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).

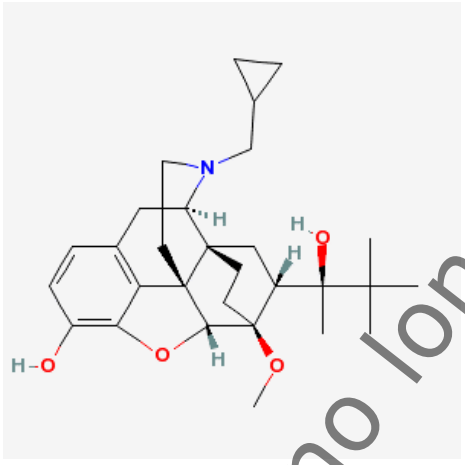
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- 8 mg / 2 mg containing 8.64 mg buprenorphine hydrochloride (equivalent to 8 mg buprenorphine base) and 2.44 mg naloxone hydrochloride dihydrate (equivalent to 2 mg naloxone base).

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

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more stringent than that mentioned in the current Ph. Eur. Monograph. All analytical methods have been validated according to the ICH guideline on "Validation of Analytical methods".

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.

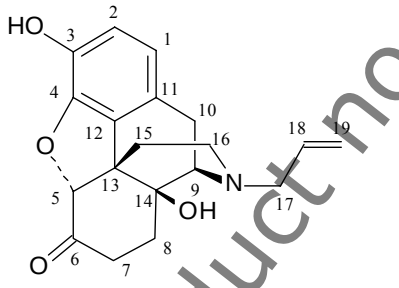
- Stability

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

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substances, UV identification, sieve analysis and the melting range of naloxone base). The stability-indicating HPLC assay has been fully validated and was shown to have satisfactory linearity, 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

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provided, it can be concluded that the process is capable of consistently producing batches of the required quality.

- 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 ($t^{1}/_{2}$ 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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hinting at a low endogenous opioidergic tonus. Because of its almost complete first pass metabolism, naloxone administered orally or sublingually is not expected to exert antagonistic activity. No documents dealing with the pharmacodynamics of naloxone were submitted.

Receptor Binding:
In the review presented in association with this application the receptor binding affinities of buprenorphine and naloxone for narcotic receptors are outline in the following table.

Table: *In vitro* receptor-binding affinities for Buprenorphine and Naloxone.

Drug	**Ki (nM)**				
	Mu (μ)	Delta (δ)	Kappa (κ)	Sigma (σ)	Ratio (σ/κ)
Buprenorphine	0.77	2.2	1.1	>100000	>91000
Naloxone	1.2	19	12	>1000000	>83000

- Primary pharmacodynamics

In vivo studies have been carried out in order to examine the interaction of both substances as regards effects (antinociception), precipitation of withdrawal in morphine dependent rats, drug discrimination in rats and avoidance behaviour in monkeys.

Antinociceptive effects of buprenorphine and morphine given alone or in combination with naloxone (subcutaneous route) were measured in the rat tail pressure test: the results provided some evidence that buprenorphine is antagonised by naloxone, although less readily than morphine.

Buprenorphine and naloxone administered intraperitoneally to precipitate withdrawal signs in morphine-dependent rats suggest that buprenorphine did not affect the ability of naloxone to precipitate signs of opiate withdrawal.

To test whether buprenorphine plus naloxone mixtures are still perceived like buprenorphine alone, a drug discrimination study was performed. Male rats with about 300 g b.w. were trained to discriminate between subcutaneous (s.c.) injection of buprenorphine 0.03 mg/kg in an operant chamber with two levers, where repeated pressure of the correct lever (10x) resulted in the delivery of a food pellet. 30 min after application the pattern of lever pressing was recorded. No food reward was given during generalisation trials. Generalisation was considered to have occurred, if the percent responding on the relevant lever was 70 % or more. Responding to the buprenorphine-appropriate lever was 97 % following buprenorphine, 2 % following saline and 8 % following naloxone. Addition of naloxone 0.002, 0.01 and 0.02 mg/kg to buprenorphine resulted in 93 %, 59 % and 23 % buprenorphine lever pressing, respectively. It is concluded that buprenorphine combined with naloxone in a ratio 3:2 is not probable to be a narcotic cue to support opiate misuse.

Negative reinforcing properties of naloxone were studied in the non-dependent rhesus monkey: scheduled infusions of naloxone (1-100 μg/kg/inf.) and of buprenorphine (250 μg/kg/inf.) generated drug avoidance behavior in the non-dependent rhesus monkey under a continuous avoidance-escape paradigm. Pentazocine (1-100 μg/kg/inf.) codeine, (1-100 μg/kg/inf. and tilidine (1-250 μg/kg/inf.) were ineffective. Addition of varying doses of naloxone to scheduled infusions of codeine, tilidine, and pentazocine generated avoidance behavior not present with scheduled infusions of these opioids alone. The naloxone doses necessary for generation of avoidance behavior were low with the agonists codeine and tilidine, higher with the weak antagonist pentazocine, and highest with the strong antagonist buprenorphine.
Monkeys were trained to avoid conditioned noxious stimuli. Subsequently, avoidance behaviour was extinguished and scheduled intravenous infusions of drugs were tested for their ability to re-introduce avoidance behaviour. Comparable to nalorphine, the opioid antagonist naloxone exerted negative reinforcing properties. The agonists codeine and tilidine had no effects on the behaviour of their own, as had the mixed agonist/antagonist pentazocine, while buprenorphine had a weak negative reinforcing effect only in the highest dose tested. Naloxone was added to equi-analgesic doses of the test compounds. Low doses were needed to induce negative reinforcement in the presence of codeine and tilidine, somewhat higher doses in the presence of pentazocine and high doses in the presence of buprenorphine.

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Overall, where interaction between buprenorphine and naloxone was shown, the routes of administration used in the pharmacology studies may have limited relevance to the proposed clinical route of administration (sublingual) and the ratios chosen in these studies (3:1) do not reflect the proposed clinical ratio of 4:1. Thus 'proof of principle' that co-administration of naloxone will prevent intravenous misuse of buprenorphine has further to be derived from clinical studies and clinical evidence.

Buprenorphine and norbuprenorphine did not displace peripheral [3H]PK 11195 binding and central [3H]flunitrazepam binding, indicating lack of interaction with the $GABA_A$-receptors.

Diazepam and flunitrazepam have no significant affinity to human μ- and δ- opioid receptors and poor affinity to human κ-opioid receptors.

- Secondary pharmacodynamics

In order to look for blood compatibility (protein precipitating and haemolytic effects) of the combination of buprenorphine and naloxone 3: 2, the powdered product was dissolved in 5 % aqueous glucose or was diluted from a pre-prepared solution and added to citrated blood withdrawn from beagle dogs. The slight haemolysis observed with therapeutic concentration is not likely to be of clinical significance in the case that intravenous abuse of the product should occur.

- Safety pharmacology programme

No new studies were submitted. Due to the well-known pharmacology of the single substances and since no adverse interactions between these to substances are expected this procedure is acceptable.

- Pharmacodynamic drug interactions

No unexpected pharmacodynamic drug interactions have been identified.

Pharmacokinetics

Pharmacokinetics of both buprenorphine and naloxone are well known. Buprenorphine is sufficiently absorbed following sublingual administration and is eliminated with a long half-life. Naloxone has a low oral bioavailability and and is rapidly eliminated when given parenterally.
In a preclinical study it is shown, that co-administration of buprenorphine and naloxone had little or no effect on their individual pharmacokinetic profiles following administration by i.v. or i.m or by oral dosing.

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Table. Results of single dose pharmacokinetic studies in rats and dogs with ^{3}H-buprenorphine and ^{3}H-naloxone alone or in combination with non-radiolabelled naloxone or buprenorphine respectively.

SPECIES	ROUTE	^{3}H-Buprenorphine			^{3}H Buprenorphine + Naloxone			^{3}H-Naloxone			^{3}H-Naloxone + Buprenorphine		
		C_{max} Plasma ng/g	AUC $_{(0-8\ hr)}$ ng/g h	C_{max} Brain ng/ equiv	C_{max} Plasma ng/g	AUC $_{(0-8\ hr)}$ ng/g h	C_{max} Brain ng/ equivs	C_{max} Plasma ng/g	AUC $_{(0-8\ hr)}$ Ng/g h	C_{max} Brain ng/ equiv	C_{max} Plasma ng/g	AUC $_{(0-8\ hr)}$ ng/g h	C_{max} Brain ng/ equiv
Rat	i.v.	1442	1799	4763	1306	1653	3626	761	726	2141	574	690	1736
	i.m.	892	2248	1051	839	1453	760	865	908	1756	833	760	1850
	p.o.	571	188	1456	915	243	1564	313	48	8518	134	26	5853
Dog			Auc $_{(0-24\ hr)}$ ng/g h			Auc $_{(0-24\ hr)}$ ng/g h			Auc $_{(0-24\ hr)}$ ng/g h			Auc $_{(0-24\ hr)}$ ng/g h	
	i.v.	788	65	*	739	67	*	349	18	*	357	20	*
			Auc (0-96 hr) ng/g h			Auc (0-96 hr) ng/g h			Auc (0-96 hr) ng/g h			Auc (0-96 hr) ng/g h	
	i.m	103	68.5	*	129	64	*	258	26	*	258	25.5	*
	p.o.	ND	ND	*	ND	ND	*	ND	8	*	ND	5.5	*

The only clinically relevant pharmacokinetic interaction detected is confined to inhibitors of CYP3A resulting in enhanced bioavailability of buprenorphine. Based on these studies inhibitors of CYP 3A enzyme can potentially increase the hepatic toxicity of buprenorphine. Patients concomitantly administered inhibitors of CYP 3A should be closely monitored for markers of liver toxicity.
This is reflected in the clinical pharmacokinetics and is taken into account in the SPC.

Toxicology

- Single dose toxicity

Extensive acute toxicity studies employing different routes of administration (i.v., s.c. i.m. and oral) are presented in which the toxicity of buprenorphine and naloxone are compared with the toxicity of mixtures of these components. These studies demonstrate that there is no synergistic enhancement of toxicity when buprenorphine and naloxone are co-administered.

- Repeat dose toxicity (with toxicokinetics)

Dietary toxicity studies of 28 days and 13 weeks duration in rats were conducted using buprenorphine: naloxone at a ratio of 4:1 in terms of the bases (i.e. the ratio intended for human use).
The dietary route was selected for repeated dose toxicity evaluation of Suboxone since this route was relevant to the proposed sublingual route of human exposure. In addition to data on the dietary toxicity of Suboxone in rats, data on the toxicity of development formulations containing ratios of buprenorphine and naloxone of 1:1 and 3:2 for periods of up to 28 days in both the rat and the dog by a variety of enteral and parenteral routes of administration are presented.

Clinical observations were aggressive behaviour and excessive grooming. An analgesic effect (prolonged time to tail flick) has been observed in females of the 2000 ppm group. Bodyweight was significant lower throughout the study for males only. Food consumption and food utilisation was decreased in males also. A treatment-related increase in adrenal weight adjusted for body weight was recorded for males receiving Suboxone. The adrenals were histologically normal and this apparent weight change was not considered to be of toxicological importance. No other organ weight changes were apparent that were considered to be related to treatment and no treatment-related abnormalities were observed at autopsy. Histological examination revealed an increased incidence and severity of mononuclear cell infiltration of the Harderian gland in females of all groups receiving Suboxone and in males receiving ≥500 ppm. However, as there is no known clinical effect of insult to the Harderian gland, the toxicological importance of these findings remains unclear. No toxicological relevant target

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organ toxicity was apparent apart from weight changes of the liver and histological effects on the kidneys, probably adaptive effects due to the high doses administered.

Safety margins based on AUC were calculated based on human data from Clinical Study CR97/007:

Table 7 Rat : human buprenorphine ratios based on AUC (ng·h/ml)

Dietary concentration of Suboxone (ppm)	**Buprenorphine dose (mg)**			
	4	**8**	**16**	**24**
100	7.3	4.4	2.5	2.0
500	28.2	17.1	9.7	7.6
1500	73.6	44.7	25.4	20.0
2000	93.9	57.0	32.4	25.5

Table 8 Rat : human naloxone ratios based on AUC (ng·h/ml)

Dietary concentration of Suboxone (ppm)	**Naloxone dose (mg)**			
	1	**2**	**4**	**6**
100	NC	NC	NC	NC
500	15.1	8.5	5.0	4.4
1500	231.8	130.8	76.1	68.0
2000	244.5	137.9	80.3	71.7

NC = Not calculated. Plasma concentration less than LLOQ (0.5 ng/ml).

The toxicokinetic data obtained in rats following dietary administration of buprenorphine: naloxone at a ratio of 4:1 also suggests that both rats and dogs receiving development formulations of buprenorphine: naloxone at a ratio of 1:1 by the oral route would have received toxicologically significant exposures to both of the active ingredients.

No novel toxicological aspects rose from the studies with a mixture of buprenorphine/naloxone in comparison with knowledge about the compounds alone. Based on toxicokinetic data raised from the dietary study with Suboxone, an exposure of animals sufficiently above the maximum therapeutic dose in humans has been reached. Clinical signs reflected the pharmacodynamics of the active ingredients.

- Genotoxicity

Standard in vitro and in vivo genotoxicity tests with buprenorphine and naloxone were negative indicating that both compounds are devoid of genotoxic properties.

A 7-day dietary palatability study in rats, a subacute 28 day dietary toxicity study in rats and associated mutagenicity studies have also been completed in order to investigate the potential toxicity and genotoxicity of synthesis impurities and degradants of Suboxone.

Synthesis impurity D (7,8-didehydronaloxone) present in naloxone was found clastogenic in vitro studies with human lymphocytes. The proposed specification limit of 7,8-didehydronaloxone will result in exposure below the Threshold of Toxicological Concern (TTC) of 1.5 µg/day which is recommended for setting acceptable daily intake limits of genotoxic impurities by the EU Draft Guideline on the Limits of Genotoxic Impurities (CHMP/SWP/5199/02).

A series of other synthesis impurities and degradants was reviewed for structure-activity relationship and were reported to be devoid of structural alerts. However, the process used to determine alerting structures was not fully clear and needed further clarification. The applicant further provided sufficient information about the approaches used (in house and at FDA) in assessing structural alerts as part of

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the toxicological qualification of impurities and degradants. The applied approach for qualifying the impurities/degradants is acceptable.

- Carcinogenicity

A 2-year dietary carcinogenicity study with Suboxone was conducted in rats at doses of 7, 30 and 120 mg/kg/day, with estimated exposure multiples of 3 to 75 times, based on a human daily sublingual dose of 16 mg calculated on a mg/m² basis. Statistically significant increases in the incidence of benign testicular interstitial (Leydig's) cell adenomas were observed in all dosage groups.

A dose-related reduction in the incidence of adenomas in the pars distalis (male and female rats) and a decreased incidence of mammary hyperplasia were also observed. The reduced incidence of these finding were below internal as well as historical controls. Similar findings had been reported for Buprenorphine alone but at a lower incidence.

The Applicant supplied a number of possible explanations for the discrepancy between Suboxone and Buprenorphine alone regarding Leydig cell adenoma formation and proposed a mechanism for tumour formation, the modification of GnRH release could results in downstream effects on sexual hormone levels due to interference at the opiate receptors this would be responsible for the induction of Leydig cell adenomas in male rats and the accompanying hyperplasia. However, the mechanistic hypothesis was not accompanied by hormonal determinations.

To further elucidate the mechanism of induction of the Leydig cell tumours, the Applicant was asked to provide acceptable historical control data on the same strain of rat and, information on sexual hormone levels and buprenorphine and bupernorphine/naloxone administration and/or conducting a new study.

After consideration of new made available published data, an additional study in rats to investigate the hormonal effects of Suboxone appeared not longer justified.

This issue is taken into account in section 5.3 of the SPC.

- Reproduction Toxicity

Suboxone was evaluated in a fertility and early embryonic development study in the rat with dietary admixture of the test substance. Toxicokinetic data were obtained concomitantly with the fertility study. Embryotoxicity studies of development formulations (buprenorphine:naloxone 1:1 for oral or 3:2 for intramuscular administration, in terms of bases) were conducted in rats and rabbits by both, oral and intramuscular application. Studies were conducted according to GLP. No study on prenatal and postnatal development was performed. However, the applicant appropriately discussed and evaluated different studies, which investigated effects of buprenorphine or naloxone on the prenatal and postnatal development in the ARD.

In the fertility study, suboxone induced toxicity in the parental generation at all dose groups. At dose levels of 100 ppm or greater an increase in the incidence of non-pregnant females was observed. High pre-implantation losses were noticed at doses of 500 ppm or greater.

No teratogenic effects of the development formulations of buprenorphine and naloxone were noted in the embryotoxicty studies in rats and rabbits. However, treatment of pregnant rats and rabbits caused maternal toxicity. Reduced body weight gain, reduced food consumption and adverse clinical signs were frequently observed. In the rat, dose-related increases in the number of resorptions and decreases in the number of live fetuses were noticed after oral application of 10 mg/kg/day or greater. After i.m. administration in the rat, high post-implantation-losses, and consequently a reduced number of fetuses occurred at 30 mg/kg/day. In the rabbit, two dams receiving the highest oral dose (40 mg/kg/day) aborted and one dam receiving the highest i.m. dose (30 mg/kg/day) showed a total resorption of litter.

Despite the availability of toxicokinetic data in the fertility study in the rat, as part of the total package of reproductive and developmental toxicity studies, the applicant failed to discuss NOAEL levels and did not calculate any exposure margins in relation to human exposure. In the anwers the applicant identified NOAEL levels for reproductive and developmental toxicity. Exposure margins were

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calculated in an adequate manner. As far as toxicokinetic data were available, exposure margins were based on AUC otherwise exposure multiples were based on mg/m^2 comparisons. The calculated exposure margins replaced the mg/kg –details in section 5.3 of the SPC.

- Local tolerance

No specific local tolerance studies were conducted with Suboxone in animal models. The intended human sublingual route is not a practical route of administration in common laboratory animal species. Extensive data from human clinical trials indicate that Suboxone is well tolerated when administered by the sublingual route in man.

- Other toxicity studies

N.A.

Ecotoxicity/environmental risk assessment

The predicted environmental concentration (PEC) calculation initially provided by the applicant was incorrect.
The applicant has not provided an environmental risk assessment according to Phase II of the guideline on the environmental risk assessment of medicinal products for human use (CHMP/SWP/4447/00). This would have been necessary because the concentration in the aquatic environment predicted according to Phase I of the guideline exceeds the trigger of 10 ng/l.

As the marketing authorization procedure for Suboxone started in October 2005, before the publication of the adopted guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00), it would be accepted an environmental risk assessment according to the draft of the guideline published in January 2005.
According to the draft of 2005 the trigger of 10 ng/l is exceeded and a phase II environmental risk assessment following this draft would be necessary.

In his response to the Day 180 LoOI, the applicant uses the guideline adopted in June 2006 for the environmental risk assessment of Suboxone. The default Fpen for the calculation of the predicted environmental concentration in surface water in Phase I of the guideline is 1 %. It is possible to refine the factor based on reasonably justified published data. The PEC-refinement based on published UN data on the prevalence of the abuse of opiates is agreed. However, the further refinement of Fpen conducted by the applicant is not acceptable. No valid data have been presented to justify the refinement based on market share and according to the guideline; the maximum daily dose is used for PEC-calculations in Phase I for all products. Using the Fpen of 0.43 %, the trigger of 10 ng/l is still exceeded. Therefore, a phase II environmental risk assessment is required. Besides that, the guideline of 2006 demands a Phase I pbt assessment for substances with a log Kow >4.5 like Buprenorphine. This has been taken into account in the FUM, non- clinical.

Discussion on the non-clinical aspects

Where suboxone has been developed for long-term use in humans, the duration of repeated dose toxicity studies with the combination of the active ingredients does not meet the criteria of current guidelines.
However, taking into account that both sufficient chronic toxicity studies with buprenorphine alone, and data about naloxone from a 6- month repeated dose combination study with tilidine/naloxone are available, the non clinical programme on repeated dose toxicity is considered sufficient for the combination of the two substances which are established in clinical use.

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4. Clinical aspects

Introduction

This is an application for a fixed combination. The new product is containing known active substances not used previously in combination (Article 10.1.(b)).

The Note for Guidance on fixed combination medicinal products describes some general rules for fixed combinations. Each substance of the fixed combination must have documented contribution within the combination and it will be necessary to show therapeutic advantages of the combination in the clinical situation against possible disadvantages. A simplification of therapy as the only justification will be acceptable in particular situations only.
The applicant justifies the development of Suboxone with the objective of having a similar sublingual effectiveness and safety profile as buprenorphine tablets, but with a lower intravenous misuse potential. From a regulatory point of view and after application of the Note for Guidance on fixed combination medicinal products the reduction of misuse potential is not a convincing justification for the application of a fixed combination with buprenorphine and naloxone.

However, in clinical view the advantages result, that on the one hand the medicinal product is not practical for misuse and on the other hand could be made available as take home medication. This fact contributes to a higher acceptance of the substitution therapy.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Pharmacokinetics

Suboxone is a fixed dose combination tablet of buprenorphine and naloxone in a 4:1 ratio. Most of pharmacokinetic studies of Suboxone and buprenorphine (as a reference) were undertaken in volunteers experienced in opiate use but not dependent on opiates.

The sublingual bioavailability of buprenorphine and naloxone from Suboxone was examined in five studies. In all studies a LC/MS/MS analysis was used for the determination of buprenorphine, norbuprenorphine and naloxone in human plasma and urine samples.

Pharmacokinetic parameters of buprenorphine and naloxone were determined from plasma concentration-time profiles. Statistical analyses were performed using the SAS Statistical analysis system program to compare treatments by analysis of variance (ANOVA).

- Absorption

The CR97/07 study was an open-label, dose-ascending, four-way crossover study to evaluate the pharmacokinetics and dose proportionality of buprenorphine, in the range of 4 to 24mg, when administered in sublingual tablets in combination with naloxone (at 4:1 dose ratio) in non-dependent opiate users.

The data from the analysis of 14 subjects indicated that both buprenorphine and naloxone were quickly absorbed following sublingual administration of the combination tablet of buprenorphine and naloxone. Mean peak plasma levels of buprenorphine (Cmax 2.33, 3.53, 5.83 and 6.44 ng/ml) and naloxone (0.12, 0.25, 0.44 and 0.47 ng/ml) increased following 4 mg + 1 mg, 8 mg + 2 mg, 16 mg + 4 mg and 24 mg + 6 mg sublingual doses of Suboxone. Mean AUC_{0-t} values of buprenorphine (13.09, 23.23, 39.38 and 47.55 h.ng/ml) and naloxone (0.12, 0.30, 0.53 and 0.60 h.ng/ml) also increased with the sublingual dose of Suboxone. The mean elimination half-life of buprenorphine following sublingual dosing was 34 (14-116, N=53) hours, and that for naloxone was 1.24 (0.33-3.14, N=48) hours. Although linear, the increases in buprenorphine AUC were not proportional to the dose. There was a wide inter-patient variability in the sublingual absorption of buprenorphine.
The study results demonstrate a non-dose proportional increase of buprenorphine AUC.

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Study CR96/023 had two objectives: to assess the relative and absolute bioavailability of a buprenorphine (8mg) and naloxone (2 mg) tablet when administered orally and sublingually, and to evaluate the subjective and physiologic effects of orally and sublingually administered buprenorphine and naloxone tablets. The study was an open label, balanced 3x3 Latin square crossover design. Results shoed that absolute bioavailability of buprenorphine from the sublingually administered tablet was significantly greater than the bioavailability from the tablet administered orally (13.6 +/- 6.6 % compared to 6 .0 +/- 4.1%). Naloxone was approximately 3% bioavailable sublingually while its bioavailability from the tablet taken orally was practically zero. Therefore, the AUC data indicate that sublingual administration yields 2.5 times more buprenorphine than oral and the bioavailability of naloxone after sublingual or oral administration is very low.

Study NIDA #01-1 was conducted to compare simultaneous administration of 4 tablets comprising a 20mg Suboxone dose (2 x 2 mg tablets plus 2 x 8 mg) with sequential administration of 2 x 8 mg tablets followed later by 2 x 2 mg tablets, after the first tablets had disintegrated. These were considered as supportive data. No absorption differences were observed between simultaneous or sequential administration of 4 Suboxone tablets.

Study CR96/012 was an open-label, single dose, four-period, dose-escalation study to evaluate whether plasma concentrations of buprenorphine increase proportionally to buprenorphine dose in the range of 4 to 24 mg administered as Buprenorphine alone sublingual tablets, and to evaluate the safety, and dose-response of subjective and physiological effects of buprenorphine. The study comprised four 3-day treatment periods separated by a washout period of at least ten days.
Examination of individual patient dose–response curves following 4 mg, 8 mg, 16 mg and 24 mg Buprenorphine alone showed that mean values of buprenorphine Cmax were 1.99, 2.65, 4.42, and 5.41 ng/ml. Mean $AUC_{0\text{-}72h}$ values were 9.37, 19.92, 34.94 and 48.81 h.ng/ml from the lowest to highest dose level respectively. Although linear, the increases in AUC were not proportional to the dose. There was a wide inter-patient variability in the sublingual absorption of buprenorphine.

In accordance with the above mentioned Suboxone study (CR97/07) the study results of CR96/012 demonstrate a non dose proportional pharmacokinetic of buprenorphine after administration of Buprenorphine alone. AUC, tmax, and Cmax are comparable regarding different dose strengths in both studies. This results support the assumption that buprenorphine bioavailability is not influenced by sublingual administration of naloxone.

Study CR92/111 was designed to assess the treatment potential of sublingual buprenorphine (8mg) and naloxone (4mg and 8mg) combinations in subjects maintained on 8mg sublingual buprenorphine for 7 days. This was a double blind, double-placebo, 3x3 Latin square, within-subject study in which subjects were stabilised on 8mg buprenorphine sublingual solution and then challenged sublingually with three ratios of buprenorphine / naloxone.

The absolute bioavailability of 8 mg sublingual buprenorphine when given alone or in combination with 4 mg or 8 mg of naloxone was 42 ± 9%, 42 ± 12% and 40 ± 7%, respectively. The absolute bioavailability of 4 mg and 8 mg sublingual naloxone was 9 ± 6% and 7 ± 4% respectively. The mean elimination half-life of buprenorphine following intravenous dosing was 32 (16-55) hours, and that for naloxone was 1.0 (0.63-1.94) hours. The absolute bioavailability of buprenorphine was not influenced by simultaneous administration of naloxone, both given as sublingual solution. Therefore the bioavailability of buprenorphine in Buprenorphine alone or Suboxone is comparable and is not influenced by the presence of naloxone.

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- Bioequivalence

The proof of bioequivalence for Buprenorphine in Suboxone and Buprenorphine alone was based on a crossover study (CR95/001). According to results analysis, bioequivalence in the sense of statistical significance could not be established. In fact, knowing that intra- and interindividual variability is high the planned number of subjects was too low and T-last interval at 48 hours was also too short. Then an extrapolation of AUC data is not recommended.

However, in connection with the data of the above mentioned bioavailability studies it can be concluded that the bioavailability of buprenorphine in Buprenorphine alone or Suboxone is comparable and is not influenced by the presence of naloxone.

Because of sublingual administration of Suboxone no additional studies were conducted regarding influence of food. This is acceptable.

- Distribution

Buprenorphine

Following sublingual absorption of buprenorphine, there is a rapid distribution phase. Buprenorphine is widely distributed within the body. The mean volume of distribution obtained following intravenous administration was 2,828 litres. Buprenorphine is also highly protein bound (96%), primarily to alpha and beta globulins. The long terminal elimination phase may be due in part to reappearance of buprenorphine from deep compartments, and in part due to enterohepatic cycling of the buprenorphine glucuronide metabolite.

Naloxone

In contrast, following sublingual administration, naloxone is rapidly eliminated (median terminal half-life 1.26 hours, 54 values). The mean (range) volume of distribution of naloxone following intravenous administration was 370 (133-770) litres, which agrees with the value of 375 (151-619) litres found by Aitkenhead et al (1984). Naloxone is 45% protein bound, primarily to albumin.

- Metabolism and elimination

Following sublingual administration of buprenorphine there is a very long terminal elimination phase: the median terminal half-life values of buprenorphine following Suboxone (27.41 from 113 values) and Buprenorphine alone (27.09 from 182 values) were similar (Table below). Naloxone is rapidly eliminated.

Table: Terminal elimination half-life values for buprenorphine and naloxone

	Suboxone	**Buprenorphine alone**	**Suboxone**
	Buprenorphine Half-Life	**Buprenorphine Half-Life**	**Naloxone Half-Life**
	All data (4 studies)	**All data (3 studies)**	**All data (2 studies)**
N	113	182	54
Mean	32.49h	28.67h	1.22h
SD	19.98	11.27	0.63
Median	**27.41h**	**27.09h**	**1.26h**
Min	8.98h	2.7h	0.33h
Max	161.16h	69.3h	3.14h

Buprenorphine

The metabolism of buprenorphine in humans is by 14-N-dealkylation and by conjugation of parent drug and the N-dealkyl metabolite, norbuprenorphine, to glucuronides. The principal route of excretion is via the faeces. This was demonstrated in a study in 6 subjects dosed intravenously with 3H-buprenorphine (CR94/006). Radioactivity was completely recovered over a 9-day period, 69% ± 11% in the faeces and 30% ± 7% in the urine. Most of the radioactivity was attributed to free and conjugated buprenorphine and norbuprenorphine. Two unidentified minor metabolites in urine accounted for 0.72% and 0.9% of the dose, respectively.

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Naloxone
Two metabolites of naloxone, identified after hydrolysis and extraction of urine were 7,8-dihydro-14-hydroxy-normorphinone and N-allyl-7,8-dihydro-14-hydroxy-normorphinone (Weinstein et al, 1974). These results indicate that N-dealkylation, reduction of the 6-oxo group and glucuronidation occurs in man. The mean elimination half-life of naloxone following single sublingual doses of Suboxone was found to be 1.26 hours (54 values).

It can be concluded that the metabolism of buprenorphine is not influenced by the simultaneous administration of naloxone.

- Dose proportionality and time dependencies

The results of CR97/07 und CR96/12 regarding dose proportionality are presented above: dose proportionality could not be established. This is in accordance with the results of Buprenorphine alone studies.

As mentioned above additional multiple dose studies with Suboxone were not conducted. The kinetic data of the long term study CR96/014 demonstrate that accumulation will not occur. This is in accordance with Buprenorphine alone data.

- Special populations

Kinetic data of the target population was determined in study CR96/014 only. Different results between the target population and subjects in the short-term pharmacokinetic studies (subjects experienced in opiate use but not dependent) are not expected.

Renal elimination plays a relatively small role (less than 30% after IV administration) in the overall clearance of buprenorphine. No difference was observed in the pharmacokinetics of intravenous buprenorphine in nine subjects with end-stage renal failure compared with control subjects with normal renal function. However, plasma concentrations of the two inactive metabolites, norbuprenorphine and buprenorphine-3-glucuronide, were increased by 4 and 15 times, respectively in subjects with renal failure. No dose modification based on renal function is required. Based on the fact that the effects have been studied only under short-term dosing of buprenorphine, it is accepted to mention a precaution for use in subjects with severe renal impairment in the SPC.

Impaired hepatic function: buprenorphine is metabolised by both oxidation and glucuronidation and most of the elimination is biliary. The clearance of buprenorphine approaches hepatic blood flow. Population pharmacokinetic analysis indicated that clearance was reduced in subjects who had elevated ALT or elevated bilirubin. Therefore, the actions of buprenorphine may be prolonged in subjects with impaired hepatic function.
Buprenorphine is contraindicated in patients with severe hepatic impairment. This is also stated in section 4.3 of the SPC.

Gender, race and weight: A population pharmacokinetic assessment was undertaken using buprenorphine plasma concentration data from the Suboxone study (CR96/013 + CR96/014) and three other studies (CR94/001, CR95/001, CR97/007). The analysis showed that the pharmacokinetics of buprenorphine are described by either a one- or two-compartment disposition model with first-order absorption and an absorption lag time. The clearance of buprenorphine (>60 litres/hour) approached hepatic blood flow. The one-compartment NONMEM model predicted that increasing age and increasing AST or ALT levels were associated with at least a 20% decrease in clearance rate relative to the population standard value. Similarly, in the two-compartment model, the clearance rate of buprenorphine appeared to decrease with increased bilirubin, increased ALT and female gender.
The influence of gender, ethnicity, age and weight on buprenorphine Cmax and AUC values were examined in the meta-analysis of PK parameters from single dose studies of Suboxone and Buprenorphine alone. With the exception of 'race' in the model results for AUC(0-72) of buprenorphine following the dosing of "volunteers, naltrexone block" subjects with Buprenorphine alone, no analysis found a statistically significant effect of the four demographic variables of gender, race weight and age. The statistical significance of 'race' may have been due to the large imbalance between the numbers of Caucasians in the analysis group, compared with other races.

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Elderly: No pharmacokinetic studies were designed to be conducted with Suboxone in the elderly populations.

Children: No pharmacokinetic studies were designed to be conducted with Suboxone in children.

The pharmacokinetics of special population was evaluated in the development program of Buprenorphine alone. The results can be carried forward to Suboxone. No difference was observed in the pharmacokinetics of buprenorphine in subjects with normal renal function. Even if the concentration of metabolites were increased the dose may not be adjusted in patients with renal impairment. However, the company decided to include a statement of precaution for use in subjects with severe renal impairment in the SPC.
Suboxone should be contraindicated in subjects with severe impaired hepatic function. The influence of gender, ethnicity and weight was also evaluated in the Suboxone pharmacokinetic trials. No additional warnings regarding special populations are necessary.

- Pharmacokinetic interaction studies

Cytochrome P450 specificity studies have shown that CYP3A4 is responsible for the metabolic conversion of buprenorphine to norbuprenorphine. Therefore, potent inhibitors of CYP3A4 (e.g., protease inhibitors like ritonavir, nelfinavir, or indinavir, or azole antifungals such as ketoconazole or itraconazole) have the potential to increase plasma concentrations of buprenorphine. Similarly, inducers of CYP3A4 (e.g., phenobarbital, carbamazepine, phenytoin, rifampicin) have the potential to reduce buprenorphine plasma concentrations because of increased metabolism of buprenorphine to norbuprenorphine.
An interaction study of buprenorphine with ketoconazole has been undertaken (P01242). Subjects received 8 mg, 12 mg, or 16 mg Buprenorphine alone per day for two weeks, and ketoconazole 400 mg/day was added for six days. Ketoconazole administration resulted in clinically significant, 2-fold increases in both Cmax and AUC of buprenorphine after sublingual administration of Buprenorphine alone. The SPC contains statements in Section 4.4 'Special warnings and special precautions for use', and Section 4.5 'Interaction with other medicinal products and other forms of interaction' relating to this interaction.

Pharmacodynamics

The rationale for developing Suboxone for use in treating opioid dependency is that it should be similar in efficacy to buprenorphine alone when taken sublingually, but should produce opiate withdrawal effects if misused intravenously by an opioid-dependent subject. This rationale is grounded on the fact that sublingual bioavailability of naloxone is poor. Naloxone is not expected to exert any pharmacological effect after sublingual administration of Suboxone. Therefore, pharmacodynamic and pharmacokinetic studies were conducted using the parenteral route and/or sublingual route of administration to investigate whether Suboxone complies with this rationale

- Mechanism of action

Buprenorphine is a potent opioid analgesic. It acts as a partial agonist at the μ-opiate receptor with high affinity to this receptor type and as an antagonist at the k-receptor. Agonistic effects at μ-opiate receptors lead to euphoria, sedation, constipation, analgesia and respiratory depression. However as a partial agonist, buprenorphine has maximal opioid effects lower than those of full agonists, providing a wider safety margin. The analgesic potency of buprenorphine is 25-50 times higher (on a weight by weight basis) than that of morphine. Buprenorphine has been widely used for two decades and has proved to be a strong analgesic in relieving moderate to severe acute and chronic pain.

Naloxone hydrochloride is a semisynthetic opioid antagonist. When administered in usual doses to patients who have not recently received opioides, naloxone exerts little or no pharmacologic effect. In patients who have received large doses of opioides, naloxone antagonises most of the effects of the opioid. Because the duration of action of naloxone is generally shorter than that of the opioid, the effects of the opioid may return as the effects of naloxone dissipates.
However, 0.4 mg of naloxone administered iv or sc will precipitate potentially severe withdrawal symptoms in patients physically dependent on opioides or pentazocine. The precise mechanism of

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action of the opioid antagonist effects of naloxone is not known. Naloxone is thought to act as a competitive antagonist at μ, K or σ opioid receptors in the central nervous system.

- Primary and Secondary pharmacology

The following studies provide information about the acute effects of buprenorphine + naloxone combinations on physiological parameters, and were all conducted in opioid-dependent subjects. Different subgroups were evaluated: heroin dependent subjects; subjects stabilized with morphine; patients in controlled methadone programs.

CR93/005 Study (*Low Dose Buprenorphine and Naloxone Interactions in Opioid Dependent Volunteers)* was an inpatient, double blind, double-placebo, within subject, 4x4 Latin square study to evaluate the physiological and subjective effects of intravenous buprenorphine (0.4mg) and naloxone (0.4mg), alone and in combination, in opiate-dependent subjects On four separate occasions, at least five days apart, subjects were randomly administered: 0.4mg buprenorphine + 0.4mg naloxone, 0.4mg buprenorphine + placebo, placebo + 0.4mg naloxone, and placebo.
The opiate agonist effects of 0.4mg intravenous buprenorphine in heroin dependent subjects, measured by subjective and objective assessment, were very mild, and had a similar agonist profile to placebo at this dose. None of the subjects indicated they would pay money for this buprenorphine dose. The combination formulation acted more like an opiate antagonist than an opiate agonist on all physiological and subjective variables examined; intravenous administration of 0.4mg buprenorphine + 0.4mg naloxone gave similar pharmacological effects to 0.4mg naloxone. All the heroin dependent subjects perceived both treatments as dysphoric and unpleasant.

CR93/004 Study (*Intravenous Buprenorphine and Naloxone Interactions in Opiate-Dependent Volunteers)* was a double blind, placebo controlled, crossover study to evaluate the physiological and subjective effects of intravenous buprenorphine (2mg) and naloxone (2mg) alone and in combination in opiate-dependent subjects. Intravenous buprenorphine at a dose of 2mg gave typical opiate agonist effects in the heroin dependent subjects. Significant increases were noted in subjective ratings of global intoxication, on the opiate agonist scale and visual analogue scales for 'high', 'drug liking' and 'good drug' effect. However, as judged by the subjects' spontaneous comments, intravenous buprenorphine did not produce the same intense, immediate effect as intravenous heroin.
Intravenous injection of 2mg buprenorphine + 2mg naloxone produced short-lived but intense opiate withdrawal which was indistinguishable from the effects of naloxone alone. The combination significantly attenuated subjects' rating of global intoxication, 'drug liking' and 'good drug'. Qualitatively, naloxone effects were attenuated by buprenorphine. However during the antagonist phase immediately following injection, the buprenorphine + naloxone combination was perceived to be as dysphoric and unpleasant as naloxone alone. Therefore the buprenorphine and naloxone combination has a low abuse potential in opiate-dependent daily heroin users.

CR94/003 Study (*Buprenorphine and Naloxone Interactions in Morphine-Stabilised Opiate-Dependent Volunteers)* was a double blind, placebo-controlled, partially balanced, cross-over study. Subjects were admitted to an inpatient unit and for the first five days were stabilised on a dose of 60mg morphine per day given as four intramuscular doses of 15mg. Opiate agonist effects were substantial and similar in magnitude following 15 mg intramuscular morphine and 2mg intravenous buprenorphine administration. Combining naloxone with buprenorphine attenuated some of the pleasurable opiate agonist effects seen with buprenorphine alone: the 2:1 ratio diminished all opiate agonist measures as compared to buprenorphine alone; the 4:1 and 8:1 ratios decreased global intoxication and opiate agonist scale indices, but did not alter 'drug liking'.
Each of the three intravenously administered buprenorphine + naloxone combinations had measurable short-term opiate antagonist effects. All measures of opiate withdrawal were significantly increased by the 2:1 and 4:1 ratio combinations compared with buprenorphine alone, whereas only self-reports of global withdrawal were significantly increased with the 8:1 ratio. Antagonist effects peaked at five minutes then dissipated allowing opiate agonist effects to emerge but in a dose-dependent manner with the longest duration of antagonism produced by the 2:1 ratio.
All combination ratios significantly diminished the subject's estimated street value of buprenorphine and were generally reported by subjects as unattractive as agents for intoxication. Subjects were asked to estimate the US dollar value they would pay for the challenge dose if it were sold illicitly. Five minutes after the intramuscular challenge, subjects rated 15mg morphine the highest ($12), followed

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by 2mg buprenorphine ($8). In contrast, the 8:1, 4:1 and 2:1 ratios of buprenorphine/naloxone had markedly lower peak dollar values of $2, $2 and $0. The dollar value of the placebo was $1.
Intravenous administration of 2:1 and 4:1 buprenorphine/naloxone combinations reliably produced brief opiate withdrawal symptoms and was judged sufficiently unpleasant by opiate-dependent individuals to suggest a relatively low parenteral abuse liability by people using opiates regularly. Based on observations from this study, a 4:1 ratio of buprenorphine to naloxone was chosen for Suboxone tablet formulation development.

Bupp 4243 Study (*Effects of Buprenorphine and Naloxone in Morphine-Stabilised Opioid Addicts)*
This was a double blind, placebo-controlled randomised five-period crossover (two 5 x 5 Latin square) study, designed to evaluate the individual and combined effects of intravenously administered buprenorphine and naloxone This dosage was continued throughout the study. Over a 14-18 day period following stabilisation, subjects received single intravenous challenge doses of placebo, 15mg morphine, 2mg buprenorphine, 2mg buprenorphine + 0.5mg naloxone (4:1 ratio), and 0.5mg naloxone challenges in random order at 48h to 72h intervals. Morphine produced significant 'good' effects as assessed on the VAS-G scale whereas 2mg buprenorphine in these patients was not significantly different from placebo. Similarly the 2mg buprenorphine + 0.5mg naloxone combination was no different from placebo on this scale. On the agonist effects checklist none of the challenges was associated with typical opioid-like effects.
Both naloxone and buprenorphine + naloxone were associated with significant withdrawal effects compared to placebo as assessed by the CINA scale measured during the first 25min and 60min periods. The effects produced by the buprenorphine + naloxone combination were not significantly different from those produced by naloxone.
A combination of buprenorphine + naloxone in a 4:1 ratio produced significant intravenous opiate antagonist effects similar to those produced by naloxone. This should limit its potential for intravenous abuse by opioid addicts.
This study supports the results of study CR94/03 described above.

CR92/110 Study (*Buprenorphine and Naloxone Interactions in Methadone Maintained Subject)s* was a double blind, placebo-controlled, randomised 4x4 Latin square crossover study to evaluate the physiological and subjective effects of intravenous buprenorphine (0.2mg) and naloxone (0.1mg), alone and in combination in opiate-dependent subjects. Subjects were randomly challenged on four separate occasions at least one day apart with intravenously administered 0.2mg buprenorphine, 0.1mg naloxone, 0.2mg buprenorphine + 0.1mg naloxone and placebo. The subjects were physically dependent opiate users who had been receiving 40-60 mg daily methadone maintenance for at least three months.Intravenous buprenorphine at a dose of 0.2mg generally produced only minimal opiate agonist effects that were no different from placebo. This was not surprising since the subjects were maintained on moderate doses of methadone.
The combination of buprenorphine + naloxone produced withdrawal as great or greater than naloxone alone and resulted in one subject precipitously leaving the study. Similarly buprenorphine + naloxone and naloxone alone produced opiate antagonist effects on heart rate and systolic and diastolic blood pressure.
Therfore the combination of buprenorphine 0.2mg + naloxone 0.1mg has a low abuse liability in methadone maintained subjects as it produces significant withdrawal symptoms in methadone-stabilized subjects after intravenous low dose administration.

Bupp 5257 Study (Buprenorphine/naloxone Combination Tablet: effects in Opioid Dependent Volunteers) was undertaken to assess the subjective, objective and physiological effects of buprenorphine/naloxone combinations and buprenorphine in opioid-dependent volunteers. On separate occasions, subjects received 5 dose levels of Suboxone sublingual tablets (buprenorphine/naloxone: 1/0.25mg, 2/0.5mg, 4/1mg, 8/2mg, and 16/4mg), 8mg taste-matched buprenorphine tablet, intramuscular 4:1 buprenorphine / naloxone injections (1/0.25mg, 2/0.5mg, 4/1mg, 8/2mg, and 16/4mg), 8mg intramuscular buprenorphine, 10mg intramuscular hydromorphone, and 0.25mg intramuscular naloxone. Intramuscular administration of 4:1 combinations of buprenorphine + naloxone (1/0.25mg, 2/0.5mg, 4/1mg, 8/2mg and 16/4mg) to 8 subjects stabilised on 40mg oral hydromorphone per day produced dose-related antagonist responses for observer rating of withdrawal, and subjective 'bad effects'. Significant withdrawal effects were observed only for intramuscular buprenorphine/naloxone 16/4mg. In contrast, intramuscular buprenorphine gave only

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opioid agonist effects. Sublingual buprenorphine/naloxone was well tolerated in the opioid dependent subjects and neither precipitated withdrawal nor showed opioid agonist effects.
The study results demonstrate that different sublingual doses of the buprenorphine/naloxone 4:1 produce opioid agonistic effects only. The intramuscular administration causes antagonistic effects as expected.

Bupp 3712 Study (Buprenorphine's physical dependence potential: antagonist-precipitated withdrawal in humans) had the primary purpose to determine whether any physical dependence resulting from chronic buprenorphine maintenance could be demonstrated using a precipitated withdrawal procedure with naloxone or naltrexone. After a 2-week outpatient buprenorphine induction and stabilisation period subjects were admitted onto a closed 14-bed behavioural pharmacology research unit for approximately 6 weeks. Subjects received 2, and 4 mg buprenorphine sublingual solution on Days 1 and 2, and 8 mg/day for the rest of the two-week stabilisation period. In the experimental unit they were maintained on 8 mg/day given at 08:00h each day. On challenge days they were given one of the following at 10:00h, ordered by Latin square and presented double blind and double-dummy: placebo, naloxone 0.3, 1, 3 and 10 mg /70kg i.m. and naltrexone 0.3, 1 and 3 mg /70kg orally separated by a least 72 hours. Behavioural and physiologic responses were measured over the following 12 hours. After the final challenge session the buprenorphine dose was tapered to zero over 4 days and the subjects received placebo for a further 5 days.
Both naloxone and naltrexone produced orderly dose-related and time-related effects on multiple variables assessing withdrawal. Generally, intramuscular doses of 3mg produced withdrawal effects.

High doses of intramuscular naloxone produce withdrawal effects in subjects stabilized on buprenorphine. The dose was 10 times greater than doses that precipitate withdrawal in subjects maintained on 30mg methadone. The applicant came to the conclusion that the need for higher doses is consistent with the presence of only a low level of physical dependence in buprenorphine maintained subjects.
The observed effect could be explained by the high affinity of buprenorphine (higher than the affinity of naloxone) to μ-receptors. Therefore naloxone is not suitable for the treatment of buprenorphine intoxication.

Relationship between plasma concentration and effect

The efficacy in relation to plasma concentration was evaluated in the Buprenorphine alone studies. The effects were not influenced by simultaneous sublingual administration of naloxone in doses up to 32/8mg Suboxone.

Pharmacodynamic interactions with other medicinal products or substances

Pharmacodynamic interactions were not evaluated for the fixed combination. Post marketing information regarding pharmacodynamic interactions will be provided.

Overall conclusions on pharmacodynamics

The rationale for developing Suboxone for use in treating opioid dependency is that it should be similar in efficacy to buprenorphine alone when taken sublingually, but should produce opiate withdrawal effects if misused intravenously by an opioid-dependent subject.

The intravenous or intramuscular administration of buprenorphine/naloxone causes withdrawal effects in heroin dependent subjects, and also in morphine- or methadone- stabilized subjects. Sublingual administration of the buprenorphine/naloxone 4:1 combination produces opioid agonistic effects only.
High doses of intramuscular naloxone produce withdrawal effects in subjects stabilized on buprenorphine. The dose was 10 times greater than doses that precipitate withdrawal in subjects maintained on 30mg methadone. The applicant came to the conclusion that the need for higher doses is consistent with the presence of only a low level of physical dependence in buprenorphine maintained subjects.
It can be concluded from the results of the pharmacodynamic studies that the intravenous misuse potential for Suboxone is very low in comparison with buprenorphine alone. The intravenous or

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intramuscular administration produces withdrawal effects in all opiate dependent subjects. Sublingual or oral administration of naloxone in doses up to 8mg has no pharmacodynamic effects.

Clinical efficacy

This Section reviews the studies that show the efficacy of Suboxone for the clinical indication of "Substitution treatment for major opioid drug dependence, within a comprehensive therapeutic monitoring framework of medical, social and psychological treatment". Of the fully reported trials, one was conducted with Suboxone (CR96/013+CR96/014), and one with Buprenorphine alone (CR96/013). Three 52-week studies of Suboxone provide evidence for the long-term effectiveness of Suboxone (CR96/013+CR96/014, NIDA #1018, US08). Three double blind pilot studies of Suboxone provided dose-finding information prior to commencing study CR96/013+CR96/014, or provide information about less than daily dosing of Suboxone (CR95/002, Bupp 4729, Bupp 5113).

The main Suboxone efficacy studies are CR96/013 and CR96/014. All the other studies presented in the table are pilot efficacy studies ore long term studies in different settings. Of those only NIDA#1018 and US08 will be presented and discussed as supportive studies.

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Study ID	Design	Study Posology	Subjs by arm entred/ compl.	Duration	Diagnosis Incl. criteria	Primary Endpoint
CR96 /013	randomised, placebo-controlled, double blind, parallel group	sublingual buprenorphine/ naloxone 16/4mg or buprenorphine 16mg or placebo	109 Bupr/nalox 105 Bupr 109 Placebo	4 weeks	Opiate dependence seeking for substitution therapy	opiate craving illicit drug use
CR96 /014	open label, subjects from study 96/013 and patients from 4 new centres	flexible with buprenorphine/ naloxone doses of up to 24/6mg	472	48-52 weeks	Opiate dependence seeking for substitution therapy	illicit drug use
NID A#10 18	open label with no randomisation	Suboxone 8/2mg up to 24/6mg	582	9-52 weeks	Opiate dependence seeking for substitution therapy	illicit drug use
US08	multi center randomized open parallel group study	Suboxone up to 24/6mg	93 randomised 28 completed 52 weeks	12-52 weeks	Opiate dependence seeking for substitution therapy	illicit drug use
CR95 /002	randomised double blind parallel group	Suboxone up to 16/4mg	25 only seven completed	up to 21 weeks	Opiate dependence	illicit drug use
Bupp 4729	double blind triple cross over	Suboxone up to 16/4mg	47 only 14 completed	37 days	Opiate dependence	illicit drug use
Bupp 5113	double blind triple cross over	Suboxone up to 24/6mg	46 enrolled only 13 completed	11 weeks	Opiate dependence	illicit drug use

- Dose response studies

See Clinical Pharmacodynamics.

- Main studies

CR96/013 (and CR96/014): Phase III Multicenter Efficacy/Safety Study of Suboxone for the Treatment of Opiate Dependence

METHODS

CR96/013 was a randomised, placebo controlled, double blind study intended to demonstrate the safety and efficacy of four weeks treatment with Suboxone sublingual tablets.
Matched Buprenorphine alone (mono buprenorphine) tablets were included as an active control and matched placebo tablets as a non-active control. The study was designed to compare each active buprenorphine treatment against placebo. The 4-week study was the first part of a larger safety study that offered continued open label treatment of Suboxone for up to a total of 52 weeks, including at-home use. All subjects who completed the efficacy phase (CR96/013) were offered continued treatment in the safety phase, and additional subjects were recruited directly into the safety study (CR96/014).

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Study Participants
All participants were opiate–dependent and had used heroin for a median duration of 84 months and about half of them had previously been treated with methadone or LAAM while the others were naive to treatment. 64.7% were men and 35.3% were women; mean age was 37.6 years.

Treatments
A total of 451 subjects were screened from which 326 were randomised to treatment: 110 subjects to Suboxone 16/4mg, 106 to taste-matched Buprenorphine alone 16mg, and 110 to taste-matched placebo. Three subjects, one in each group were not dosed. Therefore the intent-to-treat efficacy sample comprised 323 subjects, 109 receiving Suboxone, 105 receiving Buprenorphine alone, and 109 receiving placebo tablets.

It was decided not to use Suboxone for induction but to use the taste-matched Buprenorphine alone tablets, with the objective of achieving a rapid attainment of the target 16mg dose of buprenorphine, without the complication of withdrawal symptoms, which might have occurred during induction. Placebo group patients were inducted with matching placebo tablets and remained on this study medication throughout the 4-week trial.

Objectives
The main objective of the sudy was to demonstrate the safety and efficacy of four weeks treatment with Suboxone sublingual tablets versus placebo in reducing opiates misuse.

Outcomes/endpoints
There were two primary efficacy parameters: the number of opiate negative urine samples provided by the subjects, and opiate craving score values. It was hypothesized that buprenorphine treatment with Suboxone or Buprenorphine alone tablets would give rise to an increased number of opiate negative urine samples and would reduce opiate craving scores.
Secondary outcomes: Subject's global impression of his/her own status was reported using a 100-point scale where a score of 50 represented 'no change' and a score of 100 represented 'much better'.
Clinicians provided global impressions of their subjects' status from the perspective of the entire 4-week study period and relative to the previous clinic visit using a similar scale

Sample size
A target sample size of 128 subjects per treatment group was chosen based on power calculations for the two primary efficacy variables, urine tests negative for opiates and opiate craving score, taking into consideration a potential 33% attrition rate.
In order to detect a difference of 10% in urine tests negative for opiates between the buprenorphine and placebo groups, with a Type I error of 0.05 an a power of 0.90, 84 subjects per treatment group would be required.
A sample size of 86 subjects per group would be sufficient to detect a 10-point difference between treatment groups in opiate craving with a Type I error rate of 0.05 and a power of 0.80.

Randomisation
A total of 451 subjects were screened from which 326 were randomised to treatment: 110 subjects to Suboxone, 106 to taste-matched Buprenorphine alone, and 110 to taste-matched placebo. Three subjects, one in each group were not dosed. Therefore the intent-to-treat efficacy sample comprised 323 subjects, 109 receiving Suboxone, 105 receiving Buprenorphine alone, and 109 receiving placebo tablets.

Blinding (masking)
Blinding was accomplished by using identically appearing and tasting tablets for all three treatment groups. Flavour was added to placebo and buprenorphine tablets to match the flavour of the combination of buprenorphine/naloxone tablet.

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Statistical methods
In the protocol, pairwise normal approximation to the binomial (Z-test) was the proposed statistical test for analyzing the percentage of urine samples negative for opiates. In fact, the distribution of the percentage of urine samples negative for opiates was analyzed with the two-way ANOVA model containing the fixed effects of center and treatment and included a center by treatment interaction. The least squares means of the treatment groups were compared in pairs. The 95% confidence interval for the difference between combination therapy and monotherapy was calculated. The two-way ANOVA model was adjusted for center effect. Since the distribution of the percentage of clean urine samples was severely skewed, the data were also analyzed with the Wilcoxon test to compare each pair of treatment groups.

All statistical tests were performed as two-sided tests at the 5% level of significance. The baseline characteristics and primary efficacy variables in the efficacy study were to be analyzed using "intend-to-Treat methodology. For some of the efficacy parameters, some subsets of this sample were also planned, such as those subjects with complete data sets, however, these were not performed.

RESULTS

Recruitment
A total of 451 subjects were screened from which 326 were randomised to treatment: 110 subjects to Suboxone, 106 to taste-matched Buprenorphine alone, and 110 to taste-matched placebo. Three subjects, one in each group were not dosed. Therefore the intent-to-treat efficacy sample comprised 323 subjects, 109 receiving Suboxone, 105 receiving Buprenorphine alone, and 109 receiving placebo tablets. All subjects enrolled in the efficacy study were opiate-dependent and had used heroin for a median duration of 84 months (range 3 to 468 months) at the time of entry into the study. About half of the subjects had previously been treated with methadone or LAAM while the others were naive to treatment. The majority of subjects were white men in their mid-thirties. Of the 323 subjects in the efficacy study, 64.7% were men and 35.3% were women; mean age was 37.6 years. There were no statistically significant differences in any baseline characteristic between treatment groups.

Conduct of the study
The study terminated after significant statistical effects were shown between treatment and placebo groups. For the 296 subjects who were not affected by the early closure of the study, retention in the study was high; 243 subjects (82%) completed and 53 (18%) discontinued. Five of these subjects discontinued due to adverse events. Three of them had received Suboxone; their adverse events included nausea, vomiting, and withdrawal symptoms (1 subject); withdrawal symptoms alone (1 subject); and irritability, headache, and decreased appetite (1 subject). The remaining two subjects had received Buprenorphine alone and experienced nausea (1 subject) and sedation and dizziness (1 subject).

Baseline data
The study was conducted in the target population. Baseline data were comparable fort he three treatment groups.

Numbers analysed
Of the 296 subjects who entered the dosing phase 243 completed the study.This is acceptable, as the retention in study was high. 85% combination therapy; 84% monotherapy, and 77% placebo.

Outcomes and estimation

Negative urine samples: Statistical analysis of the results showed that patients treated with Suboxone or Buprenorphine alone tablets had a significantly higher percentage of urine samples that were negative for opiates than patients treated with placebo tablets. There was a statistically significant effect of centre but the treatment-by-centre interaction was not significant. There was no significant effect of age, gender or ethnicity on the percentage of clean urine samples, and there was no significant interaction between these variables and treatment.

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Mean Percent (SE) Urine Samples Negative for Opiates by Treatment Group for Subjects in the Efficacy Study

Treatment Group	N	Mean Percent (SE)	P-value *vs.* Placebo[†]
Buprenorphine/naloxone	109	17.8 (2.3)	<0.0001
Buprenorphine	105	20.7 (2.8)	<0.0001
Placebo	109	5.8 (1.7)	-
Total	323	14.7 (1.4)	-

[†]Two-way ANOVA

Craving score: Upon entry into the efficacy study, opiate craving was moderate (mean scores 62.4 to 65.6) and reflect no apparent differences between treatment groups. Over the 4-week study period there was a steady decline in mean craving scores following treatment with both Suboxone and Buprenorphine alone: at Week 4 the mean score in the Suboxone group was 29.8, and was 33.0 in the Buprenorphine alone group and both were significantly lower than the change in opiate craving in the placebo-treated group, that had a mean Week 4 craving score of 55.1. Also, at each week after baseline, the craving scores in the Suboxone and Buprenorphine alone groups were significantly lower than in the placebo group. No significant interactions between treatment and centre, age, gender or ethnicity on craving scores were detected.

Opiate Craving Score Adjusted Means (SE) by Treatment Group and Follow-up Period for Subjects in the Efficacy Study

Week	Combination Therapy		Monotherapy		Placebo	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Baseline	109	62.4 (2.6)	104	63.3 (2.7)	109	65.6 (2.4)
1	108	44.4 (2.2)	104	45.7 (2.3)	107	60.5 (2.2)
2	98	33.8 (2.4)	93	33.2 (2.6)	100	57.0 (2.3)
3	95	30.2 (2.6)	89	35.6 (2.8)	90	54.4 (2.6)
4	86	29.8 (2.8)	86	33.0 (3.0)	79	55.1 (2.8)

Combination therapy *vs.* Placebo: p<0.0001, repeated measures ANOVA, verified with split-plot analysis
Monotherapy *vs.* Placebo: p <0.0001, repeated measures ANOVA, verified with split-plot analysis

Secondary outcomes: Subject's global impression improved over the 4-week study period: the mean score for subjects treated with Suboxone increased from 64.1 to 75.7 and the mean score for subjects treated with Buprenorphine alone increased from 65.8 to 74.7. At each week, subjects who received Suboxone or Buprenorphine alone had significantly higher scores than those who received placebo.
At Week 4, mean clinician's global impression scores were 69.2 and 66.5 for the Suboxone and Buprenorphine alone groups, respectively, compared to the placebo group mean score of 57.9. The scores in the Suboxone and Buprenorphine alone groups were statistically significantly higher than the placebo score at each week.

The chosen primary and secondary efficacy endpoints were acceptable and in accordance with those chosen for studies that lead to approval of Buprenorphine alone.
Compared with placebo treated subjects, those treated with Suboxone ore Buprenorphine alone had statistical significant reduced heroin use, as judged by the higher percentages of urine samples that were negative for opiates. Subjects also had a marked reduction in craving for heroin.

There was no effect of age on the efficacy results and there were no meaningful differences between the genders or the different ethnic groups.

The study also showed that Buprenorphine alone treatment was similarly effective, and there were no obvious differences between Suboxone and Buprenorphine alone: 16 mg doses of both products produced similar mean increases in the numbers of opioid negative urine samples, and reduced opioid craving by similar amounts. A post-hoc statistical analysis of non-inferiority of Suboxone and Buprenorphine alone was undertaken but the study was found to be underpowered to provide a firm

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conclusion, but it was not the intention to show non-inferiority of Suboxone to Buprenorphine alone in the context of this study. Although statistical significance was not established, the results indicate that Suboxone is as effective as Buprenorphine alone in the treatment of opiate dependency.

Ancillary analyses

NA

- Analysis performed across trials (pooled analyses and meta-analysis)

NA

- Clinical studies in special populations

All relevant studies were conducted in the target population. Studies in children, in the elderly or in patients with renal or hepatic impairment were not conducted with Suboxone.

- Supportive study(ies)

NIDA#1018

Open study of Suboxone tablets to investigate 'Best Practice' for use in an office-based setting

NIDA #1018 was an open study of Suboxone tablets to investigate 'Best Practice' for use in an office-based setting. The study was conducted in the USA. Physicians could each recruit up to ten opioid-dependent subjects. Treatment was for up to one year. A total of 582 (386 males) were enrolled in the study.

Suboxone was successfully used to initiate treatment. On the first day of treatment, most patients received 8 mg (190, 32.6%), 4 mg (126, 21.6%) or 16 mg (102, 17.5%) Suboxone.

During the remainder of the study, the doses of Suboxone were adjusted to meet individual patient's needs; the most frequent average daily doses were between 8 mg and 16 mg. A total of 189 patients completed the study protocol representing a retention rate of 32%. Overall retention rates (27-35%) were similar across all the treatment settings. Of the189 patients, 162 (112 male and 50 female) received at least 47 weeks of Suboxone treatment.

Suboxone treatment was associated with reductions in the percentage of opiate-positive urine samples during the study. Overall after 3, 6 and 12 months of treatment, 29.6%, 23.65% and 19.0% of urine samples were positive for opiates compared with 90.5% at the start of treatment. Similar results were found for self-reporting of opiate use by patients. Non-opiate drug use was also reduced during treatment. Improvements were also noted in the Clinical Global Impression Scores recorded during treatment. Overall there was a good level of agreement between patients' and physicians' assessments, with most patients being scored as 'much improved'. Risk Assessment Battery (RAB) results showed marked and statistically significant reductions in 'Drug Risk' and 'RAB Scaled' scores following treatment. Addiction Severity Index results showed highly statistically significant reductions in severity of 'Drug-related Impairment' and 'Legal Status' scores and a smaller reduction in 'Family/Social (Interpersonal Functioning)' scores.

Overall there were 112,851 patient days of Suboxone dosing. The overall average daily dose of Suboxone was 15.8 mg, although there was significant use of higher and lower doses.

This study confirms the results of the randomised study CR96/013. Subjects who remained in the study exert reduced misuse of opiates. The low retention rate is typical for this patient group.

US08 Study (*Randomized comparison of the use of Suboxone for opioid dependence in three office based settings in the USA)* A 52-week study compared the use of Suboxone for opioid dependence in three office-based settings in the USA (US08). The study aims were: to document physicians' preferred prescribing practices, including induction, dose adjustment, maintenance, and take-home dosing; to document the ease or difficulty they encounter in delivering Suboxone in the three treatment settings; and to document the acceptance, compliance, response and necessary adjustments from the patients' perspective. The three treatment settings were: an office-based psychosocial treatment setting, using the Matrix Recovery / Relapse Prevention Model, within which buprenorphine treatment was introduced by making available the service of a physician; a private physician's office within which buprenorphine is prescribed and supplemented with relapse prevention delivered by an appropriately trained medical assistant; and a research clinic housed in a traditional opiate

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maintenance treatment (methadone) clinic but with personnel experienced in the clinical use of buprenorphine.
A total of 128 patients were screened for participation in the study. Of these, 16 failed the screening process, two others who passed the screening process failed to show for randomization. The efficacy evaluable (EE) population comprised 93 patients and the intent to treat (ITT) population comprised 103 patients (EE population + 10 partners). The safety population comprised 104 patients (ITT population + a subject treated at two settings).
On the first day of treatment, patients saw the physician and received a 2, 4 or 8mg first dose of Suboxone taken sublingually at the clinic. Most (97) of the 103 patients were given 4mg Suboxone as their first dose of Suboxone. Of the other 6 patients, 4 received 2mg and 2 received 8mg Suboxone as their first dose. On the first day, patients could receive an additional Suboxone dose up to 8mg at the treating physician's discretion. Most patients were recorded as having taken 8mg Suboxone (50 patients) or were prescribed 8mg Suboxone (35 patients) as their total dose on Day 1. Twelve patients received just 4mg total dose of Suboxone on Day 1. The other patients received a higher total dose of Suboxone on Day 1. Patients were prescribed or dispensed enough medication to continue dosing until the next office visit. Patients made contact with the study physician on the following day and were seen by the physician at least one more time during the first study week for follow-up evaluation to include drug use, signs and symptoms of opiate withdrawal or over-medication, and any adverse effects. At that time, dosage could be adjusted by 8 mg/day increments, to a maximum of 24 mg buprenorphine.
During weeks 2-6 patients saw the study physician once weekly for evaluation of treatment progress, medication effects and side effects. A urine sample was obtained at each visit to screen for drugs of abuse. Additional visits were to be scheduled as medically indicated. After Week 6 the study physician reviewed and discussed treatment progress and options with the subject to determine whether to begin detoxification, continue further maintenance, or explore other treatment options. Buprenorphine treatment could continue for up to 52 weeks.
Urinary opiate results are not available from the study.
Retention of patients in treatment is an important indicator of treatment efficacy. Of the 104 patients, 28 completed the study, 26 of who completed at least 47 weeks of Suboxone treatment. Of the 76 patients who discontinued early, 47 failed to return to the clinic at some point in the study, and 14 patients requested early termination from the study. Three patients discontinued due to unwanted effects of the medication.

This study report provides limited efficacy information since urinary opiate results are not available.

Studies CR95/002, Bupp4729, and Bupp5113 were pilot studies. Only a few subjects completed the studies. No additional results were obtained to demonstrate efficacy.

- Discussion on clinical efficacy

Study CR96/013 demonstrates statistical significant superiority of Suboxone compared to placebo regarding all primary and secondary efficacy endpoints. The results also indicate that Suboxone is as effective as Buprenorphine alone in the treatment of opiate dependency.

This conclusion is endorsed by the results of the open Suboxone studies CR96/014, NIDA#018 and US08 including more than 1000 patients.

Successful detoxification can be obtained with Suboxone titrated downward to 2mg before termination of the therapy. However, in some patients it is necessary to titrate downward from 2mg in small steps of 0.4mg before termination of the therapy.

The CHMP was concerned, as for these patients a titration would be possible only with Buprenorphine alone. As Suboxone is indicated for substitution treatment for opioid dependence, be it acute detoxification or maintenance treatment, is clinically justified to have 0.4mg/0.1mg Suboxone tablets.

The Applicant argued that the efficacy and safety of Suboxone and Buprenorphine alone when used as directed are comparable. Therefore, it should be acceptable to patients to use the 0.4 mg Buprenorphine alone tablet for those exceptional circumstances when doses below 2 mg buprenorphine are required and, since detoxification of patients who are continuing to inject opioids is

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not likely to be considered an appropriate course of treatment, the lack of a combination tablet in this dose range should not present a significant clinical issue.

Where it is not desirable to switch detoxification therapy from Suboxone to Buprenorphine alone (or any other buprenorphine that might be available for the treatment of opioid addiction in the future), the CHMP agreed with the applicant's position that the lack of a combination tablet in this dose range should not present a significant clinical issue. Therefore a follow up measure is adequate.

In conclusion detoxification with a switch from Suboxone to Buprenorphine alone will be monitored, as a part of the risk management plan.

Clinical safety

Suboxone is proposed for the treatment of opiate dependence. Buprenorphine alone (buprenorphine) is a well-established substitution treatment for opiate dependency as an alternative to methadone treatment. Buprenorphine has equal efficacy to other substitution treatments but has the added benefit of being safer in overdose as there is a ceiling effect on respiratory depression. Buprenorphine alone (buprenorphine alone) has been licensed in France since 1996. It became clear however that the diversion of Buprenorphine alone to the black-market and inappropriate use was occurring. There were deaths, due to respiratory depression and cardiovascular collapse in addicts who misused buprenorphine, especially with the concomitant use of benzodiazepines. The concept of combining buprenorphine and naloxone in a single tablet stemmed from the goal of deterring intravenous misuse of buprenorphine by opiate addicts.

- Patient exposure

The total exposure to Suboxone is **1631** patients. The total **long-term** exposure is **1158** patients. In CR96/013 and CR96/014 the 16mg and the 20mg/day doses were the most frequently administered. The 16 mg dose had the highest exposure

Study	**Product**	**N. subjects**	**Men**	**Women**	**Duration**
CR95/002	Suboxone	25	16	9	6-20 wks
CR96/013+CR96/014	Suboxone 4mg-24mg	472	327	145	52 weeks
US08	Suboxone 4mg-24mg	104	66	38	52 weeks
NIDA #1018	Suboxone 4mg-24mg	582	386	196	52 weeks
0600201	Suboxone 4mg	40	31	9	12 weeks
Bupp 4729	Suboxone 8mg	47	33	14	11 weeks
Bupp 5113	Suboxone 8mg	46	30	16	11 weeks
Bupp 6683 Australian Study	Suboxone 2mg-32mg	17	11	6	26 weeks
RC050175 Finnish Study	Suboxone 2mg-32mg	64	52	12	Up to 75 weeks
10.CTN-001 and CTN 002	Suboxone 1mg – 8mg	234	161	73	2 weeks

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Table: Demographic characteristics of Patients in the long term Suboxone studies

Race	Total	Age range	Women	Age range	Men	Age range	% Male
White	754	(15-61)	252	(15-61)	502	(16-61)	66.6
Black	202	(18-65)	76	(18-60)	126	(22-65)	62.4
Hispanic	138	(21-66)	25	(21-52)	113	(21-66)	81.9
Other Hispanic	29	(33-65)	10	(33-45)	19	(34-65)	65.5
Asian/Pacific Islander	12	(21-56)	4	(23-41)	8	(21-56)	66.7
Native American	11	(24-60)	7	(24-47)	4	(36-60)	36.4
Asian	9	(19-39)	4	(19-36)	5	(28-39)	55.6
Other	3	(24-42)	1	24	2	(24-42)	66.7
Total	**1158**	**(15-66)**	**379**	**(15-61)**	**778**	**(16-66)**	**67.3**

Suboxone Doses used in Clinical Trials

When the number of dose levels to which each subject was exposed was counted, including induction and titration doses, the 16 mg/day and the 20 mg/day doses of Suboxone were the most frequently administered. The minimum and maximum Suboxone doses used for maintenance treatment were 4 mg/day and 24 mg/day, respectively. A 2 mg/day dose was used during dose-reduction at the end of the study.
Individual subjects attained a stable dose level of buprenorphine/naloxone and tended not to deviate from this dose during the study.
Overall, there was a total of 92,930 person-days exposure (average of 197 person-days per subject) among the 472 subjects in the safety study. The 16 mg Suboxone dose had the highest exposure (32,448 person-days), with an average of 82 person-days per subject

- Adverse events

A profile of adverse events relating to clinical use of Suboxone is obtained from the 52-week pivotal efficacy/safety study (CR96/013 + CR96/014) and from the 52-week Suboxone Safety/Best Practice study (NIDA #1018). Comparison of Suboxone, Buprenorphine alone and placebo is made from the 4-week efficacy study (CR96/013).

Common Adverse Events
Adverse Events Following Treatment with Suboxone, Buprenorphine alone and Placebo in Study CR96/013

Overall Adverse Events
Buprenorphine, whether administered alone or in combination with naloxone, was well tolerated. The most frequently reported events during the efficacy study (reported by at least 10% of subjects) were headache, withdrawal syndrome, pain, insomnia, nausea, and sweating. Of the more common events, headache, abdominal pain, and constipation were reported somewhat more frequently by the subjects in the buprenorphine groups compared to the placebo group. Placebo subjects reported a higher incidence of back pain, withdrawal syndrome, diarrhoea, and rhinitis than buprenorphine-treated subjects.
When adverse events most frequently reported by subjects treated with either buprenorphine formulation were examined, the frequency of adverse events was similar between the treatment groups in the vast majority of cases. Amongst events that were reported by fewer than 5% of the subjects, somnolence was somewhat more common amongst buprenorphine-treated subjects; no other trends were observed.

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CR96/013: Adverse Events Reported by at Least 5% of Subjects Overall by Body System and Treatment Group

Adverse Event (COSTART Coded Term)	Suboxone (N = 107)	Buprenorphine alone (N = 103)	Placebo (N = 107)	All (N = 317)
Body As A Whole				
Asthenia	7 (6.5%)	5 (4.9%)	7 (6.5%)	19 (6.0%)
Chills	8 (7.5%)	8 (7.8%)	8 (7.5%)	24 (7.6%)
Headache	39 (36.4%)	30 (29.1%)	24 (22.4%)	93 (29.3%)
Infection	6 (5.6%)	12 (11.7%)	7 (6.5%)	25 (7.9%)
Pain	24 (22.4%)	19 (18.4%)	20 (18.7%)	63 (19.9%)
Pain Abdomen	12 (11.2%)	12 (11.7%)	7 (6.5%)	31 (9.8%)
Pain Back	4 (3.7%)	8 (7.8%)	12 (11.2%)	24 (7.6%)
Withdrawal syndrome	27 (25.2%)	19 (18.4%)	40 (37.4%)	86 (27.1%)
Cardiovascular System				
Vasodilatation	10 (9.3%)	4 (3.9%)	7 (6.5%)	21 (6.6%)
Digestive System				
Constipation	13 (12.1%)	8 (7.8%)	3 (2.8%)	24 (7.6%)
Diarrhoea	4 (3.7%)	5 (4.9%)	16 (15.0%)	25 (7.9%)
Nausea	16 (15.0%)	14 (13.6%)	12 (11.2%)	42 (13.2%)
Vomiting	8 (7.5%)	8 (7.8%)	5 (4.7%)	21 (6.6%)
Nervous System				
Insomnia	15 (14.0%)	22 (21.4%)	17 (15.9%)	54 (17.0%)
Respiratory System				
Rhinitis	5 (4.7%)	10 (9.7%)	14 (13.1%)	29 (9.1%)
Skin And Appendages				
Sweating	15 (14.0%)	13 (12.6%)	11 (10.3%)	39 (12.3%)

Source data: Table 40 of CR96/013 + CR96/014 study report. Report located in Module 5, Section 5.3.5.1.1

Treatment Relationship and Severity

The most common adverse events that were judged by the investigators to have been at least possibly related to either of the buprenorphine treatments were headache (26.2% of Suboxone subjects, 18.4% of Buprenorphine alone subjects), insomnia (10.3%, 17.5%), nausea (13.1%, 9.7%), sweating (11.2%, 9.7%), and constipation (11.2%, 6.8%). The incidence of adverse events was comparable when buprenorphine was administered as monotherapy as compared to administration in combination with naloxone.

The majority of adverse events reported were either mild or moderate in severity. Headache, pain, and withdrawal syndrome were the most frequent events reported as being severe in intensity.

CR96/013: Adverse Events Classified as Severe in Intensity

Adverse Event (COSTART Coded Term)	Suboxone (N=107)	Buprenorphine alone (N=103)	Placebo (N=107)	All (N=317)
Body As A Whole				
Asthenia	1 (0.9%)	0	0	1 (0.3%)
Fever	1 (0.9%)	0	0	1 (0.3%)
Headache	5 (4.7%)	2 (1.9%)	2 (1.9%)	9 (2.8%)
Accidental Injury	0	0	2 (1.9%)	2 (0.6%)
Pain	2 (1.9%)	2 (1.9%)	1 (0.9%)	5 (1.6%)
Pain, Abdomen	1 (0.9%)	0	2 (1.9%)	3 (0.9%)
Pain, Back	0	1 (1.0%)	1 (0.9%)	2 (0.6%)
Withdrawal Syndrome	1 (0.9%)	1 (1.0%)	3 (2.8%)	5 (1.6%)
Cardiovascular System				
Syncope	0	0	1 (0.9%)	1 (0.3%)
Digestive System				
Constipation	2 (1.9%)	0	0	2 (0.6%)
Gastrointestinal Disorder	1 (0.9%)	0	0	1 (0.3%)
Nausea	0	1 (1.0%)	0	1 (0.3%)
Nausea/Vomiting	0	0	1 (0.9%)	1 (0.3%)
Stomatitis	1 (0.9%)	0	0	1 (0.3%)

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Adverse Event (COSTART Coded Term)	Suboxone (N=107)	Buprenorphine alone (N=103)	Placebo (N=107)	All (N=317)
Tooth Disorder	1 (0.9%)	0	0	1 (0.3%)
Musculoskeletal System				
Myalgia	1 (0.9%)	0	0	1 (0.3%)
Nervous System				
Convulsions	1 (0.9%)	0	0	1 (0.3%)
Depression	1 (0.9%)	0	0	1 (0.3%)
Drug Dependence	0	0	1 (0.9%)	1 (0.3%)
Emotional Lability	1 (0.9%)	0	0	1 (0.3%)
Insomnia	0	0	2 (1.9%)	2 (0.6%)
Paresthesia	1 (0.9%)	0	0	1 (0.3%)
Respiratory System				
Rhinitis	0	0	1 (0.9%)	1 (0.3%)
Special Senses				
Conjunctivitis	0	1 (1.0%)	0	1 (0.3%)
Urogenital System				
Dysmenorrhea	1 (0.9%)	0	1 (0.9%)	2 (0.6%)
Urinary Tract Disorder	0	0	1 (0.9%)	1 (0.3%)

Source data: Table 42 of CR96/013 + CR96/014 study report. Report located in Module 5, Section 5.3.5.1.1

In study CR96/013, the more commonly reported adverse events (reported by 5% or more of the subjects overall) were reviewed for possible difference by gender, ethnicity, duration of heroin abuse, and baseline liver function.

Adverse Events Reported During Long-term Treatment with Suboxone

Adverse events following two 52-week studies of Suboxone have been reported from studies: CR96/013 /014 and NIDA #1018.

Adverse Effects

Of 472 subjects in Study CR96/014, 446 (94.5%) experienced a treatment-emergent adverse event at some time while on-treatment. Most of these reported events appear to be either events that are common in the general population, or would be expected in a population of illicit drug users. Among all subjects receiving the buprenorphine/naloxone tablet, the most frequently reported events were headache, pain, withdrawal syndrome, infection, insomnia, back pain, and constipation, each reported by more than 20% of subjects. Additionally, flu syndrome, abdominal pain, nausea, rhinitis, sweating, accidental injury, depression, anxiety, pharyngitis, vomiting, diarrhoea, and asthenia were each reported by more than 10% of subjects.

The incidence of adverse events appeared to increase with dose level; 89 of the 131 subjects (67.9%) taking the lowest dose (4mg Suboxone) reported adverse events whereas 46 of the 48 subjects (95.8%) taking the highest dose (24mg Suboxone) reported adverse events. At the most commonly prescribed dose level (16mg Suboxone), 339 of the 394 subjects (86.0%) reported adverse events. There were some events that appeared to occur with higher incidence as the dose increased. However, since the design of the study was titration with low doses and progressively increasing doses, there was also an increase in duration of exposure as the dose increased.

Adverse events reported by at least 5% of subjects in study CR96/013 + CR96/014 are summarized by body system in the Table below.

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CR96/013+CR96/014: Adverse Events Reported by at Least 5% of Subjects

Adverse Event (COSTART Coded Term)	**All Subjects (N = 472)**
Body as a Whole	
Asthenia	48 (10.2%)
Chills	44 (9.3%)
Fever	36 (7.6%)
Flu Syndrome	89 (18.9%)
Headache	202 (42.8%)
Infection	149 (31.6%)
Accidental Injury	72 (15.3%)
Pain	197 (41.7%)
Pain Abdomen	77 (16.3%)
Pain, Back	132 (28.0%)
Withdrawal Syndrome	194 (41.1%)
Cardiovascular System	
Vasodilatation	29 (6.1%)
Digestive System	
Constipation	115 (24.4%)
Diarrhoea	50 (10.6%)
Dyspepsia	45 (9.5%)
Nausea	76 (16.1%)
Tooth Disorder	37 (7.8%)
Vomiting	61 (12.9%)
Metabolic and Nutritional	
Peripheral Oedema	24 (5.1%)
Musculoskeletal System	
Myalgia	31 (6.6%)
Nervous System	
Anxiety	65 (13.8%)
Depression	70 (14.8%)
Dizziness	33 (7.0%)
Insomnia	138 (29.2%)
Nervousness	42 (8.9%)
Paresthesia	28 (5.9%)
Somnolence	40 (8.5%)
Respiratory System	
Cough Increased	36 (7.6%)
Pharyngitis	64 (13.6%)
Rhinitis	75 (15.9%)
Skin and Appendages	
Sweating	74 (15.7%)

Source data: Table 66 of CR96/013 + CR96/014 study report. Report located in Module 5, Section 5.3.5.1.1

A subset of 261 subjects in the safety study were exposed to Suboxone for at least 6 months. There were no clear differences in the frequency of adverse events in this sample compared with the overall safety sample; frequently reported adverse events (reported by at least 20% of the subjects) had a somewhat higher incidence in subjects exposed for at least 6 months and included pain, headache, infection, withdrawal symptoms, back pain, insomnia, constipation, flu syndrome, depression, accidental injury, rhinitis, and pharyngitis. Anxiety, abdominal pain, nausea, vomiting, asthenia, sweating, diarrhoea, dyspepsia, tooth disorder, chills, fever, and paraesthesia were each reported by 10% or more of the subjects. In terms of evaluation by dose, the observations for subjects exposed to Suboxone for 6 months or more are similar to those observed for all subjects, where the apparent increase with dose level may equally relate to the increased duration of exposure.

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Treatment Relationship and Severity

The most frequently reported adverse events that were judged by the investigator to have been at least possibly related to the study drug (Suboxone) were headache (30.3% of subjects), constipation (21.6% of subjects), insomnia (20.3% of subjects), withdrawal syndrome (15.7% of subjects), sweating (12.1% of subjects), and nausea (11.2% of subjects) Most of the adverse events reported in the study were mild or moderate in severity. For the treatment-related adverse events most frequently reported by all subjects, pain and back pain were the most frequently reported as being severe in 3.6% and 3.2% of subjects, respectively. Severe withdrawal syndrome was reported by 2.3% of subjects. For subjects exposed for at least 6 months, the same general trends were apparent; severe pain and severe back pain were reported for 5.4% and 5.0% of subjects, respectively. When looking at the dose distribution of severe adverse events, they tended to occur with the most frequently prescribed doses, 16mg and 20mg Suboxone per day.

- Serious adverse event/deaths/other significant events

In total, 367 non-fatal serious adverse events were reported during clinical trials of buprenorphine in the treatment of opioid dependence: 175 in subjects treated with Suboxone, 28 with Buprenorphine alone, 115 with buprenorphine solution, 25 with methadone, 12 with placebo, 7 with clonidine, 4 in undosed subjects and 1 not stated.

All Trials: Serious Adverse Event Counts by Body System

Body system	**Cases**
Application Site	3
Benign and Malignant Neoplasms	3
Body as a Whole	11
Cardiovascular	18
Central and Peripheral NS	11
Gastrointestinal	19
Immune System	4
Infection and infestation	41
Injury and Poisoning	31
Liver and Biliary	52
Metabolic and Nutritional	2
Musculo-Skeletal	11
Psychiatric	129
Renal and Urinary	5
Reproductive	3
Respiratory	17
Skin and Subcutaneous	7
TOTAL	**367**

The serious adverse event preferred term most commonly reported was Elevated Liver Function Tests (47 cases in the Liver and Biliary Body System); The next most commonly reported events were: depression (34), overdose (25), detoxification request leading to hospitalisation (23), abscess (17), chest pain (14), pneumonia (13), automobile accident (13), infection (9), suicide attempt (9), asthma (8), seizure (8), cellulitis (7), suicide ideation (7), anxiety (6), surgery (6), obstructive pulmonary disease (5), and fracture (4). The cases of overdose, depression, suicide attempt, and suicide ideation show the instability of the addict patient population and point to the need to regularly monitor progress during treatment.

Of the other less frequently reported serious adverse events reported in clinical trials, two cases of allergic reaction occurred just hours following the sublingual administration of the first dose of Buprenorphine alone. In one case the reaction was severe and life threatening while the other case was of moderate severity. Two cases of myocardial infarction occurred, both in 46-year-old male subjects being treated with Suboxone. One had a history of pulmonary disease, secondary to smoking and grain dust inhalation at work; this event was judged unrelated to study drug. The other subject had a history of smoking and hypertension; the Principal Investigator judged this event to be possibly

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related to the study drug. Both cases were mild in severity. Other serious adverse events were those that would be expected in this patient group or the general population over the study periods.

Serious Adverse Events in Subjects Receiving Suboxone in Clinical Trials of Opioid Dependence

A total of 175 serious adverse events were reported in patients receiving Suboxone in five clinical trials.
Apart from detoxification requests that led to hospitalisation (34 subjects), the most common serious adverse events reported for Suboxone treated subjects were depression (14), elevations in liver function tests (protocol reports, 11), overdose (11), pneumonia (9), abscess (8), and chest pain (7 subjects).

Adverse Events Leading to Discontinuation from Treatment in Clinical Trials

Adverse Event Preferred Term	Suboxone	Buprenorphine alone	Bup Sol	Methadone	Total
Withdrawal syndrome	13	4	5		**22**
Nausea	9	2	1		**12**
Nausea and vomiting	2	1	3	2	**8**
Abdominal Pain	1	4	2		**7**
Dizziness	2	2	3		**7**
Vomiting	3		1	1	**5**
Anxiety	1		3		**4**
Headache		2	1		**3**
Hypertension	2	1			**3**
Suicide attempt		1	2		**3**
Accidental injury			1	1	**2**
Alcoholism			1	1	**2**
Allergic reaction		2			**2**
Depression			2		**2**
Hepatitis			1	1	**2**
Rash	1		1		**2**
Abscess			1		**1**
Agitation			1		**1**
AIDS				1	**1**
Anorexia			1		**1**
Arthralgia				1	**1**
Asthenia			1		**1**
Back pain			1		**1**
Chest pain			1		**1**
Confusion			1		**1**
Constipation	1				**1**
Cramps, leg			1		**1**
Edema, peripheral	1				**1**
Edema, peripheral and rash		1			**1**
Fatigue	1				**1**
Hair loss	1				**1**
Herniated disc			1		**1**
Hostility		1			**1**
Libido decreased			1		**1**
Malaise				1	**1**
Nervousness			1		**1**
Obstructive pulmonary disease			1		**1**
Overdose				1	**1**
Pain	1				**1**
Paresthesia			1		**1**
Peri-oral eczema	1				**1**
Pneumonia		1			**1**
Strangulated intestine			1		**1**
Suicide ideation			1		**1**
Sweating increased	1				**1**

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Adverse Event Preferred Term	Suboxone	Buprenorphine alone	Bup Sol	Methadone	Total
Weight loss	1				**1**
TOTAL	**42**	**22**	**42**	**10**	**116**

Analysis of Adverse Events by Organ System or Syndrome

The serious adverse event preferred term most commonly reported was elevated liver function tests (47 cases in the Liver and Biliary Body System). A few serious cases of acute hepatic injury have been reported in subjects misusing buprenorphine by the intravenous route, and increases in liver enzymes have been reported in other patients receiving buprenorphine. This prompted a retrospective analysis of hepatic cases from clinical trials and from the marketing of Buprenorphine alone (Report RC020117). This analysis was undertaken on data from 1615 patients who took part in five clinical trials where there was a baseline measurement of hepatic parameters plus regular on-treatment measurements. Of these, 252 patients (15.6%) had liver function parameter levels greater than or equal to three times the higher limit of normal at some point during the studies. Generally, continued treatment with buprenorphine was not associated with a worsening of the condition and often was associated with a reduction or normalization of hepatic function parameters.

A large number of the serious adverse events related to the 'Psychiatric' body system: depression (34), overdose (25), detoxification request leading to hospitalisation (23), suicide attempt (9), suicide ideation (7), anxiety (6).

Another large group of adverse events, often resulting in discontinuation from treatment, relate to the 'Gastrointestinal' System and include nausea, nausea with vomiting and vomiting.

Withdrawal symptoms are the other main group of adverse events seen in clinical trials of buprenorphine, and are common to addicts undergoing transition from street opiate to pharmacological treatment.

Deaths in Clinical Studies

There have been 13 deaths that occurred in clinical trials of buprenorphine for the treatment of opioid dependence. Deaths Occurring in Buprenorphine Clinical Trials of Opioid Dependence, by Body System

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			Adverse event leading to death					
Study	**Treatment**	**Dose**	**Study day - onset**	**Preferred term**	**Verbatim term**	**Relationship**	**Action indicated**	**Study day - death**
CTN-001	Suboxone	2-16 mg schedule over 13 days	~122	Vomiting and dehydration	Acetaminophen poisoning., respiratory failure and MI	Unrelated	Hospitalization	~123
NIDA #1018	Suboxone	24 mg	~110	Infection	Necrotizing fascitis IV heroin	Unrelated	Hospitalization	~122
NIDA #1018	Suboxone	6 mg	~383	Overdose	Temazepam Overdose	Unknown	None	~383
OASIS	Suboxone	20 mg	191	Infection	Infection	Possible	Hospitalization	?
NEPOD #10	Buprenorphine alone	32 mg on alternate days		Suicide	Carbon monoxide poisoning	Unrelated	None	
CR88/130	Buprenorphine solution	8 mg	37	Overdose	Drug Overdose	Unrelated	None	37
CR92/100	Buprenorphine solution	8 mg	147	Coronary thrombosis	Coronary thrombosis	Unrelated	Hospitalization	147
CR92/100	Buprenorphine solution	32 mg	265	Infection	Dehydration and sepsis	Unrelated	Hospitalization	265
CTN-001	Clonidine	~0.4 mg per day by patch for 3 days	~127	Endocarditis	Endocarditis secondary to staphylococcus aureus infection	Unrelated	Hospitalization	~127
CR88/130	Methadone	20 mg	7	Accidental injury	Multiple injuries	Unrelated	None	7
Bupp 3773	Methadone	30 mg	18	Stab wound	Multiple stab wounds	Unrelated	None	18
CR96/005	Methadone	35 mg	~548	Accidental injury	Slipped and fell from a window	Unrelated	None	~548
Bupp 3773	Not known		Post study	Cancer		Unknown	Hospitalization	Post study

- Laboratory findings

No remarkable laboratory findings. The hepatic vulnerability will be discussed in the following section.

- Safety in special populations

Patients with Hepatic Vulnerability

A retrospective evaluation of the potential for buprenorphine-induced hepatotoxicity was undertaken in 2002; this also examined the role of viral hepatitis in increasing vulnerability to hepatotoxicity (Report RC020117). With regard to *in vitro* and preclinical work, this showed that very high concentrations of buprenorphine are toxic to hepatic mitochondria. However, the concentrations used in these experiments far exceed tissue concentrations likely from therapeutic use of buprenorphine. In clinical trials, elevations in hepatic enzymes were observed in 12.3% of patients being treated. An elevation of liver enzyme levels was not unique to buprenorphine since similar rises were also observed following treatment with methadone and LAAM. Generally, continued treatment with buprenorphine was not associated with a worsening of the condition and often was associated with a reduction or normalization of hepatic function parameters. In 81.7% of hepatic cases treatment was associated with rises in liver enzymes. However, in 8.0% of cases there was a reduction of liver enzymes, and in the other 10.3% of cases there was no obvious change in already elevated hepatic parameters.

The more confounding / contributory factors a patient has, the more likely he or she is to have an exaggerated hepatic enzymes response to treatment with buprenorphine. Thus, patients with existing HCV and / or who are taking anti-AIDS drugs are more vulnerable when treated with buprenorphine (or methadone and LAAM). In a few cases, introduction of buprenorphine to patients with no previous history of hepatitis was associated with a large elevation of liver enzyme levels, and withdrawal of the drug was associated with an improvement. However, since most addict subjects have other confounding factors, not least chaotic life-style of intravenous misuse of drugs, and their pre-treatment hepatitis status is usually not laboratory based, it could not be concluded that buprenorphine, *per se*, causes hepatitis, but it still remained a possibility.

It can be concluded that patients with existing hepatitis and/or HCV infection are probably more likely to have greater increases in hepatic enzymes during treatment with buprenorphine (or methadone and LAAM) than others without these complications.

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Differences in baseline liver functions (232 subjects in study CR96/013 had normal baseline liver function and 85 had abnormal baseline liver function) did not appear to be associated with any consistent trend in the incidence of adverse events.

Use of Suboxone in Pregnancy

Currently clinical information on the use of Suboxone tablets in pregnancy is from four women receiving the product who became pregnant during study CR96/013+CR96/014. Three of the pregnancies were aborted, one spontaneous and the other two elective; the other pregnancy went to term. The latter case was a 29-year-old woman with no noteworthy active medical problems aside from drug abuse; she was using a barrier contraceptive as her only form of birth control. She had a negative pregnancy test recorded at Week 12 and the next recorded test at Week 20 was positive, then reporting not using any form of birth control. She was terminated from the study at that time. The subject delivered a 'drug addicted' baby girl who had respiratory difficulties, and weighed slightly over 4 pounds. The baby recovered from the drug addiction and respiratory difficulties, and no birth defects or permanent abnormalities were noted. The baby was reported as doing well and gaining weight. Later she was placed in foster care.

Use of Buprenorphine alone in pregnant women

It is clear from post marketing adverse event reports that Buprenorphine alone is being used in pregnant women because a number of the most frequently reported events related to this use: Drug Exposure during Pregnancy (300 cases), Drug Withdrawal Syndrome Neonatal (212) and Tremor Neonatal (21). A number of foetal abnormalities and foetal deaths also were reported.

In some markets Buprenorphine alone is contraindicated in pregnancy and in others Buprenorphine alone use is based on evaluation by the physician of the risk of Buprenorphine alone use versus continued illicit heroin use. The cases of foetal death and deformities did not display any unusual pattern and were not specific to the use of buprenorphine. In neonates of opioid dependent mothers the following problems occur more often: small for gestational age, reduced weight and length, premature delivery, small head circumference, neonatal withdrawal, and later mental, emotional or behavioural problems.

- Safety related to drug-drug interactions and other interactions

Drug interaction profile in vitro and in vivo was described for buprenorphine alone and not for the fixed combination.

No information to interactions is present in the post marketing database. The SPC includes information regarding the interactions and the monosubstances *in section 4.5 and 4.9.*

- Discontinuation due to adverse events

In clinical trials of opioid dependence with buprenorphine there have been 116 cases of adverse events leading to discontinuation from treatment. Of the 1715 subjects who were treated with Suboxone in clinical studies, 42 (2.4%) discontinued due to adverse events. This percentage compares favourably with patients who discontinued due to adverse events being treated with Buprenorphine alone (5.9%), buprenorphine solution (4.4%), and methadone (1.8%).

Discontinuations from Treatment due to Adverse Events

Treatment	**Total Patients**	**Number discontinuing due to adverse events**	**%**
Suboxone	1715	42	2.4%
Buprenorphine alone	370	22	5.9%
Buprenorphine Solution	949	42	4.4%
Methadone	567	10	1.8%
TOTAL		**116**	

Most of the discontinuations were due to a withdrawal syndrome (19) or individual withdrawal symptoms, which are not unexpected in patients being stabilised from street opiates. Nausea (12), nausea with vomiting (8), and vomiting (5) are known side effects of buprenorphine treatment that affect some patients more than others. Dizziness (7) is a known side effect of buprenorphine.

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The discontinuation rates of Suboxone or Buprenorphine alone treated subjects are comparable.

- Post marketing experience

Post marketing exposure to Suboxone

For Suboxone, in the period from launch in the USA in April 2003 until March 31, 2005, 21.1 million tablets (6.52 million 2mg, and 14.58 million 8mg tablets) were distributed for the treatment of opioid dependent patients. This is equivalent to 16.21 million doses of 8mg Suboxone or 8.11 million doses of 16mg Suboxone taken over the 23-month period, or 23,190 or 11,595 patients treated with 8mg or 16mg Suboxone per day, respectively.

Post Marketing Exposure to Suboxone and Buprenorphine alone

	Suboxone	**Buprenorphine alone**
	Launch (April 2003) to March 2005	**Launch (February 1996) to March 2005**
Dosage form	**Millions of tablets**	**Millions of tablets**
0.4 mg tablet	Product not available	70.22
2 mg tablet	6.52	307.99
8 mg tablet	14.58	198.99
Total tablets	**21.32**	**577.2**
Number of daily doses	8.11 million 16mg doses over 23 months	279.5 million 8mg doses over 10 years
Patients per year	11,595 patients (based on 16mg per day)	76,575 patients (based on 8mg per day)

Source data: 2005 PSUR (Report RC050324). Report located in Module 5, Section 5.3.6.2

Suboxone Post Marketing Adverse Events

In the period since the launch in the USA in April 2003 to March 31, 2005, there were 89 post marketing adverse events reported for Suboxone. The types of adverse events were similar to those reported for Buprenorphine alone.

Buprenorphine alone Post Marketing Adverse Events

Safety data pertaining to the buprenorphine tablet are available from marketed use in France since February 1996.

The profile of adverse events relating to Buprenorphine alone use has been similar year on year. Overdose deaths in addicts using Buprenorphine alone in combination with other psychoactive agents continue to be the most serious events. Neonatal withdrawal symptoms, usual not serious but frequent in number, relate to the continued safe use of Buprenorphine alone in pregnant opioid dependent women. Reports of hepatitis and elevations of hepatic enzymes continue to be reported at a low incidence. Usually, these occur in subjects already compromised with HCV infection, or who are taking other drugs know to have hepatic effects. Intravenous misuse is also a contributory risk factor for hepatic adverse events.

The adverse event profiles of Suboxone and Buprenorphine alone are comparable regarding post marketing exposure.

Retrospective collection of patient data in study RC050175 in Finland regarding patients switched from Buprenorphine alone to Suboxone treatment.

Data were collected from the records of 64 patients, 52 male and 12 female. Twenty of the patients had been treated with Suboxone for over a year at follow up.

During the 4 week observation period, there were approximately 1714 patient days of dosing with Suboxone, either alone or in combination with Buprenorphine alone. There were approximately 17883 patient days of dosing with Suboxone during both the 4 week study period and the follow up period. An average daily dose during the 4 week study period was calculated by each patient by summing the doses prescribed and dividing by the number of days the patient remains in the study. The estimated

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overall average daily dose of Suboxone when not in combination with Buprenorphine alone was 22.9mg. Half of the patients were taking Suboxone at doses between 20mg and 28mg.
There were no deaths ore other serious adverse events reported for patients in the study.
During the 4-week period 32 of 64 patients reported adverse events. During the follow up 19 of 61 patients reported adverse events.

- Discussion on clinical safety

Suboxone doses in clinical trials ranged from 2mg to 32mg. Sufficient safety data is available for doses up to 24mg daily in different age and ethnic groups.

In the European Union, Buprenorphine alone (Buprenorphine) was first approved for substitution treatment of opioid dependence in 1995 and has been marketed since 1996.
Suboxone (Buprenorphine+Naloxone) have been marketed in the USA since April 2003 and therefore safety data could be presented over a period of more than two years.
In Finland, Suboxone was made available in late 2003 under special license, which made it possible for a retrospective study to be conducted on subjects who switch from Buprenorphine alone to Suboxone, thereby allowing the evaluation of safety resulting from such a switch.
The three 52-week clinical trials of Suboxone (CR96/013+CR96/014, NIDA#1018, US08) provide the main safety database for Suboxone, supported by a number of smaller Suboxone studies and the above mentioned post marketing data. A second safety database is from Buprenorphine alone clinical trials, buprenorphine sublingual solution clinical trials, and from clinical pharmacology studies.

3034 patients (2054 male, 980 female) were exposed to buprenorphine in clinical trials.

The most frequently reported events during the efficacy study were headache, withdrawal syndrome, pain, insomnia, nausea and sweating. The incidence of adverse events was comparable when buprenorphine was administered as monotherapy as compared to administration in combination with naloxone. The majority of adverse events reported were either mild or moderate in severity. Headache, pain, and withdrawal syndrome were the most frequent events reported as being severe in intensity. When looking at the dose distribution of severe adverse events, they tended to occur with the most frequently prescribed doses, 16mg and 20mg Suboxone per day.

The serious event preferred term most commonly reported was elevated liver function test. This is not a normal category of serious adverse events reporting but was designated as such in the protocols of studies CR96/013+CR96/014. The large number of serious adverse events related to psychiatric body system is explainable by the instability of the addict patient population and lead to the conclusion that a regularly monitoring during treatment is needed. Adverse events relating to the gastrointestinal system occur very often after induction of an opioid treatment, particularly in opioid naïve patients. Therefore it's not surprising that these adverse events are common reasons for discontinuation. The number of deaths is not increased in Suboxone treated subjects.

It can be concluded that patients with existing hepatitis and/or HCV infection are probably more likely to have greater increases in hepatic enzymes during treatment with buprenorphine (or methadone and LAAM) than others without these complications.
Differences in baseline liver functions (232 subjects in study CR96/013 had normal baseline liver function and 85 had abnormal baseline liver function) did not appear to be associated with any consistent trend in the incidence of adverse events.

In some markets Buprenorphine alone is contraindicated in pregnancy and in others Buprenorphine alone use is based on evaluation by the physician of the risk of Buprenorphine alone use versus continued illicit heroin use. The cases of foetal death and deformities did not display any unusual pattern and were not specific to the use of buprenorphine. In neonates of opioid dependent mothers the following problems occur more often: small for gestational age, reduced weight and length, premature delivery, small head circumference, neonatal withdrawal, and later mental, emotional or behavioural problems. This will be discussed in the preclinical assessment report in more detail.

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The adverse event profiles of Suboxone and Buprenorphine alone are comparable. This conclusion results from more than 3000 subjects in clinical trials and from post marketing data in the USA. No safety issues arise from switching the therapy from Buprenorphine alone to Suboxone.

The CHMP was concerned about spontaneous abortion with the use of Suboxone.
The applicant's deletion of this term was not agreed, as in the applicant's response there are no unequivocal data supporting causality. Pregnancy data of patients under Buprenorphine alone treatment from the literature are scarce. The applicant states that all spontaneous abortion cases in the latest PSUR covering the period 05 May 2005 to 04 Nov 2005 were from EU countries in which pregnancy is not an absolute contraindication. This would suggest a possible link with buprenorphine substitution treatment. It is accepted that polyabuse is a factor and this can be reflected in the SPC. Also in this period there were 6 cases of spontaneous abortion, 5 foetal deaths and 4 premature deaths in 93 pregnancy cases (Results of the Cumulative Prospective Pregnancy data). In the Cumulative Retrospective Pregnancy Data (119 Pregnancy Cases with 294 Pregnancies Reported) there were 11 spontaneous abortion in 10 mothers.

Neonatal drug withdrawal syndrome will be mentioned in section 4.8 of the SPC. In fact the use of Buprenorphine alone and Suboxone, whether by inappropriate diversion to pregnancy women or not, has occurred and results in a neonatal withdrawal syndrome that should be addressed appropriately. The most recently submitted PSUR describes 38 cases as the most common newborn event with symptoms compatible with drug withdrawal syndrome.

The applicant had no further information with which to address concerns relating to the use of Suboxone in pregnancy at the time of the procedure and proposed to address this issue within the Risk Management Plan.

The section 4.8 of the SPC has been adapted accordingly.

"Spontaneous abortion has been reported with both buprenorphine and buprenorphine-naloxone. It is not possible to establish a causal relationship since cases typically involve other drug use or risk factors for spontaneous abortion (see Section 4.6).

A neonatal abstinence syndrome has been reported among newborns of women who have received buprenorphine during pregnancy. The syndrome may be milder and more protracted than that from short acting full mu-opioid agonists. The nature of the syndrome may vary depending upon the mother's drug use history (see Section 4.6)."

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

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

A detailed description of the company´s pharmacovigilance system as required by the new legislation & provisions with this consolidated response documentation was presented, which included the statements of the MAH and the qualified person regarding their availability of means for the notifications of adverse reactions, the organisation and procedural aspects of global pharmacovigilance and European safety department activities within Shering-Plough.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.
Table: Summary of the risk management plan

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Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Induction with Suboxone	The applicant commits to performing a prospective study	Physician/pharmacist awareness and patient information. Also outlined in the SPC section 4.2
Switch from Buprenorphine alone to Suboxone	The applicant commits to conducting a prospective controlled study	Physician/pharmacist awareness and patient information. Also outlined in the SPC section 4.4
Switch from Suboxone to Buprenorphine alone during detoxification	The therapy will be monitored. and reported with regard to the development of a low dose (0.4/0.1) tablet of Suboxone .	Physician/pharmacist awareness and patient information. Also outlined in the SPC section 4.2
Spontaneous abortion	Annual Safety Reports and Periodic Safety Update	Physician/pharmacist awareness and patient information. Also outlined in the SPC section 4.6.
Neonatal withdrawal syndrome, other newborn conditions	Annual Safety Reports and Periodic Safety Update	Physician/pharmacist awareness and patient information. Also outlined in the SPC section 4.6.
Hepatitis, other liver abnormalities	Annual Safety Reports and Periodic Safety Update	Physician/pharmacist awareness and patient information. Also outlined in the SPC section 4.4.
Intravenous misuse	Annual Safety Reports and Periodic Safety Update	Physician/pharmacist awareness and patient information. Also outlined in the SPC section 4.4.

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

The pharmacovigilance plan included signalling reviews on events of interest: spontaneous abortion, neonatal withdrawal syndrome and other newborn conditions, hepatitis and other hepatic abnormalities, misuse, intravenous misuse, death, overdose, drug interaction, infections, psychiatric disorders, from Schering Plough and from WHO Adverse event database.

The risk minimization plan included sales force training to ensure safe and effective use and minimize the potential for diversion and misuse. Additional information packages for physicians, pharmacists, and patients should increase the awareness on the risks of drug abuse and should emphasize the importance of reporting the cases of abuse and AE's.

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

Information on development, manufacture and control of the drug substance 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.

Non-clinical pharmacology and toxicology

No novel toxicological aspects rose from the studies with a mixture of buprenorphine/naloxone in comparison with knowledge about the compounds alone. Based on toxicokinetic data raised from the dietary study with Suboxone, an exposure of animals sufficiently above the maximum therapeutic dose in humans has been reached. Clinical signs reflected the pharmacodynamics of the active ingredients.

Statistically significant increases in the incidence of benign testicular interstitial (Leydig's) cell adenomas were observed in all dosage groups during a 2-year dietary carcinogenicity study in rats.

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Based on the estimated exposure multiples of 3 to 75 times, based on a human daily sublingual dose of 16 mg calculated on a mg/m² basis, the clinical relevance of this findings remains limited.

Efficacy

The combination of an opioid antagonist with a potent μ-opioid analgesic is an established strategy for reducing the potential for intravenous misuse.

Concerning the pharmacokinetic programme, individual studies were not powered to demonstrate statistically comparable bioavailability of buprenorphine from Suboxone or Buprenorphine alone (buprenorfine alone). Nevertheless all the presented studies lead to consistently comparable pharmacokinetic results. The conclusion of comparable bioavailability of buprenorphine from Suboxone or Buprenorphine alone is therefore endorsed.

Based on the results of the pharmacodynamic studies the intravenous misuse potential for Suboxone is very low in comparison with buprenorphine alone.

The intravenous or intramuscular administration produces withdrawal effects in all opiate dependent subjects. At the same time, sublingual or oral administration of naloxone in doses up to 8 mg has no pharmacodynamic effects.

After 4 week of treatment patients treated with Suboxone had statisticallly significant reduced heroin use versus placebo, as judged by the higher percentages of urine samples that were negative for opiates (17.8% versus 5.8%). Patients on Suboxone also had a significant reduction in craving for heroin.

Results also indicate that Suboxone is as effective as Buprenorphine alone (buprenorphine alone) in the treatment of opiate dependency.

Finally, successful detoxification can be obtained with Suboxone titrated downward to 2 mg per/day before termination of the therapy. The switch to 0.4 mg of buprenorphine alone may be considered.

Safety

The adverse event profiles of Suboxone and Buprenorphine alone are comparable. This conclusion results from data of more than 3000 subjects in clinical trials and from post marketing data in the USA.

The most frequently reported events during the efficacy study (reported by at least 10% of subjects) were headache, withdrawal syndrome, pain, insomnia, nausea, and sweating. No safety issues arise from switching the therapy from Buprenorphine alone to Suboxone.

Patients with existing hepatitis and/or HCV infection are probably more likely to have greater increases in hepatic enzymes during treatment with buprenorphine than others without these complications.

Spontaneous abortion and neonatal withdrawal syndrome have consistently been reported in case of exposure during pregnancy,

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

It was ongoing at the time of assessment. It will be provided post-authorisation (see 2.7).

Risk-benefit assessment

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 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.

Suboxone is intended as a “take home” medication and treatment is intended for use in adults and, as requested by the CHMP, adolescents over 15 years of age who have agreed to be treated for addiction.

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Concerning efficacy, the clinical studies programme consistently demonstrated Suboxone is effective as substitution treatment for opioid drug dependence within a framework of medical, social and psychological treatment for addiction.

Concerning safety, Suboxone was studied over short and long term repeated administration and followed across substantial post marketing experience The safety profile of Suboxone does not raise concerns with respect to the risk already known for buprenorphine alone.

A risk management plan was submitted.

The CHMP, having considered the data submitted, was of the opinion that in addition to the use of routine pharmacovigilance, the following follow-up measures were needed:

- to performing both a prospective study of induction with Suboxone, and a prospective controlled study of the switch from buprenorphine alone to Suboxone,
- the Applicant will provide all safety information from ongoing or planned studies
- the switch from Suboxone to buprenorphine alone in detoxification therapy will be monitored and should problems occur they will reported and discussed with regard to the development of a low dose (0.4/0.1) tablet of Suboxone
- the following additional risk minimisation activities were required physician awareness on the risk of spontaneous abortion, neonatal withdrawal syndrome and other neonatal conditions, hepatitis and other liver abnormalities, (intravenous) misuse and related severe adverse events

Buprenorphine is a substance scheduled in Schedule III of the UN convention on Psychotropic substances, which requires it to be classified as special medical prescription.

It is proposed that Suboxone is prescribed by physicians experienced in the treatment of addiction /opiate dependence.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Suboxone in the treatment 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 - was favourable and therefore recommended the granting of the marketing authorisation

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