CBG MEB

Type II variation

Public Assessment Report for the suspension of

Palfium 5 mg tablets

(dextromoramide)

NL License RVG: 03170

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This module reflects the scientific discussion for the suspension of Palfium 5 mg tablets following a type II quality variation. The marketing authorisation was suspended on 28 November 2014.

I. RECOMMENDATION

Based on the review of the revised quality module on the active substance dextromoramide the MEB considers that there are several major issues and uncertainties regarding the manufacture and quality control, which has led to the rejection of the type II quality variation and suspension of the marketing authorisation for Palfium 5 mg tablets of ACE Pharmaceuticals B.V.

II. EXECUTIVE SUMMARY

II.1 Introduction and scope of the variation

Palfium® (dextromoramide) is a synthetic strong-acting opioid and full mu-opioid receptor agonist that has been registered in the Netherlands since 1974. The current indication is *severe acute or chronic pain requiring opioids, such as post-operative pain, and pain associated with bone fractures, malignancies and acute renal/biliary colic attacks* in adults.

It has been brought to the attention of the MEB that the product which is placed on the market has not been manufactured in line with the quality standards specified in the marketing authorisation, as the active substance of an unregistered drug substance manufacturer is being used.
The MEB has given the MAH the opportunity to resolve this dossier non-conformity by submitting a type II quality variation to add the respective drug substance manufacturer to the registration dossier.

In this Public Assessment Report (PAR), the quality documentation on the active substance is discussed.

As rejection of the variation application/not resolving the dossier non-conformity could lead to suspension of the marketing authorisation, the medical need and the possible consequences of shortage of the product have been assessed.
Besides Palfium there are no dextromoramide containing products registered in the Netherlands, or elsewhere in Europe, that could fulfil any shortage of stock.

This is an exclusively national procedure, and no concerned member states are directly involved.

III. SCIENTIFIC DISCUSSION

III.1 Quality aspects

The MAH has submitted a type II quality variation to register a new drug substance manufacturer in order to resolve the identified dossier non-conformity.

Based on the review of the quality data and the MAH's response to the questions raised it was concluded that the variation is not approvable as several major issues and uncertainties regarding the manufacture and quality control still remain. With the rejection of the type II variation, the dossier non-conformity remains unresolved. The details of the outstanding major objections are described below.

Drug substance
Dextromoramide tartrate is an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white, amorphous or crystalline powder which is soluble in water and sparingly soluble in ethanol. Dextromoramide tartrate contains one chiral centre. During the last step L-(+)-tartrate salt is formed by crystallisation. The consistency of the active substance is demonstrated by the specific optical rotation test. There are no reports in literature of polymorphic forms of dextromoramide tartrate.

Manufacturing process

Overall, the submitted data are outdated and insufficient to guarantee the quality of the drug substance. The following major deficiencies were identified:

- The provided description of the manufacturing process is not satisfactory. The MAH did not provide a procedural narrative including the quantities (or ranges) of raw materials, starting materials and intermediates, solvents, catalysts and reagents used in manufacture of a representatives scale commercial batch. This narrative should describe each step in the manufacturing process, and identify critical steps, process controls employed, and ranges for equipment operating conditions (e.g. temperature, pressure, pH, time, flow-rate).
- Materials used in the manufacture of the active substance (e.g., raw materials, starting materials, isolated intermediates, solvents, reagents, catalysts, process aids, etc.) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided, as well as information demonstrating that materials meet standards appropriate for their intended use.
- The MAH should propose and justify which substance should be considered as the active substance starting material, e.g. incorporated as a significant structural fragment into the structure of the active substance. The name and address of the starting material supplier(s) should be provided.
- Starting materials should be fully characterized to ascertain suitability for intended use and complete specifications should be provided, including an impurity profile. The possibility that impurities present in a starting material may be carried through the synthesis/process unchanged or as derivatives should be discussed and should therefore, if relevant, be controlled in the starting material by appropriate acceptance criteria with suitably validated methods. Acceptance criteria should be established based on evaluation of the fate of impurities present in the starting material, when subjected to the normal synthesis/process. Relevant viral safety and/or TSE data must be provided if any animal derived material is used during the active substance manufacturing process. Starting materials from vegetable origin should be fully characterized to ascertain suitability, and a contaminant profile should be established and submitted.
- Information on the quality and control of intermediates isolated during the process should be provided. The analytical methods used to control key intermediates that influence final quality should be suitably validated if they are non-compendial.

Characterisation

The drug substance specifications are set in accordance with the Ph.Eur. monograph of dextromoramide tartrate. However, the following data are lacking:

- Only a verification of the identity by means of Ph.Eur. identification reactions is insufficient proof of the actual structure of the drug substance synthesized. Full spectral data, NMR, IR, MS, elemental analysis etc., preferably against an official reference standard should be provided, along with a peak assignment.
- The possible impurities based on the specific synthetic route used and the reaction conditions should be discussed.
- Omitting a test on residual solvents is not acceptable. It should be demonstrated that all solvents used in the process or that might be present as impurities in other solvents or reagents are not present in the drug substance above the limits as stated in the Ph.Eur. monograph on Residual Solvents.
- A discussion on possible genotoxic impurities should be provided. Substances with structural alerts identified in the synthetic route should be limited in the drug substance specification to below the Threshold of Toxicological Concern (TTC) limit, together with a validated analytical method.

Quality control of drug substance

Regarding this section of the dossier, the following deficiencies were noted:

- Since the possible impurities are not described, it cannot be determined if the HPLC method used for the determination of the impurities is capable of detecting these impurities. This method should be separately validated for all impurities that might be present in the drug substance based on the route of synthesis.
- Batch analysis data for only one, older batch have been provided. Compliance with the proposed specification cannot be determined since results of the impurities tested by means

of HPLC and results on the residual solvents are missing. Furthermore, batch data on at least three batches should be provided.
- The provided justification of the specification is not acceptable. Limits for residual solvents should be set based on the solvents used in the process. The used class 2 solvents should at least be limited in the drug substance specification.
- The proposed limit for the individual unknown impurities of NMT 0.5% is not acceptable. In accordance with the Ph.Eur. monograph on Substances for Pharmaceutical Use unidentified impurities should be limited to NMT 0.10%. Impurities exceeding this limit should be identified and/or qualified.

Reference standards or materials
One batch of active substance is used as reference substance. This concerns the only batch manufactured so far. Hence the production batch and the reference standard are identical. This is unacceptable, especially since the assay value by HPLC is determined against the reference standard, which is the same batch. Furthermore, the reference standard has expired, and the structure was not adequately resolved.

Stability of drug substance
The following points of concern are unresolved:
- Only one batch has been included in the stability program. This is not sufficient to establish a re-test period and a storage condition.
- Data of storage under accelerated conditions are missing and should be submitted.
  An unknown impurity was detected which exceeds the identification and qualification threshold. Hence the impurity should be identified and qualified, and separately limited in the drug substance specification.

III.2 Clinical aspects

As rejection of the variation application/not resolving the dossier non-conformity could lead to suspension of the marketing authorisation, the medical need and the possible consequences of shortage of the product have been assessed.

When defining a product as critical, two criteria are of importance: therapeutic use and availability of alternatives.

Therapeutic use
Palfium is an oral strong opioid with a rapid onset of effect and short half-life. It has been estimated that it is about 3 times more potent than an equal dose of oral morphine.

Although severe pain is common, Palfium is rarely used in modern clinical practice. According to the Drug Information System (*Genees- en hulpmiddelen Informatie Project* - GIP) of the National Health Care Institute (*Zorginstituut Nederland*) the number of patients using Palfium dropped from 132 in 2009 to 75 in 2013. According to the MAH, about 6000-8000 packages containing 30 tablets are sold on a yearly basis, and about 180 patients are currently treated with Palfium in the Netherlands, France and the UK.
The MAH stated during an oral explanation meeting that Palfium is used for its rapid onset of effect, and as an alternative for morphine in patients who cannot tolerate morphine, e.g. because of nausea or metabolic impairment. However, in a small-scaled comparative study in post-operative setting, dextromoramide did not cause less nausea than morphine, but more respiratory depression (Keats et al, 1960[1]). Data in the literature regarding dextromoramide are scarce, and there are no other data of randomised studies available.

Palfium is not commonly used in clinical practice, which is illustrated by the fact that it has not been listed as a treatment option in recent national or European treatment guidelines on the treatment of severe pain (e.g. post-operative pain, cancer pain, or palliative care).

[1] Keats, Telford and Kurosu. Studies of analgesic drugs: III. Dextromoramide and a comparison of methods of estimating pain relief in man. Journal of Pharmacology and Experimental Therapeutics, 1960 vol. 130 no. 2 212-217

A reason why Palfium has become nearly obsolete may be that Palfium is notorious for its high abuse potential. Another reason may be that its use is advised against in *Farmacotherapeutisch Kompas*, because of high risk of hypotension and palpitations, as compared to other opioids (updated version of July 2014). Both adverse events are in fact related to rapid release characteristics of Palfium.

Availability of alternatives
There are several alternative strong opioids available that are licensed for the treatment of both acute and chronic severe pain.

For acute severe pain, immediate release (IR) oral formulations of morphine, oxycodone (twice as strong as morphine) or hydromorphone (7 times stronger) are registered. Additionally, several oro-mucosal fentanyl products have become available for the treatment of breakthrough cancer-pain, in recent years. To be noted, oromucosal fentanyl was superior to morphine IR in treating breakthrough cancer-pain according to a recent systemic review by Cochrane.
Furthermore, as these opioids target the same receptor as dextromoramide, the safety profile, warnings and contra-indications overlap.

For chronic severe pain, immediate-release formulations of strong opioids - like Palfium - are no longer the treatment of choice, because of the enhanced risk of dependence, abuse and overdose, as compared to slow-release formulations. Several oral modified-release formulations of morphine, oxycodone, hydromorphine, and fentanyl patches are registered for severe chronic pain. Transdermal formulations have the benefit that they may cause less constipation than oral opioids.

Conclusion
There is limited use of Palfium in current daily practice. There are sufficient alternative options available to fulfil the need and to cover the indications if Palfium runs out of stock or becomes definitively unavailable. In individual patients using Palfium chronically, conversion may be a challenge, however, it is not considered impossible.

IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The variation application and suspension have been discussed during the MEB Board meetings of 31 July 2014 and 27 November 2014.

Based on the quality data provided by the MAH, the Board concluded that the manufacturing of the drug substance is not compliant with the applicable quality standards. The submitted data are outdated and insufficient to guarantee the quality of the drug substance. It is for instance unknown whether toxic impurities are present in the active substance. The responses of the MAH did not address the outstanding major issues adequately. In addition, the MAH has informed the MEB that these issues regarding the manufacture and quality control of the active substance are not likely to be resolved at short notice.

Because of the deficiencies in the manufacturing of the product, and the fact that there is no other product with this active substance licensed in the Netherlands, the medical need has been assessed, It was concluded that Palfium is not considered a critical medicinal product as there are sufficient alternative treatment options available of the same class, with a comparable PK profile and mode of action to fulfil the need and to cover the indications.

Because of the unresolved dossier non-conformity regarding the manufacturing of the drug substance, the expectation that the remaining issues are not likely to be resolved at short notice and the availability of alternative treatment options, it was decided to suspend the marketing authorisation based on article 51, section 1, title and under j of the Dutch Medicines Act. The marketing authorisation was suspended on 28 November 2014. As there is no immediate risk to public health, the Dutch Health Care Inspectorate (IGZ) decided that batches of Palfium that have already been released may be sold for a period of 6 months. The MAH was requested to inform prescribers about the need for alternative treatment options.