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ADIS DRUG EVALUATION

Buprenorphine/Naloxone (Zubsolv®): A Review in Opioid Dependence

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Abstract

A new sublingual buprenorphine/naloxone tablet (hereafter referred to as buprenorphine/naloxone; Zubsolv®), combining a long-acting partial μ receptor agonist and an opioid antagonist, is approved for the treatment of opioid dependence in adults and adolescents aged > 15 years. This formulation has a higher bioavailability, better taste and faster sublingual dissolve time than a reference sublingual buprenorphine/naloxone tablet (Suboxone®), advantages that provide greater patient preference (potentially improving adherence) and importantly may reduce the risk of buprenorphine parenteral abuse by providing similar buprenorphine exposure at an ≈ 30% lower dosage than reference buprenorphine/naloxone. In large phase III trials of up to 28 days, buprenorphine/naloxone was associated with high treatment retention rates during the induction and stabilization phases, and also reduced opioid craving and opioid withdrawal symptoms. Although noninferiority of buprenorphine/naloxone to sublingual buprenorphine tablet during the 2-day induction phase was only shown in one of the two similarly designed trials, pooled analyses confirmed that treatment retention rates were similar in the buprenorphine/naloxone and buprenorphine groups. Where evaluated, noninferiority of buprenorphine/naloxone to sublingual buprenorphine/naloxone film (only approved in the USA) was also demonstrated at 15 days in the stabilization phase. During the 24-week extension study, buprenorphine/naloxone maintenance therapy sustained improvements in opioid craving and addiction severity scores. Buprenorphine/naloxone was generally well tolerated, displaying a tolerability profile that was generally consistent with that seen with reference buprenorphine/naloxone. In conclusion, with potentially greater patient preference and a lower potential for parenteral buprenorphine abuse than reference buprenorphine/naloxone, buprenorphine/naloxone expands the treatment options available for adults and adolescent (aged > 15 years) patients with opioid dependence.

Buprenorphine/naloxone (Zubsolv®): clinical considerations in opioid dependence

Improved bioavailability, permitting lower dosages [vs. reference buprenorphine/naloxone (Suboxone®)], potentially reducing risk of buprenorphine intravenous abuse.
Better taste and faster sublingual dissolve time versus reference buprenorphine/naloxone.
High treatment retention rates during induction/stabilization phase; improves opioid withdrawal symptoms and opioid cravings during these and/or the maintenance phase.
Tolerability profile consistent with that seen with reference buprenorphine/naloxone.

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1 Introduction

Opioid dependence is a relapsing chronic substance use (prescription or illicit) disorder that is characterized by a group of somatic, psychological and behavioural symptoms, with a global prevalence of opioid dependence in adolescents and adults (aged 15–64 years) of ≈0.4% [1]. Opioid dependence is associated with a high mortality rate (due to respiratory depression and overdose) and increases the risk of HIV, hepatitis B or C virus (HBV or HCV) infections and psychiatric comorbidities, thereby presenting a major public health issue and significant economic burden [2].

A number of pharmacological and psychological interventions have been proposed with the goals to reduce opioid use, prevent associated complications and improve a patient's quality of life (QOL) [3]. Pharmacological therapy with a full (e.g. methadone) or partial (e.g. buprenorphine) opioid agonist in combination with psychosocial intervention is currently the most effective treatment for patients with opioid dependence [3]. Buprenorphine can be administered alone or in combination with naloxone (i.e. an opioid antagonist) to deter buprenorphine intravenous abuse [2]. A sublingual tablet formulation of buprenorphine/naloxone (Suboxone®; hereafter referred as reference buprenorphine/naloxone) is currently available; however, despite the addition of naloxone, buprenorphine abuse remains high [4]. Moreover, many patients have reported issues with sublingual dissolve time and a bitter taste of reference buprenorphine/naloxone [5]. Thus, a new sublingual tablet formulation of buprenorphine/naloxone (Zubsolv®; hereafter referred to as buprenorphine/naloxone) has been developed to overcome these disadvantages [6].

This buprenorphine/naloxone formulation is approved in the USA [7] and EU [8] for the substitution treatment of opioid dependence in adults and adolescents aged > 15 years. This review, written from an EU perspective, focuses on the use of buprenorphine/naloxone in the treatment of opioid dependence.

2 Pharmacological Properties of Buprenorphine/Naloxone

2.1 Pharmacodynamic Properties

The pharmacodynamic profiles of buprenorphine and naloxone are well established and have been previously reviewed [9]. Buprenorphine is a long-acting partial μ receptor agonist (high affinity and low intrinsic activity) and a κ receptor antagonist [10]. Given its partial agonist effects, buprenorphine has a lower abuse potential and is associated with less severe withdrawal syndrome than full μ receptor agonists such as morphine, heroin and methadone. Moreover, at higher doses, opioid agonist effects of buprenorphine are limited by a ceiling effect [10]. Naloxone is a potent μ receptor antagonist [8]. After oral or sublingual administration, the pharmacological effect of naloxone is minimal as naloxone undergoes almost complete first-pass metabolism. However, when given intravenously, naloxone exerts its opioid antagonist effect (precipitates withdrawal symptoms), which may deter patients from parenteral buprenorphine abuse [8].

2.2 Pharmacokinetic Properties

Relative to reference buprenorphine/naloxone, buprenorphine/naloxone was designed to provide higher bioavailability and a faster sublingual dissolve time [5, 11]. In a randomized, open-label, crossover study (OX219-014) in healthy volunteers, buprenorphine/naloxone had higher bioavailability than reference buprenorphine/naloxone (EU formulated), providing similar buprenorphine exposure at an ≈30% lower dose. After a single dose of buprenorphine/naloxone or reference buprenorphine/naloxone, bioequivalence was achieved with a high dose (11.4/2.9 vs. 16/4 mg) but not with a low dose (2.9/0.71 vs. 4/1 mg) [11]. According to a post hoc analysis, the lack of bioequivalence at a lower dose could be due to improved dose proportionality across the dose strengths of buprenorphine/naloxone relative to reference buprenorphine/naloxone. The sublingual dissolve time (i.e. complete dissolution of the tablet as perceived by the patient) with buprenorphine/naloxone compared with reference buprenorphine/naloxone was significantly shorter with both high [8.5 vs. 16.2 min; estimated between-group difference (eBGD) −6.0 min; 95% CI −8.2, −3.6 min] and low (7.6 vs. 9.1 min; eBGD −1.5 min; 95% CI −2.6, −0.4 min) doses [11].

Buprenorphine/naloxone is administered sublingually, as buprenorphine undergoes almost complete first-pass metabolism following oral administration [8]. After sublingual administration, the tablet usually disintegrates (i.e. breaking up into granules of a certain size before dissolution) within 40 s (may take 5–10 min to disappear completely), with the peak plasma concentration (C_{max}) of buprenorphine reached ≈90 min post-dose; plasma concentrations of naloxone are low and rapidly decline. Buprenorphine exposure increases in a less than dose-proportional manner. Lower doses of buprenorphine/naloxone (0.7/0.18, 1.4/0.36 and 2.9/0.71 mg) are also not strictly compositionally proportional to higher doses (5.7/1.4, 8.6/2.1 and 11.4/2.9 mg). After sublingual administration, buprenorphine is rapidly distributed, with a distribution half-life of 2–5 h [8].

In the liver, buprenorphine is metabolized by 14-*N*-dealkylation and glucuronidation, whereas naloxone is primarily metabolized by glucuronide conjugation [8]. Buprenorphine is converted to *N*-dealkybuprenorphine (norbuprenorphine) via CYP3A4, which has weak intrinsic agonist activity at the μ receptor. Buprenorphine is eliminated by biliary excretion, with 70% of the dose recovered in the faeces as glucuroconjugated metabolites and the remainder recovered in the urine. Naloxone is eliminated via the urine. Estimated mean elimination half-lives of buprenorphine and naloxone are 32 and 1.2 h [8].

The pharmacokinetic profile of buprenorphine/naloxone has not been studied in elderly patients (aged > 65 years); thus, dosage recommendations cannot be made for this population [8]. Renal clearance of buprenorphine/naloxone is relatively small (≈ 30%); thus, dosage modification of buprenorphine/naloxone is not required in patients with mild or moderate renal impairment. However, buprenorphine/naloxone should be used with caution in patients with severe renal impairment (creatinine clearance < 30 mL/min), since metabolites of buprenorphine accumulate in patients with renal failure. Given buprenorphine/naloxone is mainly eliminated via the hepatobiliary route, lower initial doses and careful titration of buprenorphine/naloxone is recommended in patients with mild or moderate hepatic impairment, with the drug contraindicated in patients with severe hepatic impairment [8].

2.3 Potential Drug Interactions

Given the risk of potentially additive pharmacodynamic effects, concomitant use of buprenorphine/naloxone with certain drugs potentially results in clinically relevant drug interactions (i.e. concomitant use is contraindicated or carries a warning/precaution [8]). These interactions include an increased risk of the sudden onset of intense opioid withdrawal syndrome with other opioid antagonists (e.g. naltrexone, nalmefene), respiratory depression with benzodiazepines or alcohol, CNS depression with other opioids (e.g. methadone), alcohol or other drugs (e.g. CNS depressants, barbiturates, anxiolytics or neuroleptics), increased opioid effects with monoamine oxidase inhibitors, and potential for an overdose when coadministered with full opioid agonists (as adequate analgesia may be difficult to achieve) [8].

Exposure of buprenorphine and norbuprenorphine is increased when buprenorphine/naloxone is coadministered with ketoconazole (i.e. a potent CYP3A4 inhibitor) [8]. Close monitoring is required and dosage reduction of buprenorphine/naloxone may be necessary if used in combination with a potent CYP3A4 inhibitor such as protease inhibitors (e.g. ritonavir, nelfinavir), azole antifungals (e.g. ketoconazole) or macrolide antibiotics. Close monitoring is also recommended when buprenorphine/naloxone is coadministered with inducers of CYP3A4 (e.g. phenobarbital, carbamazepine, phenytoin and rifampicin) as exposure of buprenorphine may be reduced, leading to decreased efficacy; thus, dosage adjustments of these drugs may be required [8].

3 Therapeutic Efficacy of Buprenorphine/Naloxone

Based on bioavailability results from OX219-014 (Sect. 2.2), the efficacy of buprenorphine/naloxone for the treatment of opioid dependence during induction and maintenance treatment was bridged to the established efficacy of reference buprenorphine/naloxone [10]. The efficacy of reference buprenorphine/naloxone for the treatment of opioid dependence in clinical trials was reviewed previously [9].

There are no head-to-head trials evaluating the efficacy between buprenorphine/naloxone and reference buprenorphine/naloxone. The efficacy of buprenorphine/naloxone for induction and stabilization treatment was compared to sublingual buprenorphine tablet and/or sublingual buprenorphine/naloxone film (US formulated and not approved in the EU) in two randomized, multicentre, noninferiority phase III trials (OX219-006 [12] and OX219-007 [13]). OX219-006 and -007 included a 2-day induction phase (Sect. 3.1), followed by a stabilization phase of 20 days (OX219-006 [12]; Sect. 3.2.1) or 26 days (OX219-007 [13]; Sect. 3.2.2). Those who completed OX219-006 or -007 were eligible to enter a 24-week, open-label, extension study (OX219-008) that was primarily designed to evaluate the safety of buprenorphine/naloxone [14]. Although these studies were conducted in the USA, the enrolled patient population was similar to the opioid-dependent patient population in the EU [10].

OX219-006 and -007 enrolled patients (aged 18–65 years) who met DSM-IV-text revision (TR) criteria for opioid dependence in the previous 12 months before study entry, had at least mild withdrawal symptoms [i.e. defined as Clinical Opiate Withdrawal Scale (COWS) score ≥ 9] prior to treatment initiation and were generally in good health [12, 13]. Eligible patients were to provide a buprenorphine-negative urine drug screen before randomization. Key exclusion criteria included untreated DSM-IV-TR Axis I psychiatric comorbidity (e.g. untreated schizophrenia, patients who were suicidal or homicidal) and any clinically significant medical disorder or other condition that might compromise the participant's safety or the validity of the results [12, 13]. At baseline, most (≈ 64.5% [10]) patients reported life-time use of heroin and the mean duration of opioid dependence was 10.6 [12] and 12.44 years [13].

The primary efficacy endpoint in OX219-006 and -007 was the treatment retention rate on day 3 [12, 13], with the treatment retention rate on day 15 being a coprimary

endpoint in OX219-006 [12]. Primary efficacy analyses in OX219-006 and -007 were assessed in the per-protocol population (PPP), with secondary outcomes assessed in the full analysis set (FAS) population (i.e. all randomized patients who received ≥ 1 dose of study drug) [12, 13]. Opioid withdrawal symptoms were assessed using the COWS (physician-rated scale) and the Subjective Opiate Withdrawal Scales (SOWS; patient-rated scale). Opioid cravings were assessed using a visual analog scale (VAS) [12, 13].

3.1 Induction Phase

During the 2-day, double-blind induction phase, patients received buprenorphine/naloxone 5.7/1.4 mg or sublingual buprenorphine 8 mg tablet on day 1 [12, 13]. On day 2, patients received the same dose as day 1 or were allowed to up-titrate buprenorphine/naloxone to 11.4/2.8 mg or buprenorphine to 16 mg [12, 13].

Buprenorphine/naloxone was associated with high (≥ 88%) treatment retention rates on day 3, with noninferiority to buprenorphine demonstrated in one but not the other trial (primary/coprimary outcome) (Table 1) [12, 13]. In OX219-007, although buprenorphine/naloxone did not meet the prespecified noninferiority criteria for the retention rate on day 3, this mostly resulted from a higher study discontinuation rate in the buprenorphine/naloxone than buprenorphine group (some of which were not related to treatment efficacy) [13]. In a separate analysis, several attributing factors for discontinuation were identified in both treatment groups, including loss to follow-up/requested discontinuation, protocol driven, adverse events and non-compliance with study procedures. None of the discontinued patients in either group met the criteria for precipitated withdrawal (i.e. increase in the COWS score from baseline at 0.5 and 1 h post-dose on day 1) [13]. In OX219-006, a sensitivity analysis in the FAS for this outcome was consistent with that in the PPP [12].

In the pooled descriptive analysis of OX219-006 and -007 (both trials had a similar design and patient population), the proportion of opioid-dependent patients retained on treatment at day 3 with buprenorphine/naloxone was similar to that in buprenorphine recipients in the PPP (Table 1) and FAS (total $n = 1068$; 90.9 vs. 92.6%). This between-group similarity in treatment retention rate on day 3 was observed regardless of methadone use in the last 30 days [13].

In terms of secondary efficacy endpoints in OX219-006 and -007, clinical meaningful improvement in opioid withdrawal symptoms and reduction in opioid cravings (i.e. reductions from baseline in COWS, SOWS and VAS scores) was observed in both treatment groups as early as day 1 and these improvements were sustained during the stabilization (Sect. 3.2) and maintenance (Sect. 3.3) phases [12, 13].

3.2 Stabilization Phase

3.2.1 OX219-006

During the stabilization phase, patients continued receiving buprenorphine/naloxone ($n = 329$) or switched from sublingual buprenorphine tablet to sublingual buprenorphine/naloxone film ($n = 326$) from day 3 to 15 [12]. On the basis of clinical symptoms, the respective dosage of buprenorphine/naloxone or buprenorphine/naloxone film could be up-titrated to a maximum daily dosage of 17.1/4.2 or 24/6 mg/day. On day 15, treatments were switched using a fixed conversion factor of 5.7 to 8 mg

Table 1 Efficacy of buprenorphine/naloxone during the 2-day induction phase in phase III trials in opioid-dependent adult patients

Study	Tx (no. of pts)[a]	Tx retention rate on day 3 (%)[b]	Estimated between-group difference % (95% CI)
OX219-006 [12]	BNX (329)	93.9	1.3 (−2.6 to −5.1)[c]
	BUP (326)	92.6	
OX219-007 [13]	BNX (128)	88.3	−7 (−13.7 to −0.4)[d]
	BUP (128)	95.3	
Pooled analysis of OX219-006 and -007 [13]	BNX (457)	92.3	−1.1 (−4.4 to 2.3)[e]
	BUP (454)	93.4	

BNX or BUP was administered on day 1 and 2. See text for detailed description

BNX sublingual buprenorphine/naloxone tablet, *BUP* sublingual buprenorphine tablet, *pts* patients, *tx* treatment

[a]All randomized pts who met eligibility criteria and without treatment administration errors

[b]Primary endpoint/coprimary endpoint

[c]Noninferiority was established vs. BUP as the lower bound of the two-sided 95% CI for the between-group difference exceeded −10%

[d]Noninferiority was not established vs. BUP as the lower bound of the two-sided 95% CI for the between-group difference was below −10%

[e]No formal noninferiority test was conducted; 95% CIs for descriptive purpose only

to convert the previous dose strengths of buprenorphine/naloxone or buprenorphine/naloxone film; patients continued treatment until day 22 [12]. Mean buprenorphine dosages in the buprenorphine/naloxone and buprenorphine/naloxone film groups on day 3 were 10.9 and 14.6 mg/day and those on day 15 were 10.8 and 15.9 mg/day [12]. After switching treatments, the mean buprenorphine dosages in the respective groups on day 22 were 11.3 and 16.0 mg/day [15].

On day 15, the treatment retention rate with buprenorphine/naloxone was noninferior to that of buprenorphine/naloxone film (83.0 vs. 82.5%; eBGD 0.5%; 95% CI − 5.3 to 6.3%) [coprimary endpoint] [12]. A sensitivity analysis in the FAS for this outcome was consistent with that in the PPP [12].

During the stabilization phase, patients in the buprenorphine/naloxone and buprenorphine/naloxone film groups experienced similar improvements in scores for opioid withdrawal symptoms and opioid cravings [12], with these benefits sustained after switching treatments [15]. In buprenorphine/naloxone or buprenorphine/naloxone film recipients, the mean change from baseline to day 15 was generally similar for COWS (− 10.7 vs. − 11.2), SOWS (− 24.1 vs. − 26.6) and VAS (− 46.8 vs. − 54.2) total scores. After switching treatment, these improvements in scores were sustained in both treatment groups at day 22 [15].

Significantly ($p < 0.0001$) greater proportions of patients preferred buprenorphine/naloxone over buprenorphine/naloxone film in terms of taste (77.5 vs. 22.5%), mouthfeel (72.6 vs. 27.4%), ease of administration (71.5 vs. 28.5%) and overall preference (70.2 vs. 29.8%) [15]. These findings were supported by an open-label, crossover phase IV study in opioid-dependent patients ($n = 31$) [16]. Furthermore, in OX219-014 (Sect. 2.2), greater proportions of healthy volunteers preferred buprenorphine/naloxone over reference buprenorphine/naloxone [11].

3.2.2 OX219-007

Following the 2-day induction phase (Sect. 3.1), all patients ($n = 199$) received buprenorphine/naloxone from day 3–28 [13]. On the basis of clinical symptoms, buprenorphine/naloxone could be titrated between 5.7/1.4 and 17.1/4.2 mg. Improvements in opioid withdrawal symptoms and opioid cravings were sustained during the stabilization phase, irrespective of induction treatment. In patients who received buprenorphine/naloxone or buprenorphine during the induction phase, the mean change from baseline to day 29 was generally similar for COWS (− 12.5 vs. − 11.4), SOWS (− 30.4 vs. − 24.3) and VAS (− 52.7 vs. − 45.1) scores [13].

3.3 Maintenance Phase

In the 24-week extension study (OX219-008), 56.1% of 665 patients withdrew (most of whom were lost to follow up), with 292 patients completing the study [14]. The proportion of patients completing OX219-008 (43.9% at week 24) was generally consistent with that observed in long-term studies with buprenorphine treatment [10]. Buprenorphine/naloxone 11.4/2.8 mg was the most commonly used dose at screening through to week 12, and the most commonly used dose of buprenorphine/naloxone at weeks 16 and 20 was 5.7/1.4 mg. Efficacy analyses in OX219-008 were descriptive only [14].

Buprenorphine/naloxone reduced scores for opioid craving and addiction severity [measured by the patient-rated Addiction Severity Index-Lite (ASI-Lite) and the investigator-rated Clinical Global Impression-Severity (CGI-S)] [14]. At week 24, VAS and CGI-S scores were reduced by 60.5 and 2.0 from respective baseline scores of the primary studies OX219-006 and -007. Buprenorphine/naloxone was also associated with a numerical decrease from primary study baseline for all seven ASI-Lite subscale scores, with most patients considered to be much improved for severity of symptoms at week 24 (i.e. investigator CGI-Improvement score of 2). Similarly, clinically meaningful improvements in QOL [assessed by SF-36 questionnaire, SF-36 physical and mental component (PCS and MCS)] and health economic outcomes (assessed by Work Productivity and Activity Impairment Questionnaire: Specific Health Problem) were seen with buprenorphine/naloxone treatment [14].

In the absence of psychotherapy, the majority (88.8%) of patients tested positive for the buprenorphine urine drug screen at week 24; however, 24.1% of patients also had a positive urine drug screen for nonbuprenoprhine opioids at this timepoint (the clinical significance of this outcome remains to be determined) [14].

4 Tolerability of Buprenorphine/Naloxone

Buprenorphine/naloxone was generally well tolerated for the treatment of opioid dependence in the three OX219 trials (Sect. 3), with most treatment-related adverse events (TRAEs) of mild or moderate intensity [12–14].

In patients receiving buprenorphine/naloxone or buprenorphine during the induction phase, the incidence of TRAEs was 15.9 versus 14.7% in OX219-006 [12] and 20.6 versus 24.5% in OX219-007 [13]. During the stabilization phase (< 4 weeks treatment), the incidence of TRAEs in patients receiving buprenorphine/naloxone was 8.3% (vs. 7.5% with sublingual buprenorphine/naloxone film) in OX219-006 [15] and 18.7% in OX219-007 [13]. In either phases in OX219-006 and -007, treatment discontinuation due to TRAEs [12] or treatment-emergent adverse events [13] were infrequent in

patients receiving buprenorphine/naloxone, buprenorphine/naloxone film or buprenorphine (≤ 1.3%). Moreover, none of TRAEs were serious or resulted in death in either phase [12, 13].

The tolerability profile of buprenorphine/naloxone in the OX219 trials was similar to that observed with reference buprenorphine/naloxone in clinical trials and post-marketing surveillance [10]. For instance, the most common (≥ 1/10) TRAEs with reference buprenorphine/naloxone include insomnia, headache, constipation, nausea and hyperhidrosis [8]. In OX219-006, the most common TRAEs occurring in > 2% of buprenorphine/naloxone recipients were headache (5.2 vs. 5.1% with buprenorphine), vomiting (3.1 vs. 2.9%), nausea (2.1 vs. 4.0%) and dry mouth (2.1 vs. 0.5%) during the 2-day induction phase [12]. Constipation (1.9 vs. 2.2% with buprenorphine/naloxone film) was the most commonly occurring TRAE during the stabilization phase of this study (up to day 22); constipation generally improved over time in both groups [15].

During the 24-week extension study OX219-008 (Sect. 3.3), the tolerability profile of buprenorphine/naloxone was generally similar to that observed in OX219-006 and -007 during the induction and stabilization phases and revealed no new safety signals [14]. The incidence of TRAEs was 10.7%, with the most common being constipation (2.9%). Three severe TRAEs occurred in four patients (one each due to depression and drug withdrawal syndrome and two due to constipation) and one patient experienced a serious TRAE (i.e. depression). TRAEs, such as laboratory abnormalities (primarily related to hepatitis C and liver function), vomiting, depression and constipation, led to treatment discontinuation in 0.9% of patients. Of the two reported deaths, none were treatment-related or treatment-emergent [14].

Cases of acute hepatic injury have been reported in patients with opioid addiction [8]. Indeed, increases in alanine aminotransferase, aspartate aminotransferase and gamma glutamyl transferase levels (one case each) were reported in OX219-008 [14]. As pre-existing mitochondrial impairment (e.g. liver enzyme abnormalities, HBV or HCV infections) and ongoing drug injection may play a causative role in acute hepatic injury, these underlying factors should be assessed prior to therapy [8]. Regular liver function monitoring is required during therapy, and in the event of suspected hepatic injury, biological and etiological evaluations should be conducted; treatment may be continued or discontinued depending on the findings [8].

5 Dosage and Administration of Buprenorphine/Naloxone

Buprenorphine/naloxone is indicated in the EU for the substitution treatment of opioid dependence, within a framework of medical, social and psychological support in adults and adolescents aged > 15 years [8]. Buprenorphine/naloxone should not be swallowed or consumed with food or drink. This formulation of buprenorphine/naloxone is not interchangeable with existing buprenorphine or buprenorphine/naloxone products, as the new formulation has higher bioavailability (Sect. 2.2). Consequently, dosage adjustment is required in patients switching from other buprenorphine-containing products [8].

The recommended starting dosage of buprenorphine/naloxone on day 1 is 1.4/0.36 or 2.9/0.71 mg/day; an additional dose of 1.4/0.36 or 2.9/0.71 mg can be administered if required [8]. Following treatment induction, the dosage of buprenorphine/naloxone should be individually titrated based on clinical effects; various strengths of buprenorphine/naloxone (0.7/0.18, 1.4/0.36, 2.9/0.71, 5.7/1.4, 8.6/2.1 and 11.4/2.9 mg) are available to enable dose individualization. The three higher strengths cannot be substituted with multiples of the three lower strengths because of deviations in compositional proportionality across the doses (Sect. 2.2). The maximum single daily dosage of buprenorphine should not exceed 17.2 mg (e.g. 2 × 8.6/2.1 or 11.4/2.9 plus 5.7/1.4 mg) during the maintenance phase. The daily regimen of buprenorphine/naloxone can be reduced to every other day or thrice weekly after satisfactory stabilization has been established. Prior to induction therapy, multiple factors should be considered, including the type of opioid misuse (i.e. long- or short-acting), the time since last opioid use and the severity of opioid dependence. For instance, for patients who are dependent on short-acting opioids (e.g. heroin), buprenorphine/naloxone should be initiated > 6 h after the last dose. To prevent withdrawal precipitation, buprenorphine/naloxone is only administered to patients with clear signs of withdrawal. During therapy, adolescents (aged 15 to < 18 years) should be more closely monitored as the efficacy and safety profiles of buprenorphine/naloxone in these patients are lacking [8]. Local prescribing information should be consulted for details regarding full dosage and administration recommendations, contraindications, warning and precautions, drug interactions and use in special patient populations.

6 Place of Buprenorphine/Naloxone in the Management of Opioid Dependence

Guidelines recommend methadone [3, 17, 18], buprenorphine [3, 17, 18] or buprenorphine in combination with naloxone [17] for the treatment of opioid dependence.

Historically, methadone has been the standard of care, with a higher treatment retention rate than buprenorphine-containing products [19, 20]. However, with limited access to a specialized methadone clinic and strict regulations, buprenorphine with or without naloxone has been widely used in the primary care facilities (enables office-based treatment with fewer clinic visits) as an alternative to methadone, especially for patients with greater life stability [2]. Moreover, recent studies (including a Cochrane meta-analysis [20]) indicated that treatment retention rate with buprenorphine-containing products increases with higher doses [19, 20]. In addition, buprenorphine/naloxone has a more flexible dosage regimen than methadone [2].

The new formulation of buprenorphine/naloxone has higher bioavailability and a faster sublingual dissolve time than reference buprenorphine/naloxone (Sect. 2.2), thereby potentially reducing the risk of buprenorphine intravenous abuse by managing opioid dependence with lower dosages [11]. Indeed, in the clinical trial comparing the efficacy of buprenorphine/naloxone to sublingual buprenorphine/naloxone film, the mean dosage of buprenorphine was ≈30% lower with buprenorphine/naloxone (Sect. 3.2.1); suggested dose conversion for patients switching from reference buprenorphine/naloxone to buprenorphine/naloxone is reported in Table 2. Furthermore, compared with reference buprenorphine/naloxone, the new formulation of buprenorphine/naloxone also improved taste, mouthfeel and ease of administration, potentially improving adherence to treatment (Sect. 3.2.1) [11]. Comparing patient preference, treatment adherence and the diversion rate with buprenorphine/naloxone relative to buprenorphine alone, reference buprenorphine/naloxone and methadone in the real-world setting would be of interest.

Based on pharmacokinetic data provided by OX219-014 (Sect. 2.2), the efficacy of buprenorphine/naloxone was bridged to the established efficacy of reference buprenorphine/naloxone [10]. In large phase III trials, buprenorphine/naloxone was associated with high treatment retention rates during the induction (Sect. 3.1) and stabilization (Sect. 3.2) phases, and also reduced opioid craving and opioid withdrawal symptoms. Although noninferiority of buprenorphine/naloxone to buprenorphine during the 2-day induction phase was only shown in one of the two similarly designed trials, pooled analyses confirmed that treatment retention rates were similar in the buprenorphine/naloxone and buprenorphine groups. Moreover, additional analyses indicated that failure to meet noninferiority of buprenorphine/naloxone to buprenorphine was likely due to several mitigating factors, including the difference in withdrawal rates in two groups [10]. Where evaluated, noninferiority of buprenorphine/naloxone to buprenorphine/naloxone film was also demonstrated at 15 days in the stabilization phase. During the 24-week maintenance treatment (Sect. 3.3), buprenorphine/naloxone therapy sustained improvements in opioid craving and reduced the severity of addiction scores. To investigate the longer-term efficacy of buprenorphine/naloxone, additional studies in patients with adequate treatment retention rates or follow-up studies in those who discontinued treatment would be of interest [14].

Buprenorphine/naloxone was generally well tolerated in the OX219 trials, with a tolerability profile that was similar to that established with reference buprenorphine/naloxone (Sect. 4) [10]. TRAEs were mostly of mild to moderate intensity, with the most common being headache, vomiting, nausea and dry mouth during the induction phase and constipation during the stabilization phase. Treatment discontinuation because of adverse events was infrequent (≤1.3%) and no new safety signals were revealed during the 24-week extension study.

The WHO guideline considered opioid agonist maintenance therapy (especially methadone) to be the most cost-effective treatment option for patients with opioid dependence [3]. To date, no robust pharmacoeconomic analyses relating to the use of buprenorphine/naloxone in adults and adolescents aged > 15 years have been conducted; these data would be of interest.

In conclusion, with potentially greater patient preference and a lower potential for parenteral buprenorphine

Table 2 Suggested dose conversion when switching patients from reference buprenorphine/naloxone to buprenorphine/naloxone, based on two bioequivalence studies [5, 11]

Suboxone® (reference buprenorphine/naloxone) sublingual tablets[a]	Corresponding dose of Zubsolv® (buprenorphine/ naloxone) sublingual tablets
2/0.5 mg	1.4/0.36 mg
4/1 mg (taken as 2 × 2/0.5 mg)	2.9/0.71 mg
8/2 mg	5.7/1.4 mg
12/3 mg (taken as 1 × 8/2 mg and 2 × 2/0.5 mg)	8.6/2.1 mg
16/4 mg (taken as 2 × 8/2 mg)	11.4/2.9 mg

[a]Including generic equivalents

abuse than reference buprenorphine/naloxone, buprenorphine/naloxone expands the treatment options available for adults and adolescent (aged > 15 years) patients with opioid dependence.

Data Selection Buprenorphone/Naloxone: 309 records identified	
Duplicates removed	58
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	215
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	16
Cited efficacy/tolerability articles	4
Cited articles not efficacy/tolerability	16
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were Zubsolv, OX-219, buprenorphine, naloxone, opioid, sublingual. Records were limited to those in English language. Searches last updated 26 July 2018	

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Compliance with Ethical Standards

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