CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Morfinesulfaat TioFarma 10 mg, 20 mg and 100 mg, tablets
TioFarma b.v., the Netherlands

morphine sulphate

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.
It reflects the scientific conclusion reached by the MEB 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.

Registration number in the Netherlands: RVG 108334 - 108336

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Pharmacotherapeutic group:	analgesics, opioids, natural opium alkaloids
ATC code:	N02AA01
Route of administration:	oral
Therapeutic indication:	the treatment of severe pain requiring acute treatment with opioids
Prescription status:	prescription only
Date of authorisation in NL:	10 February 2012
Application type/legal basis:	Directive 2001/83/EC, Article 10a

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 Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Morfinesulfaat TioFarma 10 mg, 20 mg and 100 mg, tablets, from TioFarma b.v. The date of authorisation was on 10 February 2012 in the Netherlands.

The product is indicated for the treatment of severe pain requiring acute treatment with opioids.

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

Morphine acts as an agonist at opiate receptors in the CNS, particularly μ-receptors and to a lesser extent κ-receptors. μ-receptors are thought to mediate analgesia, respiratory depression, euphoria and physical dependence. κ-receptors, spinal analgesia, miosis and sedation. Morphine acts directly on the nerve plexus of the intestinal wall and causes constipation.

This national procedure concerns a well-established use application with reference to the innovator product Sevredol 10 mg and 20 mg tablets (NL License RVG 15043 and 15044) which was registered in the Netherlands by Mundipharma Pharmaceuticals B.V. since 1992. However, the innovator product is not available in the Netherlands anymore. In 2007, the IR tablet formulation was withdrawn, despite the request of the MEB to keep the product on the market. Only a morphine IR oral solution is currently available on the Dutch market (Oramorf®), but no IR tablets.
From a clinical point of view, IR tablets would be a relevant extension of the treatment arsenal. The benefit of IR formulation is that pain relief is more immediate than prolonged release forms could ever provide. This is a desired feature for patients with *e.g*. post-operative acute pain and other forms of acute pain like breakthrough pain. Patients may prefer tablets over the oral solution, especially if volumes are large as for adult and adolescent dosages. Distribution is also more feasible with tablets.

The marketing authorisation is granted based on article 10a of Directive 2001/83/EC, well-established use.

This application concerns a bibliographical application based on well-established medicinal use of morphine sulphate. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the applicant can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. ‘’Medicinal use’’ does not exclusively mean ‘’use as an authorised medicinal product’’, so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the applicant should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for generic medicinal products.

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 active substance is morphine sulphate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white to almost white crystalline powder and is soluble in water, very slightly soluble in ethanol and practically insoluble in toluene.

The CEP procedure is used for both suppliers of the active substance. 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 suitability 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 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.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the CEPs with additional requirements for particle size. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for one full scaled batch. This is acceptable since no batch analytical data are required when the CEP procedure is used.

Stability of drug substance
For one supplier, the active substance is stable for 5 years. Assessment thereof was part of granting the CEP and has been granted by the EDQM.
Stability data on the active substance from the other CEP holder has been provided for three full scaled batches stored at 25°C/60% RH (36 months), at 30°/65% RH (36 months) and at 40°C/75% RH (6 months). Changes were observed in clarity of solution and related substances. However, all values remained within specification limits. The proposed retest period of 36 months and storage condition “Store in original package, to protect from light” is justified.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Morfinesulfaat TioFarma 10 mg are white to off-white, round tablets with a diameter of 6.5 mm, a breaking line on one side and imprint ‘M10’ on the other side.
Morfinesulfaat TioFarma 20 mg are white to off-white, round tablets with a diameter of 8 mm and imprint ‘M20’ on one side.
Morfinesulfaat TioFarma 100 mg are white to off-white, oval 19 x 8 mm tablets, with a breaking line on one side and imprint ‘M100’ on the other side.

The 10 mg and 100 mg tablets can be divided in equal halves.

The tablets are packed in in transparent PVC/aluminium blister packages or hospital unit doses, and in polypropylene containers.

The excipients are: microcrystalline cellulose (E460), povidone K30, lactose monohydrate, sodium starch glycolate en magnesium stearate (E470b).

The used excipients and packaging are usual for this type of dosage form.
The tablets are fully dose proportional; different strengths are compressed from the same common blend.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The dissolution method has been adequately developed in order to show similarity of dissolution profiles between the different strengths. The dissolution profiles of the 10 mg, 20 mg and 100 mg strength at pH 1.0, pH 4.5 and pH 6.8 were determined. Over 85% is dissolved within 15 min in all cases. The dissolution profiles of the different strengths are accepted as similar. Compliance with the requirements of the Ph.Eur. on subdivision of tablets has been demonstrated.
Since this is a well established use application and taking into account the fast dissolution profiles, no bioequivalence study was performed. This is from the quality point of view acceptable. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is divided into the following steps: dry mixing, wet granulation, sifting, mixing, lubrication, compression and packaging.
The product is manufactured using conventional manufacturing techniques. Adequate process validation data of three full scaled batches of each strength have been provided.

Control of excipients
The excipients comply with Ph.Eur requirements. This is acceptable.

Quality control of drug product
The product specification includes tests for appearance, disintegration time, average mass, average mass of tablet halves, uniformity of mass, uniformity of mass of tablet halves, hardness, friability, identity, assay, residual solvent, related substances, uniformity of dosage units, microbial limits and dissolution. The release and shelf-life limits are identical except for hardness. Given the observed decrease in hardness during storage, this is acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two full scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three full scaled batches of each strength stored at 25°C/60% RH (24 - 30 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC-Alu blister and PP container with LDPE closure.
The appearance of all strengths changed at accelerated conditions. Hardness decreased in all strengths and in both packages. At accelerated conditions out of specification results were observed for all strengths in the blister and at long term conditions an out specification result was observed for hardness of the 10 mg tablet in blister.
Increases in impurities were observed in all strengths and at both conditions. However, all results remained within the proposed specification limits. The MAH has committed to perform stability studies at intermediate storage conditions on future batches. Results of a photostablity study confirmed the known photo sensitivity of morphine sulphate.
Based on the stability data provided a shelf life of 24 months for both blisters and containers can be granted. The storage conditions ‘Store below 25°C’ and ‘Store in original package in order to protect from light’ can be granted.

In-use stability data demonstrated that the drug product is stable for 30 days after first opening the container when stored at 25°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Statements of the suppliers of the drug substance and excipients regarding BSE/TSE safety have been provided. Lactose monohydrate is the only excipient of animal origin.

II.2 Non-clinical aspects

This application concerns a bibliographical application based on well-established medicinal use of morphine sulphate. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the Board agreed that no further non-clinical studies are required.

Environmental risk assessment
The product is intended as a substitute for other morphine sulphate products on the market. The approval of this product will not result in an increase in the total quantity of morphine sulphate 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

Morphine sulphate is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the Board agreed that no further clinical studies are required.

The dissolution profiles of these products indicate that release of the active substance from the tablets is very fast (>85%is dissolved within 15 min in all cases at 3 pH levels). From a clinical point of view, this is a warranted feature for an IR morphine tablet. No significant differences are expected of the pharmacokinetic profile and consecutively clinical features, in comparison to the already accepted product, *i.e*. Oramorf® oral solution. Even if C_{max} of the tablet would be slightly lower than for the oral solution as it takes some time for the tablet to dissolve in-vivo, it is not expected that this would result in clinical relevant differences. A waiver of the bioequivalence study is acceptable from a clinical point of view.

Risk management plan
Morphine sulphate was first approved in 1992, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of morphine sulphate can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the national procedure is in accordance with those accepted for other morphine containing products.

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. The test consisted of a pilot test with 5 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. In the first round 97.5% of the questions were answered correctly, in the second round 100% was answered correctly. This means that more than 90% of the participants were able to find the requested information, and of those, more than 90% were able to understand the information that was found and would act appropriately. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Morfinesulfaat TioFarma 10 mg, 20 mg and 100 mg, tablets have a proven chemical-pharmaceutical quality and are well-established medicinal products. The product is intended as a solid substitute to the immediate release liquid morphine formulations. A similar (innovator) medicinal product - Sevredol 10 mg and 20 mg tablets- is no longer marketed.

Since the application concerns a bibliographical application based on well-established medicinal use of morphine sulphate, and taking into account the fast dissolution profiles of the products no bioequivalence study was necessary.

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 morphine sulphate containing products.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that well-established use has been demonstrated, and has therefore granted a marketing authorisation. Morfinesulfaat TioFarma 10 mg, 20 mg and 100 mg, tablets were authorised in the Netherlands on 10 February 2012.

The following post-approval commitment has been made during the procedure:

- The MAH committed to perform intermediate stability studies on future batches.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
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
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