SCIENTIFIC DISCUSSION

1. Introduction

Drug addiction is a worldwide problem of which opioid dependence, notably heroin addiction, is a major component. Most addicts inject drugs, quite often with dirty or shared syringes and needles and this behaviour is linked directly with the transmission of human immunodeficiency virus (HIV) and the hepatitis viruses. A key aim of treatment programs for opioid drug dependence is to stop the subjects from injecting drugs. Substitution is the treatment approach for opioid dependence in which street heroin of unknown strength and purity is replaced with a pharmaceutical grade opioid with a longer duration of action, such as buprenorphine.

Buprenorphine is a well-known substance available in several European countries for the treatment of severe pain. For the treatment of opioid dependence it was first approved in 1995 (France) and is currently available in most European countries. Buprenorphine has lower intrinsic activity than methadone and other full agonists, produces less sedation and cognitive impairment, and has a ceiling on potential depressant effects, even if injected, particularly on cardiac and respiratory functions. Sublingual buprenorphine (marketed as Buprenorphine alone) is an established substitution treatment for opiate abuse, but there has been some diversion to the intravenous route because buprenorphine produces a moderate opiate agonist effect. Thus, in the opinion of the applicant, there is a need for a formulation of buprenorphine that has low potential for intravenous misuse.

SUBOXONE is a fixed combination product for chronic substitution therapy in opiate dependence consisting of buprenorphine and naloxone formulated into a sublingual tablet containing buprenorphine and naloxone in the ratio 4:1 of the bases.

The claimed indication for SUBOXONE is **substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter intravenous misuse. As requested by the CHMP, treatment is intended for use in adults and adolescents over 15 years of age who have agreed to be treated for addiction.**

The product is intended as a "take home" medication presented in two strengths:

1. Buprenorphine 8 mg + naloxone 2 mg sublingual tablet
2. Buprenorphine 2 mg + naloxone 0.5 mg sublingual tablet.

The combination of an opioid antagonist with a potent μ-opioid analgesic is an established strategy for reducing the potential for intravenous misuse. Naloxone is a well-known opioid antagonist. As a mono-substance it is indicated for the treatment of opioid-overdosage or –intoxication. When administered in usual doses to patients who have not recently received opioids, naloxone exerts little or no pharmacologic effect. In patients who have received large doses of opioids, naloxone antagonises most of the effects of the opioid. The addition of naloxone to buprenorphine is intended to render the product less abusable by deterring intravenous injection.

2. Quality aspects

Introduction

Suboxone is presented as sublingual tablets containing a fixed dose combination of buprenorphine hydrochloride and naloxone hydrochloride dihydrate, at a ratio of 4:1, with respect to the free bases. Suboxone is available in two strengths:

- 2 mg / 0.5 mg tablets containing 2.16 mg buprenorphine hydrochloride (equivalent to 2 mg buprenorphine base) and 0.61 mg naloxone hydrochloride dihydrate (equivalent to 0.5 mg naloxone base).

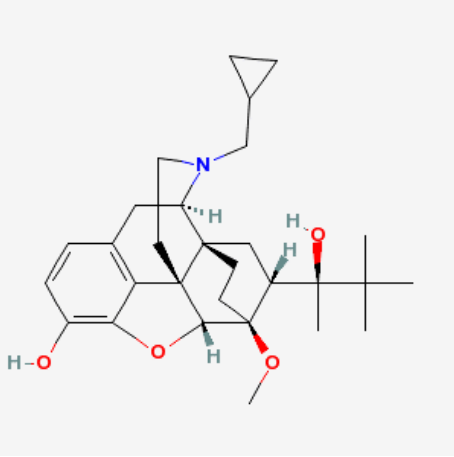
naloxone base).

The excipients used in this formulation are lactose monohydrate, mannitol, maize starch, povidone K30, citric acid anhydrous granular, sodium citrate, natural lemon and lime flavour, acesulfame potassium and magnesium stearate. Suboxone is administered via the sublingual route and is packed in nylon/aluminium/PVC blister packs containing either 7 or 28 tablets.

Active Substance 1. (Buprenorphine hydrochloride)

Buprenorphine hydrochloride is an established active substance and the subject of a monograph in the Ph. Eur.

Buprenorphine hydrochloride is designated chemically as (2S)-2-[17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol hydrochloride and its chemical structure is as follows:



Buprenorphine hydrochloride is a white or almost white, crystalline powder, sparingly soluble in water, freely soluble in methanol, soluble in alcohol, practically insoluble in cyclohexane.

Buprenorphine has several chiral centres and it is therefore optically active.

The potential for polymorphism was investigated using powder X-Ray diffraction and Differential Scanning Calorimetry (DSC) techniques. The results showed that there is no evidence for polymorphism.

- Manufacture

Buprenorphine hydrochloride is synthesized from thebaine. The structure has been confirmed by elemental analysis, spectroscopic analysis (UV, IR, NMR and MS) and X-Ray crystallography. The stereochemistry of the intermediates and the final active substance was investigated using X-ray crystallography and NMR spectroscopy. The absolute configuration was confirmed at different stages during the synthesis.

- Specification

The specification of the active substance includes physical description, visual inspection of the appearance in solution, assay by titration and by HPLC, specific optical rotation, acidity or alkalinity and related substances (HPLC). Additional tests performed are as follows: control for water content using the Karl Fisher method and residue on ignition, residual solvent, ionic chloride and particle size.

The analytical methods used were those described in the PhEur. Monograph, one major exception being the determination of related substances. The HPLC method for determination of related impurities uses specific impurity markers. It allows detection and quantitation of the five major impurities specified, whereas using the method described in the Ph. Eur. only two of the impurities can be detected. In addition, the acceptance criteria set for each specified impurity is more stringent than the limits mentioned in Ph. Eur. monograph. The maximum limit for total related impurities is also

Batch analysis data was provided for 23 batches of buprenorphine hydrochloride manufactured following the proposed synthetic method. The results showed that the active substance can be reproducibly manufactured.

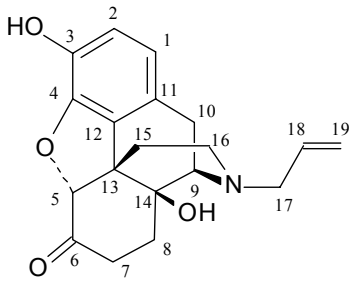
- Stability

The stability of buprenorphine hydrochloride was investigated in 3-production scale batches stored in the proposed packaging according to the ICH guideline. Stability studies were performed under long term and intermediate ICH conditions for 156 weeks, and accelerated ICH conditions for 52 weeks. An additional study was performed using a larger scale production batch. In this study the stability studies were performed under long-term and intermediate conditions for 52 weeks and accelerated conditions for 39 weeks. The results obtained demonstrate that buprenorphine hydrochloride remains physically and chemically stable for 52 week at long-term and intermediate conditions and 26 weeks at accelerated conditions.

The data provided is sufficient to confirm the proposed re-test period.

Active Substance 2. (Naloxone hydrochloride dihydrate)

Naloxone hydrochloride dihydrate is an established active substance and the subject of a monograph in the Ph. Eur. Naloxone hydrochloride dihydrate is designated chemically as Morphinan-6-one, 4,5-epoxy-3, 14-dihydroxy-17-(2-propenyl)-, hydrochloride, (5α)-dihydrate. Its chemical structure is as follows:



Naloxone hydrochloride dihydrate is a white or almost white crystalline powder, hygroscopic, soluble in water and alcohol, practically insoluble in ether. The pKa of Naloxone hydrochloride dihydrate is 7.94 at 20°C and the melting point is 200-205°C.

- Manufacture

Naloxone hydrochloride is synthesised from noroxymorphone. The assigned structure of naloxone hydrochloride dihydrate is supported by the evidence of IR spectrophotometry, and by ^{1}H-NMR and ^{13}C-NMR spectrometry.

Naloxone hydrochloride dihydrate contains four chiral centres, all of which are already present in the starting material of the synthesis, noroxymorphone, which is derived from natural opiates.

The possibility of polymorphism was investigated by standard techniques. The results showed that all batches exhibited the same morphic form.

- Specification

Naloxone hydrochloride dihydrate is tested for compliance with both PhEur. and USP monographs by the active substance manufacturer. These tests include physical description, identification by IR, TLC and chloride, specific optical rotation, loss on drying, Noroxymorphone hydrochloride and other impurities by TLC, chloride content, appearance of solution, acidity or alkalinity, related substances by HPLC, water content, sulphated ash and assay by titration. The specification also includes some additional non-pharmacopoeial tests (a stability-indicating HPLC method for assay and related

precision, accuracy and ruggedness. The peak area of naloxone decreases and degradation products are observed in samples exposed to stress conditions, confirming that the assay is stability-indicating.

Five batches of naloxone hydrochloride were manufactured using the proposed synthetic method. The results indicate that every batch complied with the limits for related substances.

- Stability

The stability of naloxone hydrochloride was investigated in 12 batches stored in the proposed packaging according to the ICH guideline. Stability studies were performed under long term, intermediate and accelerated ICH conditions for up to 60 months. No marked evidence of instability was revealed under any of the storage conditions and the proposed re-test period appears to be justified on the basis of the stability data presented.

Medicinal Product

- Pharmaceutical Development

Suboxone was developed in order to deliver a similar dose of buprenorphine compared to buprenorphine alone tablets (medicinal product containing buprenorphine that is authorised in the EU for the treatment of opioid addiction), but reducing the potential for intravenous abuse. Naloxone, an opiate antagonist, has poor bioavailability when administered by the sublingual route and consequently when Suboxone is taken sublingually it shows only the required effects of buprenorphine and delivers the same performance as an equivalent dose of buprenorphine alone tablets. However, if abused intravenously by an opiate-dependent subject, the antagonist effects of naloxone become apparent first as intense withdrawal symptoms followed by the attenuated agonist effects of buprenorphine.

Therefore the Suboxone formulation is closely based on the formulation of buprenorphine alone sublingual tablets but with naloxone added to reduce the potential for abuse by the intravenous route. A buprenorphine to naloxone ratio of 4:1 contains sufficient naloxone to produce opiate antagonist effects following intra-venous administration, but does not impair the effectiveness of buprenorphine when the mixture is taken by the sublingual route.

The excipients used in Suboxone are qualitatively and quantitatively identical to those used in the existing buprenorphine alone sublingual tablets, i.e., lactose monohydrate, mannitol, maize starch, povidone K30, citric acid anhydrous, sodium citrate and magnesium stearate. Acesulfame potassium and natural lemon and lime flavour (sweetener and flavouring agents, respectively) were included to disguise the bitter taste of naloxone. The content of lactose monohydrate was reduced slightly in order to maintain identical compression weights. All excipients have been widely used in commercial pharmaceutical dosage forms or as food additives. Except for the natural lemon and lime flavour all excipients comply with the specification of the Ph. Eur. Natural lemon and lime flavour is a natural flavouring, which complies the requirements of directive 88/388/EEC (as amended) on flavourings for use in food. Certificates of analysis have been provided for all excipients.

- Adventitious Agents

Lactose monohydrate is the only excipient of animal origin. However, it is prepared from bovine milk suitable for human consumption, which is sourced from healthy animals. Magnesium stearate is of vegetable origin.

- Manufacture of the Product

The manufacturing process of the finished product comprises standard mixing, wet granulation and compression techniques. Process parameter ranges (sieve sizes, mixing times and speed, drying time and temperature) were described for each step of the manufacturing process. Validation studies involved the preparation of 3 full-scale batches of the tablet blend. Each of the batches was then sub-divided into two sub-lots for the preparation of tablets of both strengths, i.e., 2 mg/0.5 mg tablets and 8 mg/2 mg tablets. An additional full-scale batch of each tablet strength was manufactured. All eight batches complied with final product specification. From the evidence of the process validation studies

- Product Specification

The product specifications include methods for appearance, identification (buprenorphine and naloxone) by HPLC and TLC, assay and content uniformity (buprenorphine and naloxone) by HPLC, dissolution of buprenorphine and dissolution of naloxone, disintegration time, buprenorphine degradation products, naloxone degradation products, water content and microbiological integrity.

The drug product specifications have been justified and all methods of analysis have been described and adequately validated.

- Stability of the Product

Stability data on three batches of each strength of Suboxone sublingual tablets (8 mg / 2 mg and 2 mg / 0.5 mg) packaged under a nitrogen atmosphere was provided. The studies were performed under long-term, intermediate, and accelerated conditions. The parameters evaluated during these studies were those mentioned in the shelf-life specification, except for two minor deviations. Analytical results up to 156 weeks were presented. All tests remained within specification for 156 weeks at 25°C/60% RH. The key shelf-life limiting parameter appeared to be disintegration time. There is evidence of a time-dependent increase but all samples stored at complied with the specification for 156 weeks.

Based on the available stability data, the proposed shelf life and storage conditions, as stated in the SPC, are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substances and drug product has been presented in a satisfactory manner. The results of test carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

3. Non-clinical aspects

- Introduction

Most of the preclinical studies were conducted in accordance with good laboratory practice regulations. Some studies have been performed prior to the introduction of GLP regulation and are not GLP-compliant. Since both of the active ingredients are established substances the documentation for pharmacology consists of published literature plus study reports with the combination of the active ingredients.

- Pharmacology

Buprenorphine is a semisynthetic, highly lipophilic opioid derived from thebaine with a 25 -30 fold higher analgesic potency as compared to morphine and a longer lasting effect. It is a partial agonist at the μ- and an antagonist at the κ-opioid receptor subtype. It dissociates very slowly from opioid receptors (t½ 166 min vs. 7 min for fentanyl) and is, once bound, hardly displaced by naloxone, however, prior treatment with naloxone can prevent e.g. respiratory depression. It is able to substitute for other opioids such as heroin but provides only moderate opiate agonist effects and a low degree of physical dependence. Being a partial μ-receptor agonist it may cause symptoms of abstinence in patients treated with μ-receptor agonists (e.g. morphine) and restricts its own analgesic effects once a maximum is reached, resulting in a bell-shaped dose response curve. When treatment with buprenorphine is discontinued withdrawal signs are generally mild due to slow dissociation from the μ-receptor and concomitant adaptive processes.

Naloxone is the N-allyl derivative of oxymorphone. It has antagonistic effects at μ, δ- and κ-opioid receptors and is currently marketed in injectable form for the complete or partial reversal of opiate effects or for the suspected acute opiate overdose. When given alone, hardly any effect is observed

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