EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 September 2015
EMA/774165/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Suboxone

International non-proprietary name: buprenorphine / naloxone

Procedure No. EMEA/H/C/000697/X/0029

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

ASMF	Active Substance Master File
AUC	Area Under the plasma Concentration
AUC0-inf	Area Under the plasma Concentration-time curve from time zero to infinity
AUC0-t	Area Under the plasma Concentration-time curve from time zero to t hours
BE	Bioequivalence
Cmax	Maximum plasma concentration
CEP	Certificate of Suitability of the European Pharmacopoeia
CI	Confidence interval
EC	European Commission
FTIR	Fourier transform infrared spectroscopy
GC	gas chromatography
GCP	Good Clinical Practice
HPLC	high-performance liquid chromatography
ICH	International Conference of Harmonization
IR	Infrarred
IV	intravenous
KF	Karl Fischer
NIR	Near Infrared Spectroscopy
NMR	Nuclear Magnetic Resonance
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PVC	Polyvinyl chloride
QTPP	Quality target product profile
RH	Relative Humidity
RMP	Risk Management Plan
SL	Sublingual
SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count
TEAE	Treatment Emergent Adverse Event
TLC	Thin layer chromatography
Tmax	time to maximum concentration

TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Combined Yeast and Mould Count
USP	United States Pharmacopoeia
UV	ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The MAH Indivior UK Limited submitted on 01 September 2014 an extension for a Marketing Authorisation to the European Medicines Agency (EMA) for Suboxone Sublingual Tablet (12mg/3mg and 16mg/4mg), through the centralised procedure falling under Article 19 of Commission Regulation (EC) No 1234/2008, Annex I 2.(c)

The MAH applied for two new strengths: 12mg/3mg and 16mg/4mg

Suboxone Sublingual Tablet is used in the following indication:

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. Treatment is intended for use in adults and adolescents over 15 years of age who have agreed to be treated for addiction.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008, Annex I 2.(c) Change or addition of a new strength/potency.

The application submitted is an extension application of a fixed combination medicinal product with new dosage strengths, composed of administrative information, quality, non-clinical and clinical data.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Martina Weise

- The application was received by the EMA on 1 September 2014.
- The procedure started on 24 September 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 December 2014.
- During the meeting on 22 January 2015, the CHMP agreed on the consolidated List of Questions to be sent to the MAH. The final consolidated List of Questions was sent to the MAH on 23 January 2015.
- The MAH submitted the responses to the CHMP consolidated List of Questions on

20 March 2015.

• The Rapporteur circulated the Assessment Report on the MAH's responses to the List of Questions to all CHMP members on 27 April 2015.

• The PRAC RMP Advice and assessment overview was endorsed by PRAC on 7 May 2015.

• During the CHMP meeting on 21 May 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the MAH.

• During the CHMP meeting on 25 June 2015, the CHMP agreed on a timetable extension request from the MAH.

• The MAH submitted the responses to the CHMP List of Outstanding Issues on 17 August 2015.

• The Rapporteur circulated the Assessment Report on the MAH's responses to the List of Outstanding Issues to all CHMP members on 02 September 2015.

• The MAH withdrew the12mg/3mg tablet from the line extension application on 08 September 2015

• The Rapporteur circulated the updated Assessment Report to all CHMP members on 16 September 2015.

• During the meeting on 21-24 September 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for the granting of an extension of the Marketing Authorisation for Suboxone concerning a new strength: 16mg/4mg sublingual tablets.

2. Scientific discussion

2.1. Introduction

Suboxone is a fixed combination product consisting of buprenorphine and naloxone formulated as a sublingual tablet. It is approved for the substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. Treatment is intended for use in adults and adolescents over 15 years of age who have agreed to be treated for addiction.

In accordance with the approved posology, up to a maximum of 24 mg buprenorphine can be dosed daily. As Suboxone is currently only available as 8/2 mg and 2/0.5 mg sublingual tablets, higher dose levels require multiple tablets. This line extension application introduce new dosage strengths; 12/3 mg and 16/4 mg, which aimed to minimise the number of tablets a patient would require for dosing. During the evaluation, the Applicant has withdrawn the 12/3 mg tablet as the study comparing this dose with the equimolar combination of currently marketed tablets did not demonstrate bioequivalence.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as 16mg/4 mg immediate release sublingual tablets containing a fixed dose combination (4:1 weight ratio) of buprenorphine (as hydrochloride) and naloxone (as hydrochloride dihydrate) as active substances.

This strength is introduced as a line extension to the already marketed Suboxone 2mg/0.5mg and 8mg/2mg sublingual tablets.

Other ingredients are lactose monohydrate, mannitol, maize starch, povidone K 30, citric acid anhydrous, sodium citrate, magnesium stearate, acesulfame potassium and natural lemon and lime flavour.

The product is available in Paper/Aluminium/Nylon/Aluminium/PVC blister packs.

2.2.2. Active Substance

The active substances used for the manufacture of the new strength are the same as those used for the already-authorised presentations. Minor changes were made to the active substance section as part of this line extension but these are administrative in nature and do not impact the quality of the finished product.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development
Suboxone 16mg/4mg sublingual tablets were developed with the aim of producing a formulation delivering an equivalent sublingual dose of buprenorphine as the existing buprenorphine sublingual tablets, but with a reduced potential for intravenous abuse. Since the combination of naloxone, an opiate antagonist, with buprenorphine an opiate partial agonist is an established strategy for reducing potential of IV misuse, a fixed dose combination was pursued.

Two strengths of Suboxone, namely Suboxone 2 mg / 0.5 mg and 8 mg / 2 mg sublingual tablets, are currently authorised in Europe. The posology scheme of these tablets supports dosing up to 24 mg buprenorphine daily. These dose levels currently require the administration of multiple tablets. In order to reduce the number of tablets a patient would require to take daily and thus increase convenience and compliance, two additional strengths, Suboxone 12 mg / 3 mg and Suboxone 16 mg / 4 mg tablets, have been developed and were initially presented in this line extension application.

Specifically, the quality target product profile (QTPP) was for sublingual immediate release tablets containing 12 mg buprenorphine / 3 mg naloxone and16 mg buprenorphine / 4 mg naloxone, differentiated from the other strengths by shape and/or tablet size and embossing, bioequivalent to the already EU authorised Suboxone strengths, containing the same excipients, packaged in child resistant blisters and stable for at least 36 months under ICH long-term storage conditions (25°C/60%RH and 30°C/75%RH).

The new tablet strengths contain the same excipients as the current formulations of Suboxone, sublingual tablets registered in Europe (EU/1/359/001-4). All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The *in vitro* dissolution profiles of the two new strengths were compared with the previously-approved strengths using the registered dissolution test method. As more than 85 % is released within 15 minutes, the dissolution profiles are deemed to be similar (CPMP/EWP/QWP/1401/98 rev. 1.).

The formulation used during clinical studies is the same that is used for marketing.

The discriminatory power of the dissolution method has been satisfactorily demonstrated.

The primary packaging is blister packs Paper/Aluminium/Nylon/Aluminium/PVC. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

As mentioned under pharmaceutical development section, the manufacture of Suboxone 16 mg/4 mg tablets was based on the registered manufacturing process of the already approved Suboxone 2 mg/0.5 mg and 8 mg/2 mg tablets.

In general, the manufacturing process consists of three main steps: wet granulation, tabletting and packing. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identification of buprenorphine and naloxone (HPLC, TLC), buprenorphine content (HPLC), buprenorphine content uniformity (HPLC), buprenorphine related impurities (HPLC), naloxone content (HPLC), naloxone content uniformity (HPLC), naloxone related impurities (HPLC), water content (Karl Fischer), mean tablet weight (gravimetric), dissolution of buprenorphine, dissolution of naloxone, disintegration time and microbiological quality (Ph. Eur.).

Batch analysis results are provided for four commercial scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data on three commercial scale batches of each of the proposed tablet strength stored under long term conditions for up to 24 months at 30 ºC / 65% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Supporting stability data from tablets used for clinical studies packed in foil without a child resistant closure stored for up to 25 months at 30 °C / 65% RH and 9 months at 40 °C / 75% RH were also presented.

Further supporting stability data on three batches each of the already registered strengths, Suboxone 2 mg/0.5 mg and 8 mg/2 mg, stored at 30 ºC / 65% RH for up to 24 months were also provided.

Samples were tested for appearance, identification of buprenorphine and naloxone, buprenorphine content, buprenorphine related impurities, naloxone content, naloxone related impurities, mean tablet weight, dissolution of buprenorphine, dissolution of naloxone, disintegration time, water content and microbiological quality. The analytical procedures used are stability indicating.

No out of specification results or trends were observed for any of the measured parameters at any of the conditions tested. Based on available stability data, the shelf-life of 3 years as stated in the SmPC is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate 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 clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

No new non-clinical data has been submitted with this line extension application.

2.3.2. Ecotoxicity / environmental risk assessment

The introduction of the additional strength is not expected to significantly increase the use of Suboxone in the treatment of opioid addiction. Consequently, the Environmental Risk Assessment does not need to be updated.

2.3.3. Discussion on non-clinical aspects

NA

2.3.4. Conclusion on the non-clinical aspects

No new non-clinical studies have been performed in support of this application. This was considered acceptable as the route of administration and the pharmaceutical form remain unchanged. The higher strength sublingual tablets are within the maximum daily dose and the posology recommendations are not affected.

2.4. Clinical aspects

2.4.1. Introduction

To support this application, the MAH conducted 2 bioequivalence studies of the new dosage strengths. However, only one study is discussed below to support the new strength 16/4mg Suboxone.

Study RB-UK-12-0007 evaluated bioequivalence of the newly proposed 12/3mg tablet with the equivalent dose obtained with a combination of the current marketed product.

The application for the 12/3mg strength was withdrawn by the MAH during the evaluation and results of study RB-UK-12-0007 will not be discussed further in this report.

Study RB-UK-12-0008 evaluated 2 formulations of the 16/4 mg dosage strength, one hexagonal and one circular. Marketing authorisation was sought for the circular formulation only.

No further studies related to bioavailability or efficacy were submitted and none were required.

GCP

The Clinical trials was performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

Study RB-UK-12-0008

Methods

This was a randomised, single dose, open label, cross over study in healthy volunteers, using the currently marketed Suboxone 8/2 mg tablets as a reference. Treatment periods were separated by a washout period of at least 14 days.

All study treatments were administered under the tongue until they dissolved.

Blood (plasma) pharmacokinetic characteristics were assessed after each dose of study medication. Blood samples for PK analysis were collected at the following times: 0 h (predose), 0.083, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, and 144 h post dose.

Study populations

The study was conducted in opioid-naive and/or nondependent healthy volunteers under a naltrexone block in order to improve the tolerability of the study drugs.

The study enrolled healthy Caucasian adult subjects. 44 of them were male and 4 female and all were non-smokers. The mean age was 34.3 years (range 18-55 years) and the BMI range was 19.7-29.9 kg/m².

Test and reference products

Test formulation (Treatment A) sublingual tablet (hexagonal)	Buprenorphine / naloxone 1 x 16/4 mg
Manufacturer:	Reckitt Benckiser Healthcare Ltd, UK

	Batch No. 3025140
Test formulation (Treatment B) sublingual tablet (circular) Manufacturer:	Buprenorphine / naloxone 1 x 16/4 mg Reckitt Benckiser Healthcare Ltd, UK Batch No. 3018249 Date of manufacture 20.08.2012
Reference treatment (Treatment C) sublingual tablet Manufacturer: Date of manufacture	Suboxone 2 x 8/2 mg Reckitt Benckiser Pharmaceuticals Ltd. Batch No. 228506 28 Sep 2012

Pharmacokinetics variables

Cmax, AUClast, and AUCinf were calculated for the actives and metabolites, respectively. In addition, AUC0-72h was calculated for buprenorphine and norbuprenorphine.

Analytical methods

Plasma concentrations for the actives and metabolites were determined using a validated liquid chromatography tandem mass spectrometry method. Maximum storage time for samples was 90 resp. 87 days. All samples were analysed within the 404 days demonstrated long-term storage stability in human plasma containing tripotassium EDTA at -20 °C.

3088 original human plasma samples, containing tripotassium EDTA were analysed. To demonstrate reproducible quantitation of incurred subject samples, approximately 10% of the study samples were re-assayed. Incurred sample repeats were considered acceptable if the original and re-assay values from two-thirds of the repeated samples had a relative percent difference of ≤ 20%. The results of the incurred sample repeats met the acceptance criteria.

Statistical analysis

Comparison of the natural log-transformed PK parameters Cmax, AUClast, and AUCinf, for the actives and metabolites, and AUC0-72h, for buprenorphine and norbuprenorphine, across treatments was performed using a mixed-effects analysis of variance (ANOVA) model and Schuirmann's two 1-sided t-tests procedure. The ANOVA model included sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect. The ratios of the geometric means (A/B) and 90% confidence intervals (CIs) were reported after back exponentiation. An analysis following the CHMP Guideline on the Investigation of bioequivalence was also performed. In this analysis, fixed subject within sequence effect was used in the ANOVA models and other aspects and result presentation were kept similar. Subjects with paired data for a particular parameter (ie, from both treatment periods) were included in this analysis.

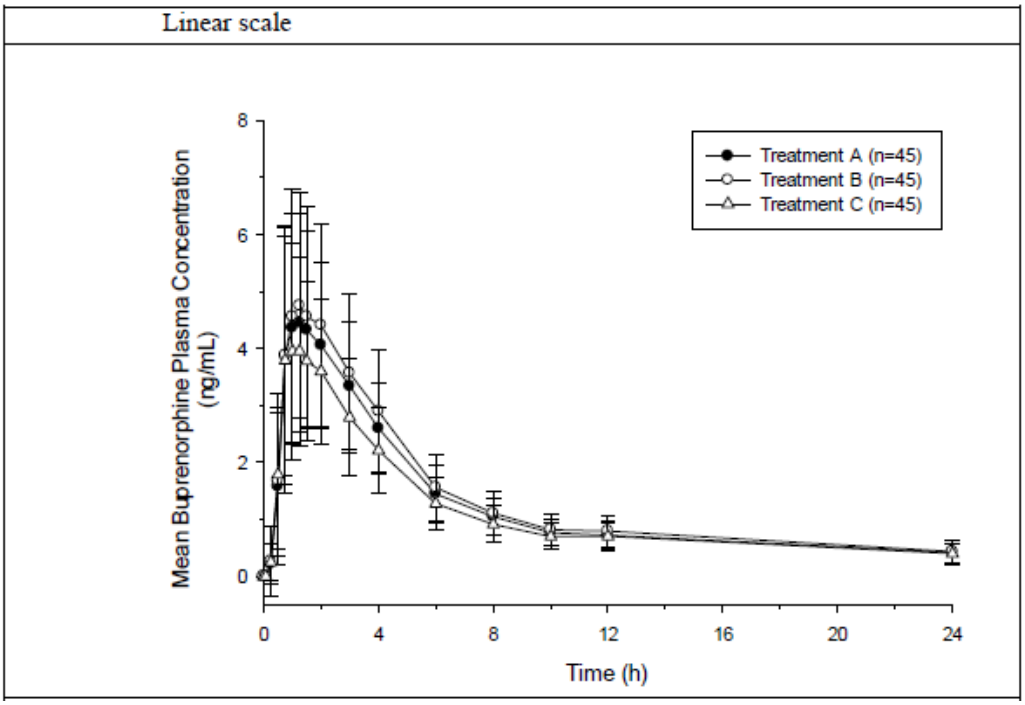
Bioequivalence was demonstrated if the 90% CIs for the geometric mean ratios (test/reference) for C_{max}, AUC_{last}, AUC_{inf}, and AUC_{0-72h} were entirely contained within the predefined no-difference interval of 80% to 125%.

Results

Of the 48 subjects who were randomized, 45 subjects completed all treatments and were included in the PK population. Three subjects failed to complete all 144-hour PK assessments and were excluded from PK analyses.

Mean buprenorphine concentrations over time are presented on linear scale in Figure 1 below.
In Treatment A, Treatment B, and Treatment C, the mean buprenorphine concentrations rose to a peak between 1.00 and 1.25 hours and declined bi-exponentially through 144-hours post dose.

Of the 45 subjects in the PK population, 39 subjects receiving Treatment A, 40 subjects receiving Treatment B, and 38 subjects receiving Treatment C had quantifiable buprenorphine plasma concentrations throughout the 144-hour observation period.



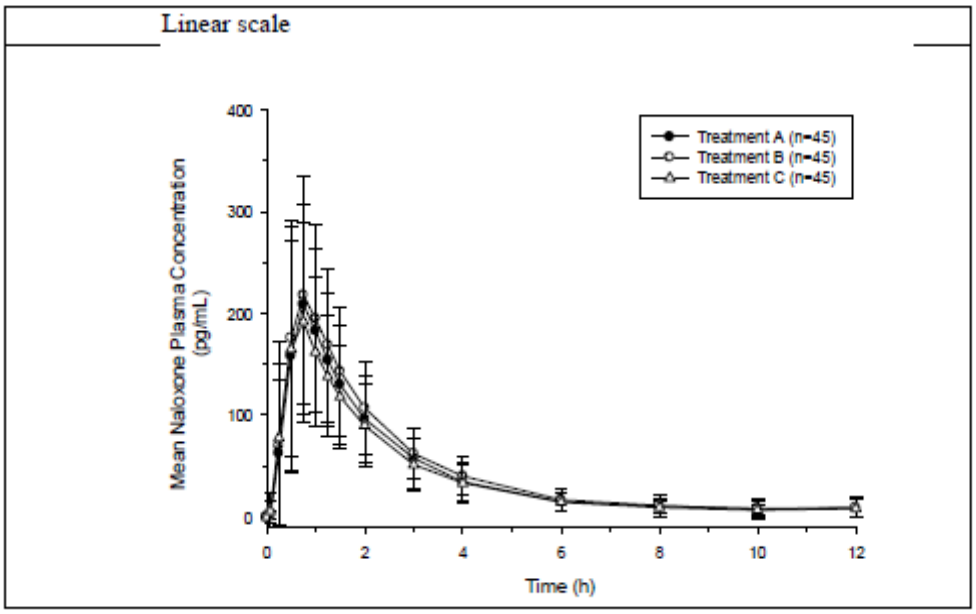
The statistical analysis of the buprenorphine PK parameters is presented in the Table 1 below.
No difference in buprenorphine AUCinf, AUClast, AUC0 72h, and Cmax was observed when comparing both test treatments (Treatment A and Treatment B) to the reference treatment (Treatment C) since all the 90% CIs of the geometric LS mean ratios were contained within the predefined equivalence limits of 80% to 125%.

Statistical Comparison of Primary Buprenorphine Pharmacokinetic Parameters

Parameter (unit)	Treatment	N	Geometric LS Mean	Treatment Comparison Pair	Ratio (%)	90% CI
AUC_{inf} (ng*h/mL)	A	44	48.0	A/C	108.59	(102.53, 115.02)
	B	44	50.9	B/C	115.21	(108.77, 122.04)
	C	44	44.2			
AUC_{last} (ng*h/mL)	A	45	45.5	A/C	107.94	(102.02, 114.21)
	B	45	48.6	B/C	115.38	(109.05, 122.08)
	C	45	42.2			
AUC_{0-72h} (ng*h/mL)	A	45	39.9	A/C	108.82	(103.22, 114.73)
	B	45	42.6	B/C	116.08	(110.11, 122.38)
	C	45	36.7			
C_{max} (ng/mL)	A	45	4.92	A/C	109.62	(101.95, 117.86)
	B	45	5.05	B/C	112.57	(104.70, 121.03)
	C	45	4.49			

Mean naloxone concentrations over time are presented on linear and semi-logarithmic scales in the Figure 2 below. For Treatment A, Treatment B, and Treatment C, mean naloxone concentrations rose to a peak at approximately 0.75 hours and declined thereafter. Of the 45 subjects in the PK population, 42 subjects receiving Treatment A, 44 subjects receiving Treatment B, and 41 subjects receiving Treatment C had quantifiable naloxone plasma concentrations 12 hours post dose. By 24 hours post dose, the majority of subjects receiving all treatments had naloxone plasma concentrations that were BLQ.

Figure 9 Mean (SD) Naloxone Plasma Concentration-time Profiles by Treatment on Linear and Semi-logarithmic Scales



No difference was observed in naloxone AUC last and Cmax comparing Treatment B (test) to Treatment C (reference) since the 90% CIs of the geometric LS mean ratios for these parameters were contained within the predefined equivalence limits of 80% to 125%.

However, the 90% CI of the geometric LS mean ratio for naloxone AUCinf comparing Treatment B to Treatment C was partially contained with these limits.

Table 20 Statistical Comparison of Primary Naloxone Pharmacokinetic Parameters Following European Medicines Agency Guidelines

			Geometric	Treatment Comparison		
Parameter (unit)	Treatment	N	LS Mean	Pair	Ratio (%)	90% CI
AUC_{inf} (pg*h/mL)	A	30	543	A/C	106.12	(96.02, 117.27)
	B	30	595	B/C	116.22	(105.20, 128.40)
	C	30	512			
AUC_{last} (pg*h/mL)	A	45	501	A/C	106.26	(97.92, 115.32)
	B	45	538	B/C	114.31	(105.34, 124.06)
	C	45	471			
C_{max} (pg/mL)	A	45	209	A/C	110.85	(100.72, 122.01)
	B	45	213	B/C	112.91	(102.59, 124.27)
	C	45	189			

ANOVA = analysis of variance; CI = confidence interval; EU = European Union; LS = least squares; HCl = hydrochloride; N = number of subjects

Results based on linear mixed ANONVA model with sequence, treatment, period, and subject nested within sequence as fixed effects. The data were logarithmically transformed prior to the analysis then transformed back for the presentation. Subjects with complete data for a particular parameter (ie, from all 3 treatment periods) were included in this analysis.

2.4.3. Discussion on clinical pharmacology

The purpose of this application was to introduce additional dosage strengths of Suboxone, whilst maintaining the current posology of up to 24 mg buprenorphine daily. In order to justify this application, the new dosage strengths were expected to demonstrate bioequivalence to an equivalent dose obtained with a combination of the current marketed product.

The concept of conducting a single dose BE study under fasting conditions was acceptable and in accordance with the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1/Corr**).

Elimination of buprenorphine is bi-or tri-exponential, and has a mean half-life from plasma of about 33 hours. The elimination half-life of the dealkylated metabolite norbuprenorphine with weak μ-agonist intrinsic activity is even longer (40-50 hours). Therefore, the chosen wash-out period of 14 days was long enough to cover the minimally required five elimination half-lives in order to avoid carry-over.

Tmax was expected at about 1.5 hours, based on data obtained for already approved SL tablets. Eight samples were taken within the first two hours post-administration in order to allow an accurate calculation of Tmax.

The bioanalytical method for determination of buprenorphine and naloxone plasma concentrations was adequately validated. Standard statistical methods and acceptance criteria for bioequivalence were applied.

Following oral administration, naloxone is barely detectable in plasma due to high first pass metabolism. Following sublingual administration of buprenorphine/naloxone, naloxone plasma concentrations are low. No systemic pharmacological activity of naloxone is expected or desired.

Equally, norbuprenorphine was shown not to exert marked pharmacodynamic effects after administration of SL buprenorphine formulations. In line with the provisions of the Bioequivalence Guideline, the decision upon bioequivalence between the two dosage forms will mainly focus upon the results for the parent compound buprenorphine.

In line with Bioequivalence Guideline provisions, the 90% CIs for the primary PK parameters AUCt and Cmax were required to comply with the 80-125% acceptance criteria. Bioequivalence for AUClast and Cmax was demonstrated. The fact that the upper limit of the acceptance range was exceeded for AUCinf of naloxone (116.22; 90% CI 105.20 – 128.40) does not compromise the conclusion of bioequivalence between the newly developed 16/4 mg SL tablets and the established 2 x 8/2 mg SL tablets.

2.4.4. Conclusions on clinical pharmacology

Based on the results of the submitted bioequivalence study, the new 16/4mg SL tablet formulation (circular) is considered bioequivalent with the combination of two 8/2 mg SL tablets.

Clinical safety

Safety data were collected from the PK data package submitted in support of this application.
The studies were performed under a naltrexone block to reduce opiate-related adverse events (AEs).

Patient exposure
A total of 98 subjects participated in the studies.

Safety was assessed by monitoring of treatment-emergent AEs (TEAEs) and serious adverse events (SAEs), clinical laboratory tests, vital signs and electrocardiograms.

Adverse events
The most frequently reported TEAEs (≥ 10% incidence in all subjects) by system organ class were typical for the opioid therapy and included nervous system disorders (such as headache, somnolence, and dizziness) and gastrointestinal disorders (such as nausea and vomiting).

There were no trends in vital signs, ECGs, clinical laboratory evaluations, physical examinations, or oral examinations that were considered clinically significant.

Serious adverse event / deaths / other significant events
There were no deaths or Serious Adverse Events in the studies.

Safety in special populations

NA

Safety related to drug-drug interactions and other interactions

NA

Post marketing experience

NA

2.4.5. Discussion on clinical safety

Safety data do not indicate any new or unexpected toxicities or safety concerns for the newly developed tablet formulations. No changes to the safety information for Suboxone are considered necessary.

The CHMP noted that addition of new high dose strength increases the risk of respiratory depression/arrest in case of medication errors, paediatric intoxication, misuse and abuse. Furthermore, the high dose strength could increase the misuse of high doses of buprenorphine.
The MAH provided an overview of current risk minimisation measures which have been assessed to be adequate. Consequently, no further updates to the RMP were deemed necessary.

2.4.6. Conclusions on the clinical safety

The overall frequency of TEAEs does not point to a general difference in the safety profile between the newly developed and the currently marketed sublingual tablets.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the MAH fulfils the legislative requirements.

2.6. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 11 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the Risk Management Plan version 11 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	• Fatal overdose - Severe respiratory failure (mechanism for death by overdose) - Use in patients with alcoholism/*delirium tremens* • Misuse and/or abuse (injection/intranasal/pediatric use) • Hepatitis, hepatic events, use in patients with hepatic failure • Dependence • Drug Withdrawal Syndrome • Use during Pregnancy, and lactation (effects on newborn and infant) • CNS Depression (effects on driving ability) • Allergic Reactions • Differences in posology between SUBOXONE and SUBUTEX
Important potential risks	• Use in patients with head injury and increased intracranial pressure • Peripheral oedema
Missing information	• Elderly patients >65 years old • Children <15 years old

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
Category 1- SUBOXONE mortality study in the UK with The Health Improvement Network Database (THIN). (PE-US005)	Assess any impact of SUBOXONE on all-cause mortality in comparison to buprenorphine and methadone in the UK based on the THIN (The Health Improvement Network) database.	Assess any impact of SUBOXONE on all-cause mortality in comparison to buprenorphine and methadone in the UK based on the THIN (The Health Improvement Network) database.	Per interim report: N=472 for Suboxone and n=4875 to buprenorphine and n=4589 to methadone	Final study report When 1,000 SUBOXONE patients are registered at THIN Interim report: 15 Nov 2013.
Category 1- RBP-FR-2012-001 INSPIRE	To describe the real-life conditions of SUBOXONE use in France according to: The physician's prescription And Patient behaviour with regard to use of medication	To characterise patients treated with SUBOXONE, 12-month retention rate of SUBOXONE patients, patients' quality of life, and changes in social status	Interim analysis report due 4th Quarter 2013 Final report due 1st Quarter 2015	Interim analysis report due 4th Quarter 2013 Final report due 1st Quarter 2015
Category 1- A retrospective observational Survey on SUBOXONE use in France (PE-US004)	To characterise SUBOXONE users in France. To Detect switchers to Buprenorphine in France. To monitor AEs of general and specific concern in France.	To monitor Adverse Events of general and specific concern in France	started	Interim study report – 22 Jan 2014 and 28 Nov 2014 Final study report – 27 Nov 2015

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
fatal overdose; severe respiratory failure as cause of death; use of suboxone in patients with alcoholism	SmPC includes text on misuse, abuse and diversion in Section 4.4, contraindications in Section 4.3, and Overdose in Section 4.9	Not needed
hepatitis, hepatic events, use in patients with hepatic failure	SmPC includes text in posology and method of administration in Section 4.2, hepatitis and hepatic events and hepatic impairment in Section 4.4, contraindications in Section 4.3,	Not needed
dependence (class effect)	SmPC includes text on dependence in Section 4.4	Not needed
drug withdrawal syndrome	SmPC includes text on precipitation of opioid withdrawal syndrome in Section 4.4	Not needed
drug exposure during pregnancy/lactation (effects on the newborn and the infant)	SmPC includes text on pregnancy and breast-feeding in Section 4.6	Not needed
misuse/abuse (intravenous / intranasal / paediatric use)	SmPC includes text on misuse/abuse in Section 4.4	Not needed
CNS depression (effects on driving ability)	SmPC includes text on CNS depression in Section 4.4	Not needed
allergic reactions	SmPC includes text on contraindications in Section 4.3	Not needed
differences in posology between suboxone and subutex in switching	SmPC includes text on contraindications in Section 4.4	Not needed
use in patients with head injury and increased intracranial pressure	SmPC includes text on contraindications in Section 4.4	Not needed
peripheral oedema	SmPC includes text on contraindications in Section 4.8 and US Prescribing information	Not needed

2.7. Product information

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: The line extension to add Suboxone 16/4mg strengths using the same route of administration and pharmaceutical form has identified no additional safety issues and therefore the MAH defers to the existing consultation report. No further user testing was deemed necessary.

3. Benefit-Risk Balance

Benefits

The Suboxone Summary of Product Characteristics (SmPC) states that up to a maximum of 24 mg buprenorphine can be dosed daily. As Suboxone is currently only available as 8/2 mg and 2/0.5 mg sublingual tablets, the higher dose levels currently require multiple tablets. Availability of the newly developed Suboxone 16/4 mg dose is expected to facilitate treatment by minimising the number of tablets patients would require for dosing.

Risks

The addition of new high dose strength 16/4 mg increases the risk of respiratory depression/arrest in case of medication errors, paediatric intoxication, misuse and abuse. Furthermore, the high dose strength could increase the misuse of high doses of buprenorphine. However, the current risk minimisation measures remain sufficient to minimise the risks of the product in the proposed indication.

Benefit-risk balance

The overall benefit-risk balance of the newly developed 16/4 mg sublingual tablet is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and bioequivalence, the CHMP considers by consensus that the risk-benefit balance of Suboxone 16/4mg as substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.