxSS}	105.1	91.6 - 120.6	23.2
C_{minSS}	115.9	104.8 – 128.1	16.8

Confidence intervals calculated for the comparison of test and reference confirm bioequivalence of both investigational products.

- Patch adhesion

The mean detachment of patch a (test) rose linear from 0% to maximal 5% at 72 hours after each patch application

and

The mean detachment of patch b (reference) rose nearly linear from 0% to maximal 14% at 72 hours after each patch application

The patch adhaesion properties of the test patch were better than those of the reference b.

Treatment Patch adhesion

Frequency	>/= 90% adheared	>/=75 to </= 90% adheared	>/=50 to </= 75% adheared	Total
A	403 (94.82%)	21 (4.94%)	1 (0.24%)	425 (100%)
B	391 (86.89%)	48 (10.67%)	11 (2.44%)	450 (100%)

- Safety

A total of 180 adverse events (AE`s) were observed, 87 of these events during test treatment and 85 events during reference treatment.

The majority of 172 (AE`s) were classified with a suspected relationship to the study treatments.

The adverse events most frequently observed were dizziness, nausea, vomiting, headache, tiredness, sleep disturbance / sleeping disorder, itching general, itching under patch and loss of appetite.

All of these AE´s are well known side effects after administration of fentanyl containing products.

Within the course of the study no serious adverse events occurred.

No clinically relevant changes in body temperature and laboratory parameters were observed.

- Dermal tolerability

During 170 adverse events (minimal erythrma, barely perceptible - all with full recovery) were reported in this study (94 cases after Test treatment and 76 after Reference treatment).

In general it can be stated that both treatments were well tolerated.

4.3 Discussion on the clinical aspects

Bioequivalence of Fentanyl-Regiomedica 25 (50, 75, 100) Mikrogramm/h transdermal patch with the reference product Durogesic 25 Mikrogramm/h has been demonstrated by the results of

the bioequivalence studies presented above.

5. Overall discussion, benefit / risk assessment and recommendation

Fentanyl-Regiomedica patches, have a proven chemical-pharmaceutical quality and are a generic form of Durogesic patches. Durogesic is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SPC is consistent with that of the reference product.

Satisfactory chemical-pharmaceutical documentation has been provided assuring a consistent quality of the product.

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

The SPC, PL and packaging fulfil the legal requirements.
User consultation revealed that the PL fulfils the criteria described in the readability guideline.

The proposed common renewal date is 12.04.2011.