

Public Assessment Report

Scientific discussion

Norspan 5, 10 and 20 micg/h transdermal patches Buprenorphine

DK/H/0718/001-003/E/001

This module reflects the scientific discussion for the approval of Norspan. The procedure was finalised on 3 March 2008. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Norspan 5, 10 and 20 micg/h transdermal patches, from Norpharma A/S, were first authorised in the RMS on 16 July 2003. Following national approval Denmark acted as reference member state in a Mutual Recognition Procedure which was finalised on 15 March 2005. Following the first round MRP, the MAH sought recognition of the marketing authorisation by other Member States via a repeat use procedure. This report concerns the 2nd wave MRP.

Based on the review of the quality, safety and efficacy data, the Member States in this repeat use procedure have granted a marketing authorisation for Norspan 5, 10 and 20 micg/h transdermal patches, from Norpharma A/S.

The product is indicated for treatment of severe opioid responsive pain conditions which are not adequately responding to non-opioid analgesics.

The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC. The original product is Temgesic 0.2 mg and 0.4 mg sublingual tablets from Schering-Plough.

With the present application, the applicant wants to introduce buprenorphine as a transdermal patch. Other forms of buprenorphine available are as injectable, buccal, and sublingual formulations. Norspan 5, 10 and 20 micg/h transdermal patches have been developed to provide continuous systemic delivery of buprenorphine for up to seven days from a single patch. The three strengths differ only in size of each patch as they are cut from the same bulk material. The transdermal delivery of this partial opioid agonist will provide continuous pain relief for patients with severe opioid responsive pain conditions that does not respond to non-opioid analgesics.

After finalisation of the first round Mutual Recognition procedure 4 variations were approved:

- Type II: Update of SPC, section 4.8 to harmonise with Company Core Data Sheet. The variation was submitted following the evaluation of the Periodic Safety Update Report covering the period 16-07-2004 to 15-01-2005.
- Type IA no. 15a: Submission of a new or updated European Pharmacopoeia certificate of suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance from a manufacturer already approved.
- Type II: Harmonisation of Package Leaflet and Labelling. During the clock stop a user consultation was performed. The user consultation was acceptable.
- Type IB no. 41.a.2: Addition of pack sizes 8, 10 and 12 in Germany only.

Since the first round MRP Module 3 of the dossier has been updated to CTD format and the applicant has performed a number of non-clinical and clinical studies.

II. QUALITY ASPECTS

II.1 Introduction

Norspan 5, 10 and 20 micg/h transdermal patches contain as active substance 5 mg, 10 mg and 20 mg, respectively of buprenorphine.

The 5 micg/h transdermal patch is a square, beige coloured patch with rounded corners marked: 5 µg/h.

The 10 micg/h transdermal patch is a rectangular, beige coloured patch with rounded corners marked: 10 µg/h.

The 20 µg/h transdermal patch is a square, beige coloured patch with rounded corners marked: 20 µg/h.

Norspan transdermal patches are packed individually in sealed sachets, composed of identical top and bottom layers of heat-sealable laminate, comprising (from outside to inside) paper, LDPE, aluminium and poly(acrylic acid-coethylene). Pack sizes of 1, 2, 3, 4, 5, 8, 10, 12 transdermal patches have been approved. However, not all pack sizes may be marketed.

The excipients in the adhesive matrix (containing buprenorphine) are: [(Z)-octadec-9-en-1-yl] oleate, povidone K90, 4-oxopentanoic acid, and poly[acrylic acid-co-butylacrylate-co-(2-ethylhexyl)acrylate-co-vinylacetate] (5:15:75:5), cross-linked.

The adhesive matrix (without buprenorphine) contains: Poly[acrylic acid-co-butylacrylate-co-(2-ethylhexyl) acrylate-co-vinylacetate] (5:15:75:5), not cross-linked.

The separating foil between the adhesive matrices with and without buprenorphine is composed of poly(ethyleneterephthalate)-foil while the backing layer consists of poly(ethyleneterephthalate)-tissue. Release liner (on the front covering the adhesive matrix containing buprenorphine) (to be removed before applying the patch) consists of poly(ethyleneterephthalate)-foil, siliconised, coated on one side with aluminium.

Compliance with Good Manufacturing Practice

The RMS 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.

II.2 Drug Substance

The active substance buprenorphine is an established active substance described in the European Pharmacopoeia (Ph.Eur.).

The CEP procedure is used for the active substance. A Certificate of Suitability is included in the file. The drug substance is controlled according to the Ph. Eur. Monograph.

The active substance buprenorphine base, is a potent opioid analgesic at low dose, and has an octanol/water partition coefficient (log P) of 3:085 which makes it suitable for transdermal delivery. The active substance is dissolved in a polyacrylate adhesive matrix system, commonly used in other transdermal patches on the market. A PET separating foil is used to prevent diffusion of the active substance into the matrix rim. The PET liner is removed before application, giving direct contact with the skin. The adhesive is pressure-sensitive.

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided.

Stability data on the active substance have been provided in accordance with applicable European guidelines. Based on the data submitted, a retest period of 2 years could be granted.

II.3 Medicinal Product

The product is intended for local application on skin with systemic analgesic effect. The patches are developed to give constant and low in-vivo flux rates in man of 5 micg, 10 micg, and 20 micg per hour respectively, with maintenance of blood/plasma levels up to 7 days. The difference in strength is obtained by proportional difference in patch size.

The development of the product is adequately described in accordance with the relevant European guidelines.

The choice of excipients is justified and their functions explained. The used excipients are well known and safe in the proposed concentrations.

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented in accordance with the relevant European guidelines.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. The batch analysis results show that the finished products meet the specifications proposed.

On the basis of the presented data, a shelf-life of 2 years can be established with the storage condition 'Do not store above 25°C'.

III. NON-CLINICAL ASPECTS

Norspan was first approved in Denmark on 16 July 2003. The initial non-clinical review resulted in a request for an update of the Expert Report with additional bibliographical and experimental data. These were subsequently provided by the applicant and integrated in the non-clinical assessment report.

In connection with the present 2nd wave MRP, the non-clinical dossier has been updated with 10 study reports:

Pharmacodynamic studies

- A study evaluating the binding affinities and functional (GTPγ[³⁵S] binding) activities at recombinant human opioid receptors.

Pharmacokinetic studies

- The distribution, elimination, and metabolism of ³H-buprenorphine were studied in mice following a single intravenous administration at a nominal dose of 10 mg ³H-buprenorphine free base/kg.
- Study measuring the inhibitory effect of ketoconazole on norbuprenorphine and buprenorphine glucuronide formation using human hepatocytes and pooled human liver microsomes. The effect of ketoconazole was investigated using human hepatocytes derived from 3 subjects or human recombinant UGT1A1 and UGT2B7 enzymes.
- Study investigating the effect of ketoconazole using human hepatocytes derived from 3 subjects or human recombinant UGT1A1 and UGT2B7 enzymes.
- One last pharmacokinetic study investigating the extent of buprenorphine binding to mouse, rat, rabbit, dog, monkey and human plasma proteins by equilibrium dialysis at 37 °C at concentrations of ³H-buprenorphine ranging from 0.0001-50 µg/mL.

Toxicology studies

- A toxicity study evaluating the potential toxicity, the maximum tolerated dose and toxicokinetics of buprenorphine base dissolved in acetone when administered to rats for three or six months by skin painting at dose levels corresponding to 0, 20, 60 and 200 mg/kg/day.
- A Pre- and Postnatal Dose Range-Finding Study in Rats with topically applied buprenorphine patches and subcutaneously administered buprenorphine HCl.
- A Pre- and Postnatal (Segment III) Study in Rats with topically applied buprenorphine patches and subcutaneously administered buprenorphine HCl.
- A 31-week dermal (skin painting) chronic toxicity study in mice with a 4-week recovery phase.
- A two year dermal (skin painting) carcinogenicity study in rats.

Conclusion

In connection with the 2nd wave MRP, the dossier has been updated with 10 non-clinical study reports pertaining to the pharmacology, pharmacokinetics and toxicology of buprenorphine. None of these studies have produced results that impact the benefit risk assessment or require any changes or amendments to the SPC; in particular as it is already mentioned in section 5.3 that buprenorphine may be associated with perinatal toxicity and as Norspan is not intended for use during pregnancy and lactation.

IV. CLINICAL ASPECTS

IV.1 Introduction

Norspan was first approved in Denmark on 16 July 2003. In connection with the present 2nd wave MRP, the clinical dossier has been updated with new studies submitted after the finalisation of the 1st wave MRP.

The Applicant has performed one study to determine the irritancy potential of topically applied buprenorphine HCl, 15 studies to evaluate the pharmacokinetics of buprenorphine from Norspan and one to assess the pharmacokinetics of intravenous buprenorphine. The studies meet the requirements of the NfG on Modified Release Oral and Transdermal Dosage Forms: Pharmacokinetic and Clinical Evaluation (CPMP/EWP/280/96). *In vitro* metabolism and drug interaction studies with buprenorphine have been performed following its incubation with human liver microsomes, recombinant human cytochrome P450 isoforms and human hepatocytes. A study was also performed to evaluate the effect on QT intervals of 10 mg and 40 mg buprenorphine delivered by Norspan.

The Phase II/III Norspan clinical efficacy and safety program consists of 11 studies with 2227 unique Norspan-treated subjects. There are five pivotal studies:

- an active-comparator study comparing the efficacy of Norspan to sublingual buprenorphine conducted in patients with moderate-to-severe osteoarthritis pain,
- an active- and placebo-controlled study in patients with moderate-to-severe chronic back pain,
- a placebo-controlled study in subjects with severe osteoarthritic pain, and
- two placebo-controlled, maintenance-of-analgesia design studies in subjects with non-malignant pain requiring opioid analgesia or osteoarthritis inadequately treated with non-opioids.

Osteoarthritis and back pain were selected as the efficacy model in several studies since they are common chronic conditions, internationally accepted as well-validated pain models in which to conduct analgesic clinical trials, the results from which may be extrapolated to the management of many other painful conditions (e.g. cancer pain).

None of the additional studies submitted by the applicant have revealed new concerns regarding the efficacy or safety of the product. Therefore, the risk/benefit-ratio of Norspan transdermal patches is considered unchanged and favorable.

V. PRODUCT INFORMATION

SmPC and Package leaflet

The present procedure is a repeat-use procedure and consequently no changes to the product information (SPC, PL and labelling) can be introduced during the procedure. SPC, PL and labelling therefore remain as agreed during the 1st wave MRP.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The present procedure is a repeat-use procedure and consequently no changes to the product information (SPC, PL and labelling) can be introduced during the procedure. SPC, PL and labelling therefore remain as agreed during the 1st wave MRP.

Agreement between Member States was reached after discussion in the CMD(h). The procedure was referred to the CMD(h) due to issues related to the effect size, the maintenance of effect and due to a lack of proven efficacy in a major indication. In the February 2008 CMD(h) meeting the Member States agreed that the applicant had submitted an acceptable response addressing the issues raised and were satisfied with the applicant's commitment to update the SPC in accordance with the comments received (section 4.1 and other relevant sections) via a type II variation.

The repeat use procedure was finished on 3 March 2008.

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

The Applicant commits to submitting a Renewal Application to both the 1st and 2nd wave Member States and in parallel the Applicant will also submit a Type II variation to include all of the agreed changes to the SPC within 30 days from the closure of the CMD(h) referral procedure on Monday 3 March 2008.

The updated SPC to be included in both the Renewal and the Type II variation will include:

- a) All proposals agreed during the 2nd wave MRP.
- b) Recent proposals from SE & NL and consideration of those from other Concerned Member States resulting from the CMD(h) referral including an update of the SPC section 4.1 to the following: 'Treatment of non-malignant pain of moderate intensity when an opioid is necessary for obtaining adequate analgesia'.
- c) Updates required from previous commitment arising from PSUR submissions.