LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Generic applications

Scientific discussion

Matrifen, transdermal patch, 12 microg/hour, 25 microg/hour, 50 microg/hour, 75 microg/hour and 100 microg/hour (fentanyl)

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This module reflects the scientific discussion for the approval of Matrifen. The procedure was finalised at 2006-08-04. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Nycomed AB has applied for a marketing authorisation for Matrifen, transdermal patch, 12 microg/hour, 25 microg/hour, 50 microg/hour, 75 microg/hour and 100 microg/hour claiming essential similarity to Durogesic, transdermal patch, 12 microg/hour, 25 microg/hour, 50 microg/hour, 75 microg/hour and 100 microg/hour marketed in Sweden by Janssen-Cilag. The product contains fentanyl as active substance and is indicated for the treatment of severe chronic pain which can be adequately managed only with opioid analgesics. The reference product used in the bioequivalence study is Durogesic, transdermal patch, 50 microg/hour and 100 microg/hour marketed by Jansen-Cilag.

During the procedure, a potential serious risk to public health concerns was raised by one CMS and a CMD referral was initiated. A list of questions was agreed upon regarding the wording of the indication. The CMD referral ended positively and the indication for the product is *"Severe chronic pain, which can be adequately managed only with opioid analgesics"*.

II. QUALITY ASPECTS

II.1 Introduction

Matrifen is presented in the form of transdermal patch releasing 12 microg/hour, 25 microg/hour, 50 microg/hour, 75 microg/hour and 100 microg/hour of fentanyl.

The excipients are dipropylene glycol, hydroxypropyl cellulose, dimeticone, silicone adhesives (amine resistant), ethylenvinylacetate (EVA) as release membrane, polyethylene terephthalate film (PET) as backing film, fluoropolymercoated polyester film as removable protective film.

Each patch is packed in a heat-sealed sachet made of paper, aluminium and polyacrylonitrile (PAN).

II.2 Drug Substance

Fentanyl base has a monograph in the Ph Eur. Information on fentanyl has been supplied in the form of an ASMF.

Fentanyl is a white, crystalline powder which is soluble in aqueous acids and organic solvents but insoluble in water. The structure of fentanyl has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism and chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Matrifen, transdermal patch is formulated using excipients described in the current Ph Eur, except for silicone adhesive, dipropylene glycol, EVA membrane, polyethylene terephthalate film and fluoropolumercoated polyester film which are controlled according to acceptable in-house specifications. All raw materials used in the product are of vegetable origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as poor aqueous solubility.

The manufacturing process is a standard process. It has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf-life of 2 years with no special storage precautions.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Two bioequivalence studies, one single-dose study and one multiple-dose study, have been performed under concomitant naltrexone intake (100 mg q.d. days 1-5). The single-dose study was a four-period, two-sequence crossover where the test (Nycomed transdermal fentanyl patch 100 µg/h batch no 7059572) and reference (Durogesic 100 µg/h, Janssen-Cilag, Denmark) were given as two replicate doses each. The multiple-dose study was a two-way crossover. The test patch was Nycomed 50 µg/h (batch no 7059552) and the reference patch was Durogesic, 50 µg/h Janssen-Cilag, batch no 02KB538). In each period, the patch was administered three times with 3-day intervals.

Bioequivalence has been shown under multiple-dose conditions between Matrifen transdermal patch 50 µg/h and Durogesic transdermal patch 50 µg/h. In the single-dose study, bioequivalence was shown for AUC_{0-t} and $AUC_{0-\infty}$ but not for C_{max} (the test/reference-ratio is 113.4 with a 90% confidence interval of 98.8-130.2). Very high plasma concentrations were observed in one subject during two treatment-periods (one test one reference). The reasons for this are unknown. The results were calculated both with (Table 1a) and without (Table 1b) this subject. By exclusion of this outlying subject bioequivalence is shown also for C_{max} (the test/reference-ratio is 111.4 with a 90% confidence interval of 100.4-123.6). The clinical relevance of a slightly higher C_{max} is probably low, not the least considering the therapeutic use of the patch (often used together with additional opioid treatment as needed). In addition, bioequivalence has been shown under multiple-dose conditions. Therefore, the clinical documentation for Matrifen transdermal patch 50 µg/h is considered satisfactory.

Table 1a. Single-dose study results (All subjects included), mean (CV)

Formulations	Cmax (pg/ml)	Tmax (hrs)	AUC0-t (pg*h/ml)	AUC0-∞ (pg*h/ml)
Nycomed	2527 (64)	31.6 (35)	149495 (42)	152017 (41)
Durogesic	2264 (57)	33.2 (40)	141438 (36)	144470 (36)
Ratio of LSM (90%CI)	113.4 (98.8-130.2)		107.0 (98.2-116.5)	106.6 (97.9-116.0)

Table 1b. Single-dose study results ("Outlier" excluded), mean (CV)

Formulations	Cmax (pg/ml)	Tmax (hrs)	AUC0-t (pg*h/ml)	AUC0-∞ (pg*h/ml)
Nycomed	2352 (35)	31.5 (36)	142682 (25)	145126 (25)
Durogesic	2116 (27)	33.1 (40)	135877 (22)	138822 (23)
Ratio of LSM (90%CI)	111.4 (100.4-123.6)		105.5 (99.4-112.0)	105.3 (99.3-111.6)

Table 2. Multiple-dose study results (Mean (CV))

Formulations	Cmax (pg/ml)	Tmax (hrs)	$AUC_{144-.216}$ (pg*h/ml)	Cmin (pg/ml)
Nycomed	1680 (50)	28.0 (43)	84838 (48)	678 (56)
Durogesic	1753 (35)	26.8 (37)	87701 (41)	648 (59)
Ratio of LSM (90%CI)	94.0 (83.1-106.3)		95.4 (87.2-104.3)	104.8 (96.2-114.2)

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has been performed.

The results of the conducted bioequivalence study can be extrapolated to other strengths since the criteria for biowaiver for additional strengths are fulfilled according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence.

The risk/benefit ratio is considered positive and Matrifen, transdermal patch, 12 microg/hour, 25 microg/hour, 50 microg/hour, 75 microg/hour and 100 microg/hour is recommended for approval.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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