14 September 2017
EMA/CHMP/12714/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zubsolv

International non-proprietary name: buprenorphine / naloxone

Procedure No. EMEA/H/C/004407/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Administrative information

Name of the medicinal product:	Zubsolv
Applicant:	Mundipharma Corporation Limited Milton Road Cambridge Science Park Cambridge CB4 0AB UNITED KINGDOM
Active substance:	BUPRENORPHINE HYDROCHLORIDE / NALOXONE HYDROCHLORIDE DIHYDRATE
International Non-proprietary Name/Common Name:	buprenorphine / naloxone
Pharmaco-therapeutic group (ATC Code):	Other nervous system drugs, drugs used in addictive disorders (N07BC51)
Therapeutic indication(s):	Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter intravenous misuse. Treatment is intended for use in adults and adolescents over 15 years of age who have agreed to be treated for addiction.
Pharmaceutical form:	Sublingual tablet
Strengths:	0.7 mg / 0.18 mg, 1.4 mg / 0.36 mg, 2.9 mg / 0.71 mg, 5.7 mg / 1.4 mg, 8.6 mg / 2.1 mg and 11.4 mg / 2.9 mg
Route of administration:	Sublingual use
Packaging:	PVC/OPA/Alu/PVC/Alu/PET/Paper
Package size:	30 tablets

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List of abbreviations

AE	Adverse event
AUC0-72h	Area under the plasma concentration-time curve from time zero to 72 hours after dosing
AUC0-t	Area under the plasma concentration-time curve from time zero to time t
AUCinf	Area under the plasma concentration-time curve from time zero extrapolated to infinity
BfArM	Federal Institute for Drugs and Medical Devices (Germany)
CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Cmax	Maximum observed plasma concentration
COWS	Clinical Opiate Withdrawal Scale
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicines Agency
EU	European Union
FCP	Final commercial product
FDA	Food and Drug Administration (US)
GC	Gas Chromatography
GMP	Good manufacturing practice
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
HIV	Human immunodeficiency virus
IR	Infrared
MAA	Marketing Authorisation Application
MIA	Manufacturing and Importation Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MPA	Medical Products Agency (Sweden)
NDA	New Drug Application
OOS	Out of Specifications
OPA	Oriented polyamide film
Ph. Eur.	European Pharmacopoeia
PVC	Polyvinylchloride
PET	Polyethylenetherethphalate
PK	Pharmacokinetic(s)
RH	Relative Humidity
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SOWS	Subjective Opiate Withdrawal Scale
TEAE	Treatment-emergent adverse event
Tmax	Time to maximum plasma concentration

US	United States
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XR(P)D	X-Ray (Powder) Diffraction
VAS	Visual Analogue Scale

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mundipharma Corporation Limited submitted on 3 October 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Zubsolv, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 February 2016

The application concerns a hybrid medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 10b of Directive 2001/83/EC.

The applicant applied for the following indication.

Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter intravenous misuse. Treatment is intended for use in adults and adolescents over 15 years of age who have agreed to be treated for addiction.

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, a bioequivalence study with the reference medicinal product Suboxone and appropriate non-clinical and clinical data

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

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

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Suboxone, 2 mg/0.5 mg, 8 mg/2 mg, 16 mg/4 mg, Sublingual tablet.
- Marketing authorisation holder: Indivior UK Limited
- Date of authorisation: 26-09-2006
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/06/359/001-006

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Suboxone, 2 mg/0.5 mg, 8 mg/2 mg, 16 mg/4 mg, Sublingual tablet.
- Marketing authorisation holder: Indivior UK Limited
- Date of authorisation: 26-09-2006
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/06/359/001-006

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Suboxone, 2 mg/0.5 mg, 8 mg/2 mg
- Marketing authorisation holder: Indivior UK Limited
- Date of authorisation: 26-09-2006
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number(s): EU/1/06/359/001-004
- Bioavailability study number(s): OX219-014

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Patrick Salmon Co-Rapporteur: Radka Montoniová

- The application was received by the EMA on 3 October 2016.
- The procedure started on 27 October 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 January 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 January 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 27 January 2017.

- During the meeting on 23 February 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 February 2017.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 May 2017.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 26 June 2017.
- During the PRAC meeting on 06 July 2017, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP. The PRAC assessment Overview and Advice was sent to the applicant on 20 July 2017.
- During the CHMP meeting on 20 July 2017, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 14 August 2017.
- During the meeting on 14 September 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to Zubsolv on 14 September 2017.

2. Scientific discussion

2.1. Introduction

2.1.1. Disease or condition

Opioid dependence is associated with considerable health risks and severe economic and psychosocial consequences for opioid-dependent persons and their families. It is linked to a substantially increased risk of premature death from drug overdose, violence, and suicide. Furthermore, sharing of needles among intravenous users contributes to the spread of potentially fatal blood infections, such as human immunodeficiency virus (HIV) and hepatitis C.

2.1.2. Epidemiology

In Europe there are 1.3 million adult problem opioid users. The main opioid used is heroin, with an estimated 37,800 heroin use/possession offences and 17,000 heroin supply offences reported in 2013 (European Monitoring Centre for Drugs and Drug Addiction: EMCDDA, 2015). An estimated 700,000 opioid users received substitution treatment in 2013; opioids were the principal drugs reported in approximately 41% of all drug treatment requests. For the same year, average annual prevalence of high-risk opioid use among individuals aged 15 to 64 years was around 0.4% (4 per 1,000 population) although prevalence estimates vary among EU countries from less than 1 to around 8 cases per 1,000 population aged 15 to 64 years.

2.1.3. Management

World Health Organisation guidelines for treatment of opioid dependence recommend a combination of both pharmacological and psychosocial interventions, with the following aims: reducing or ceasing opioid use, preventing future harms associated with opioid use, and improving the quality of life and well-being of the opioid-dependent patient (WHO 2009).

Opioid substitution is recognised as an effective therapy for keeping patients in treatment programmes and reducing the use of illicit opioids. The principle is to replace the opioid of abuse with a more long-acting opioid which will not give a rush or a high but will relieve the opioid-dependent person of cravings and enable return to a more normal life. Those μ-receptor agonists with a rapid onset of action and short half-life (e.g., heroin) are the main opioid drugs of abuse, having the greatest potential to engender destructive behaviour, because addicted individuals obtain an immediate reward, and the drive to further use is accentuated by rapid and severe withdrawal symptoms.

In contrast, μ-receptor agonists with a slower onset of action and longer half-life, such as the synthetic opioid methadone, cause physical dependence without necessarily providing such a potent stimulus towards addictive behaviour. Methadone (which can be dosed once daily) has little impact on mood, judgment, and psychomotor skills in opioid-tolerant patients, and was thus a mainstay of treatment of opioid dependence for many years. However, the combination of its long terminal half-life and potent full μ-opioid receptor agonism is associated with toxicity problems and fatal.

Buprenorphine is an alternative option for substitution therapy, administered either alone or combined with naloxone. Buprenorphine is a partial μ-receptor agonist and a κ-receptor antagonist, which has very high affinity and low intrinsic activity at the μ-receptor and will displace morphine, heroin, methadone, and other opioid full agonists. Its partial agonist effects give buprenorphine several clinically desirable pharmacological properties compared with opioid full agonists, including lower abuse potential, lower level of physical dependence (less severe withdrawal syndrome), a ceiling effect with respect to clinical effects at higher doses, and greater safety in overdose. These properties have led to widespread use of buprenorphine in both the detoxification and maintenance therapy of opioid dependent individuals. Previously administered alone, buprenorphine is now more commonly used in combination with the opioid antagonist naloxone. Naloxone has negligible oral or sublingual bioavailability and does not reach clinically significant concentrations in the general circulation when administered orally or sublingually. The naloxone component is included to deter abuse by other routes (particularly intravenous), by which it result in systemic levels sufficient to cause unpleasant withdrawal effects.

In the EU, buprenorphine only (Subutex) was first approved for use in France in 1996 and subsequently in other European countries, and the buprenorphine and naloxone combination Suboxone was first approved in the EU via the Centralised Procedure in 2006. Suboxone sublingual tablets, containing buprenorphine and naloxone in a 4:1 dose ratio, are well established in the EU as a substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment.

2.2. About the product

The Zubsolv buprenorphine/naloxone sublingual tablet was designed to offer improved bioavailability, faster disintegration, and improved taste masking compared with the Suboxone reference product. An improved bioavailability means that equivalent exposure with maintained efficacy could be achieved at

lower doses when taken as intended, while resulting in less buprenorphine being available for parenteral misuse/abuse. Faster disintegration times and improved taste masking may improve patient acceptability and reduce one potential hurdle to successful treatment. Additionally, faster disintegration may limit the possibility for dose sequestering for misuse or diversion when the medication is administered in a monitored intake setting.

Proposed indication is the same as that of the licensed product, Suboxone:

Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter intravenous misuse. Treatment is intended for use in adults and adolescents over 15 years of age who have agreed to be treated for addiction.

2.3. The development programme/compliance with CHMP guidance/scientific advice

Orexo AB sought Scientific Advice on the proposed PK bridging approach for this MAA from 3 national agencies: the Medicines and Healthcare products Regulatory Agency (MHRA) in July 2015, the Federal Institute for Drugs and Medical Devices (BfArM) in September 2015 and January 2016, and the Medical Products Agency (MPA) in October 2015.

Advice from the agencies was similar in many aspects. All 3 agencies advised that a hybrid application was a suitable route, that the reference product must be EU-sourced, and that it was acceptable to conduct the pivotal bridging study in healthy subjects in the US. However, advice regarding an appropriate study design to generate data to support full bridging of the efficacy and safety programme differed between the agencies.

The proposal that efficacy and systemic safety could be fully bridged by a PK comparison, based on comparative bioavailability versus EU-sourced Suboxone at a single dose strength combined with available dose proportionality data, was generally acceptable to the MHRA. The MPA also agreed that a bridging strategy based on PK data was acceptable but recommended PK bridging at 2 dose strengths of Zubsolv, considering the small deviations in dose proportionality in exposure parameters as well as the deviations from strict compositional proportionality for the lower strengths (2.9/0.71, 1.4/0.36, and 0.7/0.18 mg).

Taking into consideration the above advice from the 3 agencies, Orexo proposed a revised bridging study design, based on bioavailability comparisons at the highest and second-to lowest strengths of Zubsolv to the Suboxone reference product. BfArM accepted the revised plan at the follow-up scientific advice meeting in January 2016. The PK comparisons at the highest (11.4/2.9 mg) and second-to-lowest (1.4/0.36 mg) strengths would allow for bracketing the in-between strengths (2.9/0.71, 5.7/1.4, and 8.6/2.1 mg). A biowaiver of strength for the lowest strength (0.7/0.18 mg) was considered feasible based on the directly proportional composition to the 1.4/0.36 mg strength.

The agencies also recommended that the previous clinical studies conducted with the Zubsolv FCP should be included in the MAA as supportive data.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as sublingual tablets containing 0.7 mg / 1.4 mg / 2.9 mg / 5.7 mg / 8.6 mg / 11.4 mg buprenorphine (as hydrochloride) and 0.18 mg / 0.36 mg / 0.71 mg / 1.4 mg / 2.1 mg / 2.9 mg naloxone (as hydrochloride dihydrate) as active substances.

Other ingredients are: mannitol, citric acid anhydrous, sodium citrate, microcrystalline cellulose, croscarmellose sodium, sucralose, levomenthol, colloidal anhydrous silica, sodium stearyl fumarate.

The product is available in PVC/OPA/Al/PVC // Al/PET/Paper child resistant blister cards as described in section 6.5 of the SmPC.

2.4.2. Active substance

Buprenorphine Hydrochloride

General information

The chemical name of buprenorphine hydrochloride is (2S)-2-[17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol hydrochloride corresponding to the molecular formula $C_{29}H_{42}ClNO_4$. It has a relative molecular mass of 504.1 g/mol and the following structure:

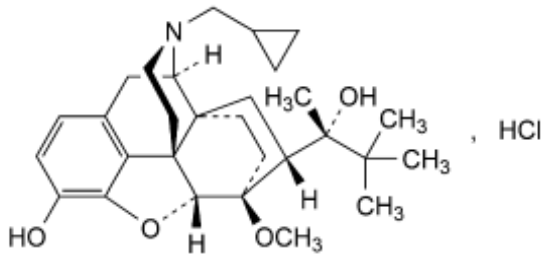


Figure 1: Buprenorphine Hydrochloride structure

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

There is a monograph of buprenorphine hydrochloride in the European Pharmacopoeia and the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for the active substance which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

The manufacturing process of active substance buprenorphine hydrochloride is covered by the CEP up to the active substance micronisation. Satisfactory information was provided on the micronisation process. Data were provided demonstrating that the crystalline structure of buprenorphine hydrochloride is unaffected by micronisation.

Specification

The active substance specification includes tests for: appearance, identity (IR, chloride), appearance of solution (Ph. Eur.), specific optical rotation (Ph. Eur.), acidity or alkalinity (Ph. Eur.), loss on drying (Ph. Eur.), assay (HPLC), related substances (HPLC), residual solvents (GC). The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph and the CEP. Additional specifications have been set for particle size distribution (Ph. Eur.). All additional methods have been adequately validated and described according to ICH Q2.

Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis data for several batches of the active substance are provided. Certificates of analysis have been provided for five production scale batches micronised at the proposed micronisation sites. Results are within the currently valid specification limits.

Stability

Unmicronized buprenorphine hydrochloride has a re-test period 5 years. Reference is made to the certificate of suitability.

Stability data were provided for six batches of micronised active substance from the proposed manufacturers stored in the intended commercial package for 36 months under long term conditions at 25 ºC / 60% RH, for 12 months at 30 ºC / 65% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines.

The following parameters were tested: appearance, appearance of solution, specific rotation, loss on drying, related substances and assay. The analytical procedures used are in accordance with the Ph. Eur. Monograph.

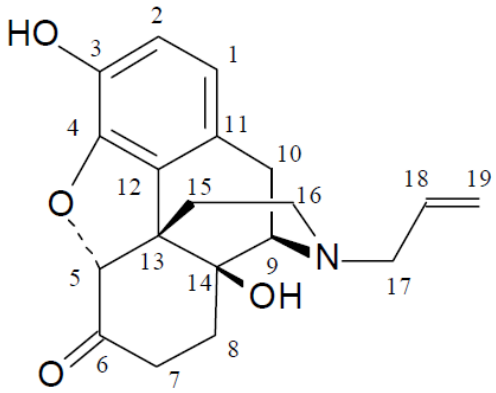
Out of specifications results were observed for the colour of solution for several batches at all storage conditions. At long-term conditions all results are within specified limits except for colour of solution which does not meet specification limits after 36 months of storage in two batches.

Based on the stability result the re-test period and storage conditions are acceptable for micronized drug substance buprenorphine hydrochloride stored in the proposed primary container.

Naloxone Hydrochloride Dihydrate

General information

The chemical name of naloxone hydrochloride dihydrate is 4,5α-Epoxy-3,14-dihydroxy-17-(prop-2-enyl)morphinan-6-one hydrochloride dihydrate corresponding to the molecular formula $C_{19}H_{22}ClNO_4,2H_2O$. It has a relative molecular mass of 399.9 g/mol and the following structure:



, HCl, $2H_2O$

Figure 2: Naloxone Hydrochloride Dihydrate structure

The active substance is a white or almost white, hygroscopic, crystalline powder, freely soluble in water, soluble in ethanol (96 per cent), practically insoluble in toluene.

There is a monograph of naloxone hydrochloride dihydrate in the European Pharmacopoeia and the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for naloxone hydrochloride dihydrate which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

The manufacturing process of active substance naloxone hydrochloride dihydrate is covered by the CEP up to the active substance micronisation. Satisfactory information was provided on the micronisation process. Data were provided demonstrating that the crystalline structure of naloxone hydrochloride dihydrate is unaffected by micronisation.

Specification

The active substance specification includes tests for: appearance, identity (IR, HPLC), appearance of solution (Ph. Eur.), specific optical rotation (Ph. Eur.), acidity or alkalinity (Ph. Eur.), water (Ph. Eur.), assay (HPLC), sulfated ash (Ph. Eur.), related substances (HPLC), residual solvents (GC). The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph and the CEP. Additional specifications have been set for particle size distribution (Ph. Eur.). All additional methods have been adequately validated and described according to ICH Q2.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for seven batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

The re-test period of the unmicronised naloxone hydrochloride dihydrate is 2 years if stored at a temperature not exceeding 25 °C in a polyethylene bag placed in either a polypropylene or aluminium or polyethylene container. Reference is made to the certificate of suitability.

Stability data on three batches of micronised active substance from the proposed manufacturers stored in the intended commercial package for 60 months under long term conditions at 25 ºC / 60% RH according to the ICH guidelines were provided.

The following parameters were tested: appearance, water, assay, related substances and appearance of solution. Related substances and appearance of solution are tested according to the monograph in Ph. Eur. and water and assay are tested according to the monograph in USP.

After 60 months of storage at long-term conditions all results are within specified limits.

The stability results indicate that the micronized active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest and storage conditions in the proposed container.

2.4.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as an immediate-release sublingual tablet containing a fixed dose combination (4:1 free base weight ratio) of the active substances buprenorphine (as hydrochloride) and naloxone (as hydrochloride dihydrate). The proposed strengths are 0.7/0.18 mg, 1.4/0.36 mg, 2.9/0.71 mg, 5.7/1.4 mg, 8.6/2.1 mg and 11.4/2.9 mg.

The tablets are white to off-white and differentiated by shape and debossing on one side of the tablet, as shown in the table 1 below. Images of the tablets will be included in the leaflet to aid in identification. They are packaged in individually sealed aluminium child resistant blister cards.

The formulations are not all dose proportional as there are three different blends used.

Table 1. Tablet Weight, Shape, Debossing and Appearance for Zubsolv

Tablet strength	Weight	Shape	Debossing	Appearance
0.7 mg/0.18 mg	50 mg	Flat-faced, radius-edged oval, length 6.8 mm, width 4.0 mm	.7	
1.4 mg/0.36 mg	100 mg	Flat-faced, radius-edged arc triangle, base 7.2 mm, height 6.9 mm	1.4	
2.9 mg/0.71 mg	105 mg	Flat-faced, radius-edged D shape, height 7.3 mm, width 5.65 mm	2.9	
5.7 mg/1.4 mg	110 mg	Flat-faced, radius-edged round, 7 mm in diameter	5.7	
8.6 mg/2.1 mg	165 mg	Flat-faced, radius-edged diamond, length 9.5 mm, width 8.2 mm	8.6	
11.4 mg/2.9 mg	220 mg	Flat-faced, radius-edged capsule, length 10.3 mm, width 8.2 mm	11.4	

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report.

The aim was to formulate rapidly disintegrating sublingual tablet for treatment of opioid dependence. Buprenorphine and naloxone in a 4:1 ratio is approved in the EU as Suboxone sublingual tablet (EU/1/06/359).

Pharmaceutical development is described in detail concerning the development of each strength; physicochemical properties of the active substance and manufacturing considerations have been taken into consideration. Satisfactory information regarding site transfers during development has been provided. Process robustness was investigated originally as a design space but stated not to be applied in commercial production: no regulatory freedom is granted in this respect.

Development formulations were found to have improved absorption compared to the reference product Suboxone. Therefore, lower strengths of active substances were chosen compared to the reference product.

1.4/0.36 mg and 11.4/2.9 mg strengths were studied *in-vivo* and biowaivers were requested for the other four strengths. Using an appropriate discriminatory dissolution method, comparable rapid dissolution was observed for two tablet strengths vs. equivalent Suboxone strengths at two pHs. The lack of further comparative dissolution data with Suboxone is accepted as Zubsolv is not to be interchanged with Suboxone, as discussed in the clinical sections below. However comparability of

in-vitro dissolution was shown for all strengths of the product within the Zubsolv product range at 3 pHs: pH 1.2, pH 4.5 and pH 5.8. Whilst some further data dissolution was provided at pH 6.8, the applicant's argumentation that such is not relevant due to the buffer effect in the sublingual cavity is accepted. As bioequivalence failed at the low concentration blend, the biowaiver within the range of the product cannot be assured at the low blend. This therefore also affects the medium concentration blend. As per clinical report, the SmPC will state that the 3 lower strengths are not to be substituted for the higher strengths.

The development of the dissolution method was sufficiently described, and the discriminatory power of the method was considered acceptable.

The primary packaging is PVC/OPA/Al/PVC // Al/PET/Paper child resistant blister cards. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of the following main steps: mixing/blending followed by compression and packaging. Due to the low content of active substances in the composition, the manufacturing process is considered to be non-standard.

The in-process controls are adequate for this type of manufacturing process. Critical process parameters (CPPs) were discussed and appropriately controlled. The critical steps were identified and the CPPs controlled in these steps were presented.

The final proposed commercial process has been validated. The CHMP recommended the in-process controls and manufacturing process to be reviewed as part of the manufacturing process validation of the next three batches of each strength and as appropriate, the registered details will then be updated by variation.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form: appearance, identification (HPLC, UV), assay (HPLC), uniformity of dosage units (Ph. Eur.), related substances (HPLC), disintegration (Ph. Eur.), friability (Ph. Eur.), water (Ph. Eur.), microbiological Control (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analyses data for key batches used in clinical studies, stability, validation and other relevant development studies are provided and confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data were provided for batches of each strength of the finished product stored according to the ICH guidelines conditions. Detailed information on batches used in the stability studies and stability data available for each strength/storage condition are provided in the table below:

Table 2: stability data description

Strength	Batch	Storage conditions (°C/% RH)	Stability data available
0.7 mg/0.18 mg	3 production scale batches	25/60 40/75	Up to 24 months 6 months
1.4 mg/0.36 mg	3 production scale batches	25/60 30/65 40/75	54 months 12 months 6 months
	2 production scale batches	25/60 40/75	48 months 6 months
2.9 mg/0.71 mg	2 production scale batches	25/60 40/75	Up to 36 months 6 months
	1 production scale batch	25/60	12 months
5.7 mg/1.4 mg	3 production scale batches	25/60 40/75	54 months 6 months
	2 production scale batches	25/60 40/75	48 months 6 months
8.6 mg/2.1 mg	2 production scale batches	25/60 40/75	36 months 6 months
	1 pilot scale batch	25/60 40/75	36 months 6 months
11.4 mg/2.9 mg	2 production scale batches	25/60 40/75	36 months 6 months
	1 pilot scale batch	25/60 40/75	36 months 6 months

The batches of medicinal product are either identical or representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested according to the shelf-life specifications. The analytical procedures used are stability indicating.

Naloxone assay results were out of specification at accelerated conditions for many batches. Intermediate storage conditions have not been tested for all strengths. Therefore, the storage condition "do not store above 25 °C" was required.

For the 1.4 mg/0.36 mg strength and the 5.7 mg/1.4 mg strength, all data is within specification therefore a 48 months shelf life was considered acceptable.

For the 0.7 mg/0.18 mg strength, the applicant claimed 24 months shelf life as this strength shows the same trend during stability as the 1.4 mg/0.36 mg strength (both low concentration blend). 24 months shelf life was accepted.

The applicant claimed 36 months shelf life for the 2.9 mg/0.71 mg strength since it shows the same trend during stability as the 1.4 mg/0.36 mg and 5.7 mg/1.4 mg strengths (this medium concentration blend is in-between the low and high concentration blends). As trends are seen in the naloxone stability in the 1.4 mg/0.36 mg, but not in the 5.7 mg/1.4 mg, a conservative approach was requested and a shelf life of 30 months was applied.

For the 8.6 mg/2.1 mg and 11.4 mg/2.9 mg strengths, stability results are within specification, therefore a 36 months shelf life was accepted.
Buprenorphine Hydrochloride and Naloxone Hydrochloride dihydrate are well-known pharmaceutical substances and the European Pharmacopoeia recommends that they should be stored protected from light. The finished product is packed in PVC/OPA/Al/PVC // Al/PET/Paper blisters as the primary pack for the sublingual tablets. This packaging is completely impenetrable to light. The patient is instructed

that the blister should not be opened until just before administration. This is primarily a safety precaution but also protects the product from light up to the point of administration.

The applicant, therefore, did not consider it necessary to conduct a photostability studies in line with ICHQ1B. The justification was considered acceptable.

Based on available stability data, the proposed shelf-life of 2 years for the 0.7 mg / 0.18 mg strength, 4 years for the 1.4 mg / 0.36 mg and 5.7 mg / 1.4 mg strengths, 30 months for the 2.9 mg / 0.71 mg strength, 3 years for the 8.6 mg / 2.1 mg and 11.4 mg / 2.9 mg strengths when stored in the original package below 25°C as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. At the time of the CHMP opinion, there were a number of minor unresolved quality issues on process validation having no impact on the Benefit/Risk ratio of the product.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The in-process controls and manufacturing process will be reviewed for the next three batches of each strength as appropriate by additional sampling according to Ph. Eur. 2.9.40 and as per the provided process validation scheme; the registered details will then be updated by variation.

2.5. Non-clinical aspects

2.5.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The

non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.5.2. Ecotoxicity/environmental risk assessment

A Phase I, Phase II Tier A and relevant Tier B environmental risk assessments were conducted for both buprenorphine and naloxone. Buprenorphine and naloxone do not show the potential to affect the environment when examined in sludge micro-organisms, aquatic, sediment, or soil. However, both buprenorphine and naloxone meet the persistence label criteria.

Table 1: Summary of main study results for naloxone

Substance (INN/Invented Name): Naloxone hydrochloride dihydrate (Naloxone)					
CAS-number (if available): 51481-60-8					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	-1.24 (pH 4) 0.765 (pH 7) 1.55 (pH 9)			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	0.765 (pH 7)			not B
	BCF				
Persistence	DT50 or ready biodegradability	Not readily biodegradable			P
Toxicity	NOEC (chronic fish study)	9.9 mg/L			T (> 0.01 mg/L)
PBT-statement :	The compound is not considered as PBT nor vPvB.				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$ (default)	0.022	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 (1 sludge)	K_{oc} = 874.8			List all values
Ready Biodegradability Test	OECD 301 OECD 308	Not conducted CO_2 < 1% at 100 days			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308 (Day 100 DT50)	$DT_{50, water}$ = 4.8-10.3 days $DT_{50, whole\ system}$ = 49.9-67.9 days % shifting to sediment = 55.5-81.7% at day 100			Not required if readily biodegradable > 10% by day 10 4 metabolites, none at ≥10% at day 100
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	13	mg/L	Species *Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	21	mg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	9.9	mg/L	Species *Pimephales promelas*
Activated Sludge, Respiration	OECD 209	NOEC	> 1000	mg/L	

Inhibition Test					
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/kg	
Sediment dwelling organism	OECD 218	NOEC(development) NOEC (emergence)	100 100	mg/kg	Species *Chironomus riparius*

Table 2: Summary of main study results

Substance (INN/Invented Name): Buprenorphine			
CAS-number (if available): 52485-79-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD123	1.01 (pH 4) 3.40 (pH 7) 5.05 (pH 9)	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.40 (pH 7)	not B
	BCF	81.3 L/kg	not B
Persistence	DT50 or ready biodegradability	Not readily biodegradable	P
Toxicity	NOEC or CMR	0.24 mg/L	Potentially T
PBT-statement :	The compound is not considered as PBT nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$ (default) (e.g. prevalence, literature)	0.086	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106 (3x soil/2x sludge)	$K_{oc\ (soil)}$ = 26085, 183588, 223686 $K_{oc\ (sludge)}$ = 1193, 155	List all values
Ready Biodegradability Test	OECD 301 OCED 308	Not conducted CO_2 < 1% at day 100	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308 (day 100, DT50)	$DT_{50,\ water}$ =1.5 – 1.8 d $DT_{50,\ whole\ system}$ = 1.7 – 1.8 d % shifting to sediment = 92 - 97 at day 100	Not required if readily biodegradable 5 metabolites: none > 10% at day 100
Phase IIa Effect studies			

Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	3.6	mg/L	Species *Pseudokirchneriell subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	0.26	mg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	0.24	mg/L	Species *Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC10 EC50	673 >1000	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF EPIsuite model	57 81.3	L/kg	%lipids: not reported
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$	3.4-4.9		for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/kg	No inhibition at 100 mg/kg
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	100	mg/kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	100	mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC	100	mg/kg	
Sediment dwelling organism		NOEC (development, emergence)	13, 100	mg/kg	Species *Chironomus riparius*

2.5.3. Discussion on non-clinical aspects

No nonclinical studies have been performed for this MAA which is acceptable for an Article 10(3) Hybrid Application under Directive 2010/83/EC. The relevant nonclinical information on the pharmacology, pharmacokinetics and toxicology for the proposed buprenorphine/naloxone combination has been provided by the overview of the literature.

2.5.4. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Zubsolv was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non-clinical studies were not considered necessary.

2.6. Clinical aspects

2.6.1. Introduction

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

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

Clinical studies

Table 1. Tabular overview of clinical studies

Clinical studies conducted with Zubsolv final commercial product

Study number	Type of study	Type of subjects	No. of subjects randomised and treated
'Pivotal' bridging study:			
OX219-014	Comparative bioavailability vs EU-sourced Suboxone sublingual tablet	Healthy subjects under naltrexone block	125
Supportive studies:			
OX219-003	Comparative bioavailability vs US-sourced Suboxone tablet	Healthy subjects under naltrexone block	60
OX219-004	Dose proportionality	Healthy subjects under naltrexone block	61
OX219-005	Pharmaceutical characterisation (evaluation of formulation properties of Zubsolv vs a US-marketed sublingual film formulation of Suboxone)	Healthy subjects under naltrexone block	28
OX219-006	Randomised, controlled Phase III study to evaluate early treatment efficacy and safety versus generic buprenorphine and Suboxone Film	Opioid-dependent patients	758
OX219-007	Randomised, controlled Phase III study to evaluate early treatment efficacy with Zubsolv versus generic buprenorphine, and safety	Opioid-dependent patients	310
OX219-008	Uncontrolled extension study to evaluate long-term safety and efficacy in patients who completed studies OX219-006 or OX219-007	Opioid-dependent patients	665
OX219-009	Comparative bioavailability following buccal vs sublingual administration	Healthy subjects under naltrexone block	64

2.6.2. Pharmacokinetics

Biowaiver

Biowaiver was requested for the following strengths of Zubsolv: 0.7/0.18 mg, 2.9/0.71 mg, 5.7/1.4 mg, and 8.6/2.1 mg

Table 2. Zubsolv strengths used in bioequivalence trials and strengths to be waived

Zubsolv buprenorphine/naloxone	**Prove of equivalence to Suboxone**
0.7 mg / 0.18 mg	Biowaiver requested
1.4 mg / 0.36 mg	BE study OX 219-014
2.9 mg / 0.71 mg	Biowaiver requested
5.7 mg / 1.4 mg	Biowaiver requested
8.6 mg / 2.1 mg	Biowaiver requested
11.4 mg / 2.9 mg	BE study 0X219-014

Main study

Study OX219-014 *A fasting, open-label, randomised, 2-cohort, 2-period cross-over study to evaluate comparative bioavailability of OX219 compared to Suboxone tablet (EU sourced) at two dose levels in healthy volunteers under naltrexone block*

Study OX219-014 was considered to be the pivotal PK comparative bioavailability study for this application bridging Zubsolv at the strengths 11.4/2.9 mg and 1.4/0.36 mg to corresponding doses of EU-sourced Suboxone reference product in 2 cohorts:

- Cohort 1: Zubsolv 11.4/2.9 mg vs. 2 x Suboxone 8/2 mg
- Cohort 2: 2 x Zubsolv 1.4/0.36 mg vs. 2 x Suboxone 2/0.5 mg

Objectives

The primary objectives were to determine relative systemic bioavailability of buprenorphine and naloxone to:

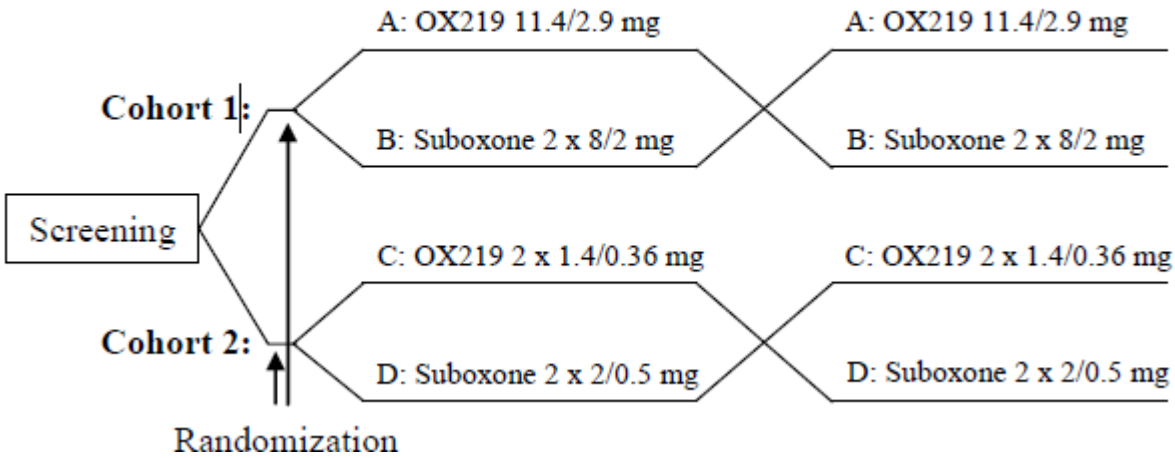
- Zubsolv 11.4/2.9 mg buprenorphine/naloxone sublingual tablet compared to 2x Suboxone 8/2 mg buprenorphine/naloxone sublingual tablets
- Zubsolv 2 x 1.4/0.36 mg buprenorphine/naloxone sublingual tablets compared to 2x Suboxone 2/0.5 mg buprenorphine/naloxone sublingual tablets

The secondary objectives were to assess local tolerability; safety and tolerability; *in vivo* dissolve time of the tablets; taste acceptability and subject preference for Zubsolv versus Suboxone tablets.

Study design

This was a fasting, open-label, randomised, 2-period, 2-cohort, 4-treatment cross-over study in healthy subjects under naltrexone block (Figure 9).

Figure 9 Schematic study design



In total, 125 healthy adult subjects entered the study and were randomised: 64 to Cohort 1 and 61 to Cohort 2. Two subjects discontinued the study: 1 subject in Cohort 1 received only 1 dose of study medication and 1 subject in Cohort 2 received both doses of study medication, but discontinued during treatment period 2. In total, 123 subjects completed the study.

All 125 subjects were included in the safety population and 123 subjects in the PK population. The PK population comprised 74 (60.2%) male and 49 (39.8%) females. All subjects were in the age range of 19 to 54 years and had a body mass index (BMI) ranging from 19.0 to 29.2 kg/m².

The PK population comprised 85 (69.1%) White, 35 (28.5%) Black or African American, 1 (0.8%) Asian, and 2 (1.6%) Multi-racial subjects. The demographic and baseline characteristics of the 2 cohorts were similar.

The PK parameters Cmax, Tmax, AUC0-t, AUC0-inf, AUC0-72h, and t½ were estimated where possible for each subject by treatment. Analysis of buprenorphine and unconjugated naloxone were considered as the primary analyses for establishing equivalence.

Metabolite data, norbuprenorphine and total naloxone, were considered as *supportive* information only. Geometric mean ratios (GMR) of AUC0-72h for buprenorphine and norbuprenorphine; AUC0-t for naloxone (unconjugated) and total naloxone; and Cmax for all analytes were estimated for the equivalence analysis.

Blood samples for measurement of buprenorphine, unconjugated naloxone, norbuprenorphine and total naloxone were taken pre-dose (0 h) and 15, 30, 45 minutes and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 5, 8, 10, 12, 16, 24, 36, 48, and 72 h post dose of each treatment period.

Results

Table 7 **Study OX219-014: Buprenorphine PK parameters for Zubsolv and Suboxone (all doses)**

PK parameter	Arithmetic mean ± standard deviation (% CV)			
	Zubsolv 11.4/2.9 mg (1 x 11.4/2.9 mg) N=60[2]	Suboxone 16/4 mg (2 x 8/2 mg) N=60[3]	Zubsolv 2.9/0.71 mg (2 x 1.4/0.36 mg) N=58[4]	Suboxone 4/1 mg (2 x 2/0.5 mg) N=58[5]
AUC_{0-t} (ng·h/mL)	39.99 ±11.67 (29.2)	45.64 ±13.35 (29.2)	14.44 ±4.40 (30.5)	17.81 ±5.04 (28.3)
AUC_{0-72h} (ng·h/mL)	39.99 ±11.67 (29.2)	45.64 ±13.35 (29.2)	14.64 ±4.21(28.8)	17.84 ±5.02 (28.1)
AUC_{0-inf} (ng·h/mL)	43.52 ±12.87 (29.6)	51.00 ±13.99 (27.4)	16.25 ±4.64 (28.6)	20.07 ±5.79 (28.8)
C_{max} (ng/mL)	5.64 ±2.4 (41.8)	6.25 ±2.82 (45.0)	2.06 ±0.67 (32.7)	2.44 ±0.74 (30.5)
Median T_{max} (h)[1]	1.50 (0.57-2.50)	1.50 (0.50-3.02)	1.75 (0.50-3.00)	1.50 (0.75-5.00)
$T_{½}$ (h)	23.36 ±4.59 (19.6)	25.31 ±6.17 (24.4)	24.71 ±7.46 (30.2)	25.71 ±7.04 (27.4)
Kel (1/h)	0.031 ±0.006 (19.8)	0.029 ±0.007 (23.2)	0.031 ±0.009 (30.1)	0.029 ±0.008 (27.6)
$\%AUC_{exp}$	8.91 ±3.76 (42.2)	10.66 ±4.49 (42.1)	9.40 ±4.71 (50.1)	10.35 ±5.11 (49.4)

[1] T_{max} expressed as the median (range).
[2] N=52 for AUC_{0-inf}, $T_{½}$, Kel and $\%AUC_{exp}$ for Zubsolv 11.4/2.9 mg.
[3] N=53 for AUC_{0-inf}, $T_{½}$, Kel and $\%AUC_{exp}$ for Suboxone 16/4 mg.
[4] N=57 for AUC_{0-72h}, and N=53 for AUC_{0-inf}, $T_{½}$, Kel and $\%AUC_{exp}$ for Zubsolv 2.9/0.71 mg.
[5] N=52 for AUC_{0-inf}, $T_{½}$, Kel and $\%AUC_{exp}$ for Suboxone 4/1mg.

AUC_{0-t}=area under the plasma concentration-time curve from time zero to time t; AUC_{0-72h}=area under the plasma concentration-time curve from time zero to 72 h; AUC_{0-inf}=area under the plasma concentration-time curve from time zero extrapolated to infinity; C_{max}=maximum plasma concentration; CV=coefficient of variation; T_{max}=time to maximum plasma concentration; Kel=elimination rate constant; $T_{½}$=Apparent terminal half-life; $\%AUC_{exp}$=percentage of AUC_{0-inf} based on extrapolation.
Data source: OX219-014 CSR, Table 14.2.2.1.

Table 8 **Study OX219-014: Unconjugated naloxone PK parameters for Zubsolv and Suboxone (all doses)**

PK parameter	Arithmetic mean ± standard deviation (% CV)			
	Zubsolv 11.4/2.9 mg (1 x 11.4/2.9 mg)	Suboxone 16/4 mg (2 x 8/2 mg)	Zubsolv 2.9/0.71 mg (2 x 1.4/0.36 mg)	Suboxone 4/1 mg (2 x 2/0.5 mg)
	N=63[2]	N=63[3]	N=58	N=58[4]
AUC_{0-t} (pg·h/mL)	861.8 ±452.2 (52.5)	902.4 ±482.7 (53.5)	189.6 ±92.0 (48.5)	281.1 ±105.7 (37.6)
AUC_{0-inf} (pg·h/mL)	865.1 ±59.9 (53.2)	944.6 ±528.4 (55.9)	198.8 ±95.1 (47.8)	288.7 ±109.8 (38.0)
C_{max} (pg/mL)	352 ±221.0 (62.8)	363 ±236.4 (65.0)	78.2 ±35.6 (45.5)	116 ±56.0 (48.3)
Median T_{max} (h)[1]	0.75 (0.50-1.75)	0.75 (0.50-1.75)	1.0 (0.50-3.00)	0.75 (0.25-1.75)
$T_{½}$ (h)	3.88 ±2.83 (73.0)	5.38 ±3.27 (60.7)	2.07 ±1.68 (81.1)	2.04 ±1.04 (51.0)
Kel (1/h)	0.263 ±0.140 (53.0)	0.184 ±0.109 (59.0)	0.412 ±0.150 (36.4)	0.392 ±0.131 (33.3)
$\%AUC_{exp}$	2.11 ±1.52 (72.1)	2.70 ±1.91 (70.8)	5.23 ±3.79 (72.4)	2.92 ±1.27 (43.7)

[1] T_{max} expressed as the median (range).
[2] N=57 for AUC_{0-inf}, $T_{½}$, Kel and $\%AUC_{exp}$ for Zubsolv 11.4/2.9 mg.
[3] N=52 for AUC_{0-inf}, $T_{½}$, Kel and $\%AUC_{exp}$ for Suboxone 16/4 mg.
[4] N=55 for AUC_{0-inf}, $T_{½}$, Kel and $\%AUC_{exp}$ for Suboxone 4/1.
AUC_{0-t}=area under the plasma concentration-time curve from time zero to time t; AUC_{0-inf}=area under the plasma concentration-time curve from time zero extrapolated to infinity; C_{max}=maximum plasma concentration; T_{max}=time to maximum plasma concentration; Kel=elimination rate constant; $T_{½}$=Apparent terminal half-life; $\%AUC_{exp}$=percentage of AUC_{0-inf} based on extrapolation.
Data source: OX219-014 CSR, Table 14.2.2.2.

Zubsolv 11.4/2.9 mg

The 90% confidence intervals (CIs) for Zubsolv 11.4/2.9 mg:Suboxone 16/4 mg GMRs for buprenorphine AUC0-72h and Cmax were fully within the standard bioequivalence limits of 80% to 125%, confirming equivalent buprenorphine exposure between the formulations (Table 9).

For unconjugated naloxone, the 90% CIs of the Zubsolv:Suboxone GMRs for AUC0-t and Cmax were also fully within the standard bioequivalence limits of 80% to 125%, confirming equivalent buprenorphine exposure between the formulations

Table 9 **Study OX219-014: Buprenorphine geometric means, ratio of means and 90% CIs (based on ANOVA of natural log-transformed data) for Zubsolv 11.4/2.9 mg vs. Suboxone 16/4 mg**

Parameter	Treatment	Geometric least-squares means	Ratio 90% CI[1]	Intra-subject % CV
AUC_{0-72h} (ng·h/mL)	Zubsolv 11.4/2.9 mg	38.481	87.79 83.73 - 92.04	15.6
	Suboxone 16/4 mg	43.834		
C_{max} (ng/mL)	Zubsolv 11.4/2.9 mg	5.220	90.88 84.60 - 97.62	23.8
	Suboxone 16/4 mg	5.744		

[1] Equivalent if confidence intervals (CIs) are within 80.00% to 125.00% limits.
ANOVA=Analysis of variance; AUC_{0-72h}=area under the plasma concentration-time curve from time zero to 72 h; C_{max}=maximum plasma concentration.
Data source: OX219-014 CSR, Table 14.2.3.1.

For both metabolites, the 90% CI of Zubsolv:Suboxone GMRs for the exposure PK parameters (AUC and Cmax) were lower than the standard bioequivalence limits of 80.00% to 125.00%, with point estimates indicative of approximately 30% lower exposure from Zubsolv compared to Suboxone.

Zubsolv 2.9/0.71 mg (2x 1.4/0.36 mg)

Derived PK parameters of buprenorphine are summarised in Table 7 for buprenorphine and in Table 8 for naloxone (above). A higher Cmax and AUC was observed for Suboxone compared with Zubsolv in this cohort.

The 90% CI of Zubsolv 2 x 1.4/0.36 mg: 2 x Suboxone 2/0.5 mg GMRs for buprenorphine did not demonstrate equivalence between the two products and were indicative of approximately 20% lower buprenorphine exposure following administration of Zubsolv (Table 12 below).

Table 12 Study OX219-014: Buprenorphine geometric means, ratio of means and 90% CIs (based on ANOVA of natural log-transformed data) for Zubsolv 2.9/0.71 mg vs. Suboxone 4/1 mg

Parameter	Treatment[2]	Geometric least-squares means	Ratio 90% CI[1]	Intra-subject % CV
AUC_{0-72h} (ng·h/mL)	Zubsolv 2.9/0.71 mg	13.804	80.87 (75.84 – 86.23)	20.7
	Suboxone 4/1 mg	17.069		
C_{max} (ng/mL)	Zubsolv 2.9/0.71 mg	1.927	83.17 (77.77 – 88.94)	21.8
	Suboxone 4/1 mg	2.317		

[1] Equivalent if confidence intervals (CIs) are within 80.00% to 125.00% limits.
[2] N=58 for Zubsolv 2.9/0.71 mg (C_{max}) and Suboxone 4/1 mg and N=57 for Zubsolv 2.9/0.71 mg (AUC_{0-72h}).
ANOVA=Analysis of variance; AUC_{0-72h}=area under the plasma concentration-time curve from time zero to 72 h; C_{max}=maximum plasma concentration.
Data source: OX219-014 CSR, Table 14.2.3.1.

Likewise, statistical analysis of the secondary PK parameters AUC0-t and AUC0-inf for buprenorphine did not demonstrate equivalence between Zubsolv and Suboxone: GMRs were 80.51 (90% CI: 75.52 - 85.82) and 79.60 (90% CI: 74.64 - 84.88).

For unconjugated naloxone, the 90% CIs of the Zubsolv:Suboxone GMRs for AUC0-t and Cmax were outside the standard bioequivalence limits of 80% to 125%, and equivalence between 2 x Zubsolv 1.4/0.36 mg and 2 x Suboxone 2/0.5 mg could not be concluded. The naloxone exposure from Zubsolv was approximately 35% lower than for the Suboxone.

For both metabolites, the 90% CI of Zubsolv: Suboxone GMRs for the primary and secondary PK parameters were lower than the standard bioequivalence limits of 80.00% to 125.00% with point estimates indicative of approximately 30% lower exposure from Zubsolv compared to Suboxone.

The subject-perceived *in vivo* dissolve times varied considerably between subjects for both dosages of both formulations. The median (minimum, maximum) subjective dissolve time was significantly shorter for 1 × Zubsolv 11.4 mg/2.9 mg (8.520 [0.88, 56.40] minutes) compared with 2 × Suboxone 8 mg/2 mg (16.210 [2.25, 53.25] minutes) (Hodges-Lehman estimate of median difference [95% CI]: −6.035 [−8.205, −3.615] minutes). The median (minimum, maximum) subjective dissolve time was significantly shorter for 2 × Zubsolv 1.4 mg/0.36 mg (7.580 [1.68, 50.97] minutes) compared with 2

× Suboxone 2 mg/0.5 mg (9.080 [3.45, 33.20] minutes) (Hodges-Lehman estimate of median difference [95% CI]: −1.485 [−2.635, −0.380] minutes). It is of note that the difference in dissolve time is a lot less with the lower dose.

Zubsolv received significantly higher VAS scores for taste and mouthfeel compared to Suboxone at both dose levels. The distribution of ratings of unpleasant aftertaste indicated a lower frequency and intensity of unpleasant aftertaste for Zubsolv than for Suboxone. There was a statistically significant preference for the Zubsolv formulations over the Suboxone formulations. In the high-dose cohort, 50 of 63 subjects (79.4%) preferred 1 × Zubsolv 11.4 mg/2.9 mg (95% binomial CI: 69.4% − 89.4%). In the low-dose cohort, 47 of 61 subjects (77.0%) preferred 2 × Zubsolv 1.4 mg/0.36 mg (95% binomial CI: 66.5% − 87.6%).

In the high-dose comparison (Zubsolv 11.4 mg/2.9 mg versus 2 × Suboxone 8 mg/2 mg) 90% CIs of the Zubsolv:Suboxone AUC and Cmax geometric least-squares mean ratios for both buprenorphine and unconjugated naloxone were fully within the predefined equivalence boundaries of 80.00% to 125.00% and equivalent exposure between these products could therefore be concluded.

In the low-dose comparison (2 × Zubsolv 1.4 mg/0.36 mg versus 2 × Suboxone 2 mg/0.5 mg) 90% CIs of the Zubsolv:Suboxone AUC and Cmax geometric least-squares mean ratios were not contained within the predefined equivalence boundaries of 80.00% to 125.00% for either buprenorphine or unconjugated naloxone and equivalent exposure could not be concluded.

Point estimates of AUC geometric mean ratios indicated approximately 20% lower buprenorphine exposure and 35% lower unconjugated naloxone exposure from Zubsolv versus the Suboxone reference product.

Exposure of metabolites (norbuprenorphine and total naloxone) was lower from Zubsolv than from Suboxone at both dose levels and equivalent exposure could not be concluded. Point estimates of AUC geometric mean ratios indicated 20% to 30% lower metabolite exposure from Zubsolv versus the Suboxone reference product.

Therefore, in this pivotal study, with the higher doses there was equivalent buprenorphine and unconjugated naloxone exposure between the formulations. However for the lower strength, there was 20% lower buprenorphine exposure following administration of Zubsolv and naloxone exposure from Zubsolv was approximately 35% lower than for the Suboxone.

The applicant performed a post-hoc, dose-normalised, within-product, parallel-group analysis to compare the strengths within each product and this suggested a less than proportional increase in buprenorphine exposure with increased dose for either Zubsolv or Suboxone. For unconjugated naloxone, a similar deviation from dose proportionality was observed between the Suboxone dosage strengths but not between the Zubsolv dosage strengths. For both buprenorphine and unconjugated naloxone, the deviation from dose proportionality appeared to be greater between Suboxone dosage strengths than between Zubsolv dosage strengths.

Dose proportionality

Dose proportionality of Zubsolv over the dose interval 1.4/0.36 mg to 11.4/2.9 mg was investigated within-subject in study OX219-004, using combinations of the tablet strengths 1.4/0.36 mg and 5.7/1.4 mg (the only strengths developed at the time of the study). This study had a fasting, single-dose, open-label, randomised, 4-treatment, 4-period crossover design, in which the subjects received 4 separate single-dose administrations of Zubsolv. Dose proportionality was confirmed for

buprenorphine AUC0-t over the tested 8-fold dose range (1.4 to 11.4 mg), but not for AUC0-inf or Cmax, which increased slightly less than proportionally to increased dose.

Dose proportionality for unconjugated naloxone was confirmed for AUC0-t and AUC0-inf over the tested 8-fold dose range (0.36 to 2.9 mg) but not for Cmax, which increased slightly less than proportionally to increased dose.

For the metabolites, dose proportionality was confirmed for norbuprenorphine Cmax, AUC0-t, and AUC0-inf, and total naloxone AUC0-inf and Cmax over the tested 8-fold dose range of parent compounds buprenorphine/naloxone (1.4/0.36 mg to 11.4/2.9 mg). Total naloxone AUC0-t increased slightly more than proportionally to increased dose.

Both buprenorphine and naloxone exposure increased with dose. Buprenorphine exposure met the pre-specified criteria for proportionality based on AUC0-t, while AUCinf indicated a slightly less than proportional increase in exposure with increased dose. This was noted by the applicant to be consistent with the reference product Suboxone, which displays a slightly less than proportional increase in buprenorphine exposure with dose, as described in the Suboxone SmPC. While less than proportional increase in buprenorphine exposure has been reported for both Zubsolv and Suboxone, exploratory post hoc data from study OX219-014 suggest that deviation from dose proportionality may be larger between Suboxone than between Zubsolv strengths. Regarding naloxone, both AUC0-t and AUCinf met the dose proportionality criteria. Cmax for both buprenorphine and naloxone increased slightly less than proportionally with dose.

Buprenorphine exposure met the pre-specified criteria for proportionality based on AUC0-t, while AUC_{inf} indicated a slightly less than proportional increase in exposure with increased dose. This was noted by the applicant to be consistent with the reference product Suboxone, which displays a slightly less than proportional increase in buprenorphine exposure with dose, as described in the Suboxone SmPC.

2.6.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application. The pharmacodynamic properties of buprenorphine/naloxone combination are well characterised and described for the reference product and in the literature.

2.6.4. Discussion on clinical pharmacology

Zubsolv has been developed in 6 strengths based on 3 different powder blends: the low concentration blend (0.7/0.18 mg and 1.4/0.36 mg strengths), the intermediate concentration blend (2.9/0.71 mg strength), and the high concentration blend (5.7/1.4 mg, 8.6/2.1 mg, and 11.4/2.9 mg strengths).

Based on scientific advice from selected EU national authorities, the bridging strategy was based on providing comparative bioavailability data on the 11.4/2.9 mg strength (representing the high concentration blend) and the 1.4/0.36 mg strength (representing the low concentration blend) to the respective strengths of the EU reference product Suboxone.

The applicant considered that additional strengths of the respective blends could then be supported by biowaivers based on comparative *in vitro* dissolution. Furthermore, being intermediate to the high and low concentration blends, the 2.9/0.71 mg strength is supported by interpolation.

Dose proportionality of Zubsolv over the dose interval 1.4/0.36 mg to 11.4/2.9 mg was investigated in study OX219-004.

Demonstration of equivalent buprenorphine and naloxone exposure between Zubsolv 11.4/2.9 mg and 2 x Suboxone 8/2 mg provides a PK bridge between the EU reference product Suboxone and the high concentration blend strengths of Zubsolv. The PK bridge between the high concentration blend strengths of Zubsolv and Suboxone is further supported by the demonstration of equivalent buprenorphine exposure between Zubsolv 5.7/1.4 mg and US sourced Suboxone 8/2 mg (US Suboxone has the same size and weight as EU Suboxone and the composition qualitatively only differs by the addition of a colouring agent in the US product.)

While equivalent buprenorphine exposure was not concluded between 2 x Zubsolv 1.4/0.36 mg and 2 x Suboxone 2/0.5 mg, the exposure difference was approximately 20% lower for Zubsolv, and this was attributed to a larger deviation from dose proportionality between Suboxone strengths than between Zubsolv strengths.

In a clinical context, buprenorphine is individually titrated to clinical effect, and if small exposure differences between products were to translate to differences in clinical effects, this would be naturally addressed by dose adjustments in the standard care of the patient. Despite the deviation from equivalence in exposure, the applicant proposes that the comparative bioavailability data between 2 x Zubsolv 1.4/0.36 mg and 2 x Suboxone 2/0.5 mg provide an appropriate link between the low concentration blend strengths of Zubsolv and the Suboxone reference product. Naloxone is insignificantly absorbed after sublingual administration. The purpose of naloxone is to deter parenteral abuse of the product and it has no utility for the intended sublingual route of administration. Thus the lower naloxone exposure compared to the Suboxone reference product seen in the comparison between 2 x Zubsolv 1.4/0.36 mg and 2 x Suboxone 2/0.5 mg (as well as between Zubsolv 5.7/1.4 mg and US sourced Suboxone 8/2 mg) would not be expected to be of any clinical significance.

2.6.5. Conclusions on clinical pharmacology

It is acknowledged that Zubsolv is not intended for generic substitution, nor should it be treated as a generic in terms of strictly following the bioequivalence criteria. Failed proof of bioequivalence to the reference product can be to a certain extent superseded by available efficacy data obtained from clinical development of the product.

The results of the comparative bioavailability study show that at higher doses, Zubsolv and Suboxone may be bioequivalent but at lower doses, Zubsolv is not equivalent and delivers lower concentrations of both components in the combination.

It is agreed that for use of Zubsolv as a stand-alone treatment, the differences in drug delivery with different doses for naloxone could be acceptable. The differences with buprenorphine are of more concern but could be handled by careful individual titration of Zubsolv doses since treatment of opioid dependence is based on titration of the individual patient response. The applicant has provided data on Zubsolv PK linearity in the proposed dosage range and differences to Suboxone (at lower strengths). These differences support the SmPC recommendation that patients are not transferred from one formulation to another.

The composition of Zubsolv tablets is not considered quantitatively proportional as three different blends are used for tablets manufacture. Dose proportionality of Zubsolv over the dose interval 1.4/0.36 mg to 11.4/2.9 mg was investigated within-subject in study OX219-004, using combinations

of the tablet strengths 1.4/0.36 mg and 5.7/1.4 mg. Both buprenorphine and naloxone exposure increased with dose. Buprenorphine exposure met the pre-specified criteria for proportionality based on AUC0-t, while AUCinf indicated a slightly less than proportional increase in exposure with increased dose. Regarding naloxone, both AUC0-t and AUCinf met the dose proportionality criteria. Cmax for both buprenorphine and naloxone increased slightly less than proportionally with dose. Because of the small deviations in buprenorphine dose proportionality exposure parameters as well as deviations from strict compositional proportionality for the three lower strengths (0.17/0.18mg, 1.4/0.36mg and 2.9/0.71mg), using multiples of the three lower dose presentations of Zubsolv to substitute for any of the three higher dose presentations is not recommended.

2.6.6. Clinical efficacy

The efficacy of Zubsolv in the proposed indication was bridged to Suboxone. Additional supportive efficacy data from clinical studies conducted with Zubsolv in the US were also included in this application. Studies OX219-006 and -007, which evaluated the early treatment efficacy of Zubsolv, were designed to support a US label extension to include induction of treatment. Study OX219-008 was a multi-centre, open-label, single-arm, uncontrolled extension study, which enrolled 665 opioid-dependent patients who had completed studies OX219-006 or OX219-007 and chose to continue treatment. In addition, a comprehensive literature review was performed to search for any relevant new findings relating to the use of buprenorphine, either alone or in combination with naloxone.

Supportive studies

Efficacy of Zubsolv in opioid-dependent patients

More than 1000 opioid-dependent male and female patients between 18 and 65 years of age were enrolled into studies OX219-006 and -007. Although the studies were conducted in the US, the patient population enrolled was considered to be relevant to the EU opioid-dependent population, with the majority of patients reporting lifetime use of heroin (62.6% in study OX219-006, and 66.4% in study OX219-007).

Study OX219-006

Study OX219-006 started with a 2-day, blinded, fixed-dose assessment period, in which patients were randomised to either Zubsolv (5.7/1.4 mg on Day 1, and 5.7/1.4 to 11.4/2.81 mg on Day 2) or generic buprenorphine (8 mg buprenorphine on Day 1, and 8 mg to 16 mg on Day 2). On Day 3, patients on generic buprenorphine were switched to open-label Suboxone Film. Doses were titrated up to a maximal daily dose of 17.1/4.2 mg and 24/6 mg buprenorphine/naloxone for Zubsolv and Suboxone, respectively, based on clinical symptoms. On Day 15, all patients switched treatments according to a fixed Zubsolv:Suboxone conversion factor of 5.7:8, so that patients who previously received Suboxone Film were given Zubsolv, and patients previously receiving Zubsolv were given Suboxone Film. The primary endpoints were retention in treatment at Day 3 and Day 15 (measured by the proportion of randomised patients retained in each treatment group). Additional measures of efficacy included symptoms of opioid withdrawal (measured by the Clinical Opiate Withdrawal Scale [COWS] and Subjective Opiate Withdrawal Scale [SOWS]), and cravings (measured by the opioid cravings VAS), illicit drug use (self-reports and urine drug screen), and addiction severity (Addiction Severity Index [ASI-Lite]). The primary analysis was based on non-inferiority testing of retention in treatment on Day

3 and Day 15 performed on the per-protocol analysis set. Zubsolv was to be considered non-inferior if the lower limit of the 95% CI for the difference between the 2 treatments in the proportion of patients retaining treatment on each of the 2 visits was ≥-10%. To preserve a 5% significance level, the Day 15 visit was tested initially and if non-inferiority was demonstrated at this visit, the Day 3 data were then to be tested for non-inferiority using the same method.

In total, 758 patients were randomised and received treatment in study OX219-006. For the primary endpoint of retention in treatment, Zubsolv was non-inferior to buprenorphine/ Suboxone at both Day 3 and Day 15. At Day 15, 83.0% of the patients (273/329) in the Zubsolv group were retained in treatment compared with 82.5% (269/326) in the Suboxone group; Zubsolv to Suboxone difference: 0.5% (95% CI -5.3, 6.3). As the lower limit of the CI was ≥-10% (the pre-specified non-inferiority margin), non-inferiority of Zubsolv was established at this time point. At Day 3, 93.9% of the patients (309/329) in the Zubsolv group were retained in treatment compared with 92.6% (302/326) in the buprenorphine group; Zubsolv to buprenorphine difference: 1.3% (95% CI -2.6, 5.1). As the lower limit of the CI was ≥-10% (the pre-specified non-inferiority margin), non-inferiority of Zubsolv was also established at Day 3. Non-inferiority was also demonstrated in the full analysis set, thus supporting the primary analysis.

Secondary efficacy endpoints (retention at each visit, COWS, SOWS, craving VAS scores, and time to first opioid-negative urine drug sample) were similar between treatments, with no statistically significant differences. Following the treatment switch at Day 15, continued improvements in COWS, SOWS, and craving VAS scores were observed for patients in both groups at the end of study. Of the patients who switched to Zubsolv at Day 15, 3.0% withdrew before Day 22, and of the patients who switched to Suboxone Film, 4.4% withdrew by Day 22.

Study OX219-007

Study OX219-007 started with a 2-day blinded, fixed-dose assessment period, in which patients were randomised to either Zubsolv (5.7/1.4 mg on Day 1, and 5.7/1.4 to 11.4/2.81mg on Day 2) or generic buprenorphine (8 mg buprenorphine on Day 1, and 8 mg to 16 mg on Day 2). On Day 3, all patients received an open-label dose of Zubsolv 5.7/1.4 mg or 11.4/2.8 mg. Doses on Day 4 through Day 28 were individually titrated between 5.7/1.4 mg and 17.1/4.2 mg. The primary endpoint was retention in treatment at Day 3. The same additional measures of clinical efficacy as in Study OX219-006 were evaluated as secondary endpoints.

310 patients were randomised and received treatment. For the primary endpoint, a lower proportion of patients in the Zubsolv group than in the generic buprenorphine group were retained at Day 3: 88.3% (113/128) versus 95.3% (122/128), respectively, Zubsolv to buprenorphine difference: -7.0% (95% CI -13.7, 0.4). As the lower limit of the CI was <-10% (the pre-specified non-inferiority margin), non-inferiority of Zubsolv was not established.

Secondary endpoints (COWS, SOWS, and craving VAS) indicated similar treatment effects for Zubsolv and generic buprenorphine.

Although non-inferiority was not demonstrated by the primary endpoint analysis in study OX219-007, examination of the reasons for discontinuation from the study and a review of the data for the secondary endpoints did not suggest that this was driven by a difference in efficacy or safety between the treatment groups. Further reassurance is provided by a post hoc analysis of retention in treatment at Day 3 using data pooled from both studies OX219-006 and -007 were supportive of a conclusion of non-inferiority of Zubsolv to generic buprenorphine, at the pre-specified non-inferiority margin of 10%.

Study OX219-008

Study OX219-008 was a multi-centre, open-label, single-arm, uncontrolled extension study, which enrolled 665 opioid-dependent patients who had completed studies OX219-006 or OX219-007 and chose to continue treatment. The aim of this study was to follow the patients on treatment with Zubsolv for an extended period of time and collect further efficacy and safety data. Patients received up to 24 additional weeks of treatment with Zubsolv.

The results provide evidence of a continued clinical effect from the previous studies, based on COWS, SOWS, and craving VAS total scores. As shown in studies OX219-006 and -007, in terms of impact upon the severity of opioid dependence, improvements from baseline continued through study OX219-008 on all 7 subscale scores on the ASI-Lite for the overall population at Week 12 and Week 24. Retention rates were consistent with previous long-term studies with buprenorphine (43.9% at Week 24/End of Study) and may reflect the absence of treatment adjuncts during the study (e.g. counselling, participation in 12-step programmes).

Results of the literature review relating to efficacy

Several studies reported efficacy data for buprenorphine versus active control for treatment of opioid dependence. Compared with naltrexone, buprenorphine maintenance treatment was associated with higher retention rates and a lower degree of positive urine samples (Bandawar et al 2015, Mokri et al 2015). Comparisons versus methadone indicate slightly higher retention rates on methadone under similar treatment settings (e.g. Hser et al 2015, Burns et al 2014, Saxon et al 2013), although this difference was not evident in all studies (e.g. Piralishvili et al 2015).

When used for short-term opioid detoxification, buprenorphine demonstrated superior efficacy based on relief from abstinence symptoms and cravings as well as on completion of detoxification compared with clonidine (Ling et al 2005, Hussain et al 2015, Steele and Cunningham 2012). Two studies examining the efficacy of different tapering durations with buprenorphine showed contradictory results. One study found that a 4-week tapering schedule followed by transfer to naltrexone maintenance had more successful outcomes than a 1- or 2- week schedule for the entire 12-week follow-up period, both on retention in treatment and opioid-negative urine (Sigmon et al 2013). In contrast, another study found that abstinence was superior at the end of a 1-week taper than after a 4-week taper (Ling et al 2009). Regardless of tapering schedule, long-term success rates for tapering remain low with prolonged abstinence of no more than 5% to 15% (e.g. Weiss et al 2011, Wright et al 2011) and clearly inferior to maintenance treatment (e.g. Fiellin et al 2014).

Efficacy data reported in the literature are in line with efficacy data in the SmPC for the reference product Suboxone and revealed no new information considered to have an impact on the current efficacy assessment for buprenorphine alone or in the combination with naloxone.

2.6.7. Discussion on clinical efficacy

This hybrid marketing authorisation application is primarily supported by the PK bridge to the reference product, Suboxone.

Studies OX219-006, -007 and -008 were conducted in support of a US label extension for including induction of treatment in the label. The applicant points out that US Suboxone has the same size and weight as EU Suboxone and the composition qualitatively only differs by the addition of a colouring agent in the US product. The Zubsolv clinical studies (OX219-006, -007 and -008), which involved a

total of 1068 opioid-dependent patients, indicate that Zubsolv could be an effective treatment option, providing support to the pivotal PK bridging data.

Additionally, a comprehensive literature review revealed no new information that would have an impact on the current efficacy assessment for buprenorphine alone or for the combination of buprenorphine with naloxone.

There are no clinical studies utilising the 0.7/0.18 mg or 2.9/0.71 mg tablets however there are almost two years of post-marketing experience with these strengths in the US with no identified post-marketing concerns or safety issues. These strengths are needed to titrate doses and provide options for prescribers and are considered to be acceptable.

2.6.8. Conclusions on clinical efficacy

The efficacy of Zubsolv in the proposed indication is supported by:

- bridging to the EU-sourced reference product Suboxone;
- the US Zubsolv clinical studies (OX219-006, -007 and -008); and
- literature review.

2.6.9. Clinical safety

The safety of Zubsolv has been bridged to Suboxone. In addition, supportive safety data from the 8 clinical trials and post-marketing data from the US licenced Zubsolv product was provided. A literature review was also conducted by the applicant, which encompassed the period from October 2002 to 1 June 2012, together with a more recent search covering the period 1 June 2012 to 2 April 2016.

In total, Orexo has performed three patient studies (OX219-006, -007 and -008) and five clinical studies in healthy subjects (OX219-014 pivotal study, OX219-003, -004, -005, -009) using the final commercial product (FCP) of buprenorphine/naloxone sublingual tablet (Zubsolv).

Patient exposure

Overall, 338 healthy adult volunteers and 1068 opioid dependent patients received test and reference products in the clinical development programme presented for Zubsolv. Including 125 healthy subjects in the pivotal OX219-014 study. Overall, 1,295 subjects were exposed to Zubsolv FCP: 330 healthy subjects and 965 patients.

The route of dosing for both the test and reference products in each study was sublingual apart from study OX219-009 where buccal administration was used (for the reference treatment [B] only). In the healthy subject studies exposure was to single doses of study treatment.

Long-term safety and tolerability in patients was investigated in Studies OX219-006, -007 and -008. The majority of patients were white and male. The patient studies provided a longer duration of exposure, representing 273.0 patient-years overall. In total, 270 patients received at least 6 months of treatment. OX219-008 was a multi-centre, open-label, uncontrolled extension study conducted in

patients who completed studies OX219-006 or -007 to assess safety and efficacy for maintenance treatment of opioid dependence with Zubsolv.

Adverse events

The adverse drug reactions listed in Section 4.8 of the proposed Zubsolv SmPC correspond to the reference product Suboxone. The data has been compiled from pivotal clinical trials in which, 342 of 472 patients (72.5 %) reported adverse reactions and adverse reactions reported during post-marketing surveillance of Suboxone.

The most commonly reported treatment related adverse reactions reported during the pivotal clinical trials for Suboxone were constipation and symptoms commonly associated with drug withdrawal (i.e. insomnia, headache, nausea, hyperhidrosis and pain). Some reports of seizure, vomiting, diarrhoea, and elevated liver function tests were considered serious.

The ADRs also correspond to the licenced US Zubsolv product. Adverse events commonly observed with administration of the licenced US Zubsolv product during clinical trials and post-marketing experience are headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, pain, and peripheral oedema.

All sections relating to safety in the proposed SPC, i.e. Section 4.3-4.9, directly correspond to the reference SPC of Suboxone.

Clinical studies in healthy subjects

(OX219-014 pivotal study, OX219-003, -004, -005, -009)

Overall, the most commonly reported AEs in healthy subjects after administration of Zubsolv were nausea (23.0%), dizziness (11.2%), vomiting (10.6%), headache (10.4%) and abdominal pain (6.1%)

In the pivotal study OX219-014, 124 AEs were reported by 52 of the 125 subjects (41.6%) who participated in this study, 7 of 63 (11.1%) after receiving Zubsolv 11.4/2.9 mg, 20 of 64 (31.3%) after receiving 2 x Suboxone 8/2 mg, 20 of 61 (32.8%) after receiving 2 x Zubsolv 1.4/0.36 mg and 17 of 61 (27.9%) after receiving 2 x Suboxone 2/0.5 mg. Across all treatments, the AEs reported by most subjects were nausea (20.8%), vomiting (15.2%), dizziness (10.4%) and headache (10.4%).

Somnolence was also reported as a common AE in both study OX219-005 and -009. Other common AEs in study OX219-009 only, were abdominal pain, fatigue and decreased appetite. Adverse events ranged from mild to moderate in severity.

Three unexpected AEs, of mild severity, were identified in study OX219-003 (2 cases of hypoaesthesia and 1 case of salivary hypersecretion). No unexpected AEs were reported in studies OX219-004, -005, -009 or -014.

There were no serious adverse events reported in healthy subjects.

Patient studies (OX219-006, -007 and -008)

Treatment-related treatment-emergent adverse event (TEAEs) were seen in ≥5% of patients in the same two System Organ Classes, SOCs (gastrointestinal disorders and nervous system disorders) in both study OX219-006 and -007. These are comprised of known events consistent with the current prescribing information for the maintenance of opioid dependence indication. Overall, most TEAEs reported during both phases of the study were mild to moderate, with severe events reported in <2.5% of patients. There were no evident imbalances between the treatment groups.

The SOCs across the 3 patient studies that had events reported in ≥5% of patients were gastrointestinal disorders, nervous system disorders, psychiatric disorders and infections and infestations. No individual PTs occurred in either the Zubsolv or reference groups in ≥5% of the population. Treatment-related TEAEs in these SOCs included most commonly nausea, vomiting, constipation, insomnia and headache.

In general there was a balanced incidence and severity of all TEAEs between Zubsolv and reference (Suboxone).

The SOCs of gastrointestinal disorders and infections and infestations had events reported in ≥5% of patients (72 [10.3%] and 47 [6.7%], respectively) in the study OX219-006. The 2% difference between the treatments in patients with TEAEs in the SOC of infections and infestations was largely driven by infections unrelated to study treatment such as upper respiratory tract infection which occurred in 5 patients in the group taking Zubsolv versus 1 patient in the group taking buprenorphine/Suboxone, and oral herpes occurring in 4 patients in the group taking Zubsolv versus no patients in the group taking buprenorphine/Suboxone.

In the SOC of psychiatric disorders in study OX219-007, insomnia was reported in ≥5% of patients only in the generic buprenorphine group (11 patients out of 155 [7.1%]). Only 4 patients out of 155 (2.6%) experienced insomnia in the Zubsolv group.

In OX219-006, -007 and OX219-008, the most commonly reported treatment-related TEAE was constipation <5%.

Serious adverse event/deaths/other significant events

The SAEs and safety data listed in the proposed Zubsolv SmPC correspond to the reference product Suboxone and are consistent with the known safety profile for the buprenorphine/naloxone combination product. SAEs for this product and opioids as a class are well known and adequate risk mitigation measures are detailed in the SmPC.

Adverse events in both healthy subjects and patient clinical studies were comparable between Zubsolv and reference product. The SAEs were consistent with the known safety profile for the buprenorphine/naloxone combination product.

Laboratory findings

The abnormalities in laboratory values listed in the proposed Zubsolv SmPC correspond to the safety profile of the reference product Suboxone and are consistent with the known safety profile for the buprenorphine/naloxone combination. Clinical studies with Zubsolv showed abnormalities in laboratory values consistent with the known adverse reaction profile.

Safety in special populations

The special populations identified in the proposed Zubsolv SmPC correspond to the reference product Suboxone and include elderly, paediatric population, pregnancy and breastfeeding, hepatic impairment and renal impairment.

The following populations of patients were excluded from participating in Zubsolv clinical studies- patients over the age of 65 years, patients below the age of 18 years, pregnant or lactating women and newborns, patients with severe liver disease.

No recommendations on posology are made for the elderly population. Adolescents age 15 to <18 years should be more closely monitored during treatment. Zubsolv is not recommended in pregnancy and breast-feeding. Caution is required when prescribing in severe renal impairment and Zubsolv is contraindicated in severe hepatic impairment.

The risk mitigations measures for special populations are in line with Suboxone and consistent with the additional supportive data in the dossier.

Safety related to drug-drug interactions and other interactions

Drug interactions included in the proposed safety information are cytochrome P-450 3A4 (CYP3A4) inhibitors and inducers, drugs which potentiate CNS depression and drugs which potentiate respiratory depression. These drug interactions adequately represent the known safety profile and correspond to the reference SmPC.

The interaction with serotonergic drugs has been identified as a risk in the licenced US Zubsolv, involving reports of the concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system resulting in serotonin syndrome.

The remaining proposed drug interactions adequately represent the known safety profile and correspond to the SmPC of a reference product.

2.6.10. Post marketing experience

Zubsolv received approval for the US market on July 3rd 2013. Since authorisation, the AEs of adrenal insufficiency and androgen deficiency were included in Section 6.2 of the post-marketing data in the US Zubsolv label.

2.6.11. Discussion on clinical safety

Both buprenorphine and naloxone are well-established medicinal products with known safety profiles. The combination of both products into a single formulation for the treatment of opioid dependence has a well-established safety profile.

The safety profile for Zubsolv has been derived mainly from Suboxone, an established buprenorphine/ naloxone product for the same indication and supported by 8 clinical studies involving 1,295 subjects who received Zubsolv, including healthy subjects and opioid-dependent patients. No new safety signals were identified in the Zubsolv studies conducted in patients and healthy subjects, and the data are consistent with the established safety profiles for buprenorphine and naloxone and Suboxone.

Furthermore, there is clinical experience with the product on the US market since July 3rd 2013, with an estimated 44,800 Zubsolv patient-years exposure. No significant additional safety signals were identified in a review of the available literature.

In the context of switching between Suboxone and Zubsolv products, the risk of under-dosing with secondary withdrawal symptoms is mitigated with amended guidance for switching formulation in Section 4.2 and 5.2 of the SmPC. In addition, in the clinical context, buprenorphine is individually titrated to clinical effect, and if small exposure differences between products were to translate to differences in clinical effects, this would be addressed by dose adjustments in the standard care of the patient.

2.6.12. Conclusions on clinical safety

No new significant safety concerns were identified for Zubsolv and the safety profile is acceptable.

2.7. Risk Management Plan

Safety concerns

Table 1. Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Fatal overdose - Severe respiratory failure (mechanism for death by overdose) - Use in patients with alcoholism/delirium tremens Misuse and/or abuse (injection/intranasal/paediatric use) Hepatitis, hepatic events, use in patients with hepatic failure Dependence Drug withdrawal syndrome
Important potential risks	Use in patients with head injury and increased intracranial pressure
Missing information	Elderly patients > 65 years old

Pharmacovigilance plan

Routine pharmacovigilance activities are considered sufficient to identify and/or further characterise the above safety concerns and to assess the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 2. Summary of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Fatal overdose	Wording in sections 4.2, 4.3, 4.4, 4.5, 4.8	None

- Severe respiratory failure (mechanism for death by overdose) - Use in patients with alcoholism/delirium tremens	and 4.9 of the SmPC Prescription only medicine Use restricted to physicians experienced in the management of opioid dependence/addiction	
Misuse and/or abuse (injection/intranasal/paediatric use)	Wording in sections 4.2, 4.4, 4.8 and 5.1 of the SmPC Prescription only medicine Use restricted to physicians experienced in the management of opioid dependence/addiction	None
Hepatitis, hepatic events, use in patients with hepatic failure	Wording in sections 4.2, 4.3, 4.4, 4.8 and 5.2 of the SmPC Prescription only medicine Use restricted to physicians experienced in the management of opioid dependence/addiction	None
Dependence	Wording in sections 4.4 and 4.8 of the SmPC Prescription only medicine Use restricted to physicians experienced in the management of opioid dependence/addiction	None
Drug withdrawal syndrome	Wording in sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC Prescription only medicine Use restricted to physicians experienced in the management of opioid dependence/addiction	None
Use during pregnancy and lactation (effects on newborn and infant) CNS depression (effects on driving ability)	Wording in sections 4.6 and 5.3 of the SmPC Prescription only medicine Use restricted to physicians experienced in the management of opioid dependence/addiction	None
Allergic reactions	Wording in sections 4.3 and 4.8 of the SmPC Prescription only medicine Use restricted to physicians experienced in the management of opioid	None

	dependence/addiction	
Differences in posology between Zubsolv and other buprenorphine formulations indicated in substitution treatment for opioid drug dependence	Wording in sections 3, 4.2, 4.4, 4.9 and 5.2 of the SmPC Prescription only medicine Use restricted to physicians experienced in the management of opioid dependence/addiction	None
Use in patients with head injury and increased intracranial pressure	Wording in sections 4.4 and 4.8 of the SmPC Prescription only medicine Use restricted to physicians experienced in the management of opioid dependence/addiction	None
Peripheral oedema	Wording in section 4.8 of the SmPC Prescription only medicine Use restricted to physicians experienced in the management of opioid dependence/addiction	None
Elderly patients >65 years old	Wording in sections 4.2, 4.4 and 5.2 of the SmPC Prescription only medicine Use restricted to physicians experienced in the management of opioid dependence/addiction	None
Children <15 years old	Wording in sections 4.2 and 4.4 of the SmPC Child resistant blister cards Prescription only medicine Use restricted to physicians experienced in the management of opioid dependence/addiction	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.3 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils

the requirements of Article 8(3) of Directive 2001/83/EC.

PSUR submission

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Opioid dependence is associated with considerable health risks and severe economic and psychosocial consequences for the opioid dependent person and their family. It is linked to a substantially increased risk of premature death from drug overdoses, violence and suicide.

Furthermore, sharing of needles among intravenous users contributes to the spread of potentially fatal blood infections, such as human immunodeficiency virus (HIV) and hepatitis C.

3.1.2. Available therapies and unmet medical need

Opioid substitution is recognised as an effective therapy for keeping patients in treatment programmes and reducing the use of illicit opioids. The principle is to replace the opioid of abuse with a more long-acting opioid which will not give a rush or a high but will relieve the opioid-dependent person of cravings and enable return to a more normal life. Methadone (which can be dosed once daily) has little impact on mood, judgement, and psychomotor skills in opioid-tolerant patients, and was thus a mainstay of treatment of opioid dependence for many years. However, the combination of its long terminal half-life and potent full μ-opioid receptor agonism is associated with toxicity problems and fatal.

Buprenorphine is an alternative option for substitution therapy, administered either alone or combined with naloxone. The naloxone component is included to deter abuse by other routes (particularly intravenous), by which it results in systemic levels sufficient to cause unpleasant withdrawal effects.

Zubsolv is a rapidly disintegrating sublingual tablet containing buprenorphine and naloxone in a combination ratio of 4:1 for substitutional treatment of opioid dependence. Buprenorphine is a partial

μ-opioid receptor agonist known to relieve drug withdrawal symptoms and cravings. Naloxone is a full μ-opioid receptor antagonist, added to deter intravenous (IV) abuse of the medication. Due to the low sublingual bioavailability, naloxone has insignificant or no effects when taken sublingually as intended.

Zubsolv has been developed using technology for sublingual delivery that was to provide comparable systemic buprenorphine exposure to Suboxone tablets at a lower administered dose of the drug due to its higher bioavailability.

3.1.3. Main clinical studies

The efficacy of Zubsolv in the proposed indication is bridged to the EU-sourced reference product Suboxone. The 'pivotal' PK bridging study for this application was study OX219-014, which bridged Zubsolv at the strengths 11.4/2.9 mg and 1.4/0.36 mg to corresponding doses of EU-sourced Suboxone reference product in 2 cohorts:

- Cohort 1: Zubsolv 11.4/2.9 mg vs. 2 x Suboxone 8/2 mg
- Cohort 2: 2 x Zubsolv 1.4/0.36 mg vs. 2 x Suboxone 2/0.5 mg

Further efficacy data from clinical studies OX219-006, OX219-007 and OX219-008 conducted with Zubsolv in the US together with results of a literature search performed to determine any new, relevant findings with buprenorphine alone or combined, are considered supportive.

Study OX219-006 was a prospective, randomised, multi-centre, parallel-group, active-controlled, non-inferiority study comparing treatment efficacy and adherence of the sublingual tablets of Zubsolv versus generic buprenorphine following induction of therapy during the first 3 days of treatment. The purpose of this study was to assess early treatment efficacy of Zubsolv vs Buprenorphine mono/Suboxone Film.

Study OX219-007 was a prospective, randomised, multi-centre, blinded, parallel-group, active-controlled study comparing the sublingual tablets of Zubsolv versus buprenorphine monotherapy for the induction component of opioid maintenance therapy. The purpose of this study was to demonstrate that induction on Zubsolv is non-inferior to induction on Buprenorphine monotherapy.

Study OX219-008 was a multi-centre, open-label, uncontrolled extension study conducted in patients who completed studies OX219-006 or -007. The purpose of this study was to assess long-term (24 weeks) safety, efficacy and effects on quality of life and health economic parameters during Zubsolv treatment.

3.2. Favourable effects

The favourable effects of Zubsolv are in line with those of Suboxone. The applicant has provided data that suggest it dissolves more rapidly, and is more acceptable to patients form the point of view of taste.

The efficacy of Zubsolv in the proposed indication is bridged to the EU-sourced reference product Suboxone whereby efficacy data for buprenorphine/naloxone are primarily derived from a one-year clinical trial, comprising a 4-week randomised double blind comparison of buprenorphine/naloxone, buprenorphine and placebo followed by a 48 week safety study of buprenorphine/naloxone. In this trial, 326 heroin-addicted subjects were randomly assigned to either buprenorphine/naloxone 16 mg per day, 16 mg buprenorphine per day or placebo. The primary study comparison was to assess the efficacy of buprenorphine and buprenorphine/naloxone individually against placebo. The percentage of

thrice-weekly urine samples that were negative for non-study opioids was statistically higher for both buprenorphine/naloxone versus placebo ($p < 0.0001$) and buprenorphine versus placebo ($p < 0.0001$).

3.3. Uncertainties and limitations about favourable effects

Favourable effects are based on adequate delivery of the constituents of the combination medicine. Buprenorphine levels should be adequate to prevent withdrawal and naloxone levels are required as a deterrent. The differences in drug delivery with the lower drug doses will require careful individual titration when using Zubsolv.

Small deviations in buprenorphine dose proportionality exposure parameters as well as deviations from strict compositional proportionality for the three lower strengths support the recommendation to not use multiples of the three lower dose presentations of Zubsolv to substitute for any of the three higher dose Zubsolv presentations.

The differences between Suboxone and Zubsolv formulations imply that switching between the two would not reproduce the same plasma concentrations of buprenorphine. A lower buprenorphine exposure from Zubsolv may potentially result in reduced opioid receptor stimulation leading to withdrawal symptoms when switching from another buprenorphine product at a dose level below 5.7/1.4 mg. In addition, owing to the long terminal half-life of buprenorphine, it would take several days to reach a new steady state when switching between formulations. This uncertainty supports the recommendation that patients should not switch between products.

3.4. Unfavourable effects

The safety of Zubsolv in the proposed indication is bridged to the EU-sourced reference product Suboxone. The tabulated list of adverse events from the reference product Suboxone SmPC has been generated from pivotal clinical trials in which, 342 of 472 patients (72.5 %) reported adverse reactions and from adverse reactions reported during post-marketing surveillance.

In addition, supportive safety data from the 8 clinical trials, three patient studies (OX219-006, -007 and -008) and five clinical studies in healthy subjects (OX219-014 pivotal study, OX219-003, -004, -005, -009) were submitted. Post-marketing data from the US licenced Zubsolv product and literature review were also provided.

The most commonly reported treatment related adverse reactions reported during the pivotal clinical trials for Suboxone were constipation and symptoms commonly associated with drug withdrawal (i.e. insomnia, headache, nausea, hyperhidrosis and pain). Some reports of seizure, vomiting, diarrhoea, and elevated liver function tests were considered serious.

The proposed ADRs were also observed for Zubsolv. Adverse events commonly observed with administration of Zubsolv during clinical trials and post-marketing experience in the US are headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, pain, and peripheral oedema.

3.5. Uncertainties and limitations about unfavourable effects

Not applicable.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The clinical efficacy and safety of buprenorphine and naloxone are well known and well established in clinical use and have been the subject of many publications. The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

As switching between Suboxone and Zubsolv formulations may create potential for prescribing error, it is not recommended. Differences in posology between Zubsolv and Suboxone and Subutex are also an important identified risk in the RMP.

3.6.2. Balance of benefits and risks

The evaluation of Suboxone has concluded positive benefit risk for the combination of buprenorphine and naloxone.

The Zubsolv buprenorphine/naloxone sublingual tablet was designed to offer higher bioavailability, faster disintegration, and improved taste masking compared with the Suboxone reference product. This application hence concerns a suprabioavailable drug (Zubsolv) which is being registered under hybrid legal basis.

From the regulatory as well as scientific point of view the pivotal BE study 014 (if bioequivalence was demonstrated) is considered sufficient to fully bridge the known efficacy and safety profile of Suboxone to the proposed product – Zubsolv. Other submitted data can be considered as supportive.

It is acknowledged, that Zubsolv is not intended for generic substitution, nor should it be treated as a generic in terms of strictly following the bioequivalence criteria. Failed proof of bioequivalence to the reference product could be to a certain extent superseded by other available data and hence the strict proof of bioequivalence was not deemed necessary. The additional information documenting PK linearity (dose proportionality) across the entire dosage range has established an adequate bridge across the dosage range of Zubsolv and provided evidence to support its use as a stand-alone therapy.

3.6.3. Additional considerations on the benefit-risk balance

Not applicable.

3.7. Conclusions

The overall B/R of Zubsolv sublingual tablet is positive.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Zubsolv is favourable in the following indication:

Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter intravenous misuse. Treatment is intended for use in adults and adolescents over 15 years of age who have agreed to be treated for addiction.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.