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THERAPIES

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Prolonged-release buprenorphine formulations

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SUMMARY

Buprenorphine and methadone are the two main opioid agonist treatments approved for opioid use disorder. Buprenorphine is a partial agonist of the mu opioid receptors, which has been merely available through sublingual form until now. In practice, the use of buprenorphine is smoother than that of methadone, and it induces reduced risks of overdose. However, sublingual buprenorphine also exposes to risks (e.g., withdrawal, misuse) and constraints (e.g., daily intake). Three new galenic formulations of prolonged-release buprenorphine (PRB) are being commercialized and should allow some improvements in patients' comfort and safety. This narrative review aims to describe the main technical features and efficacy and safety data of these PRBs, as well as patients' and professionals' expectancies and concerns, using data of the scientific literature and the regulatory texts. PRBs consist of one subcutaneous implant and two subcutaneous injection depots. Sixmo®/Probuphine® is a six-month-long implant which needs to be surgically placed and removed and is approved for subjects previously treated with a maximum daily dose of 8 mg of sublingual buprenorphine, and can be used only for two successive periods of six months before the subject needs to be switched back to sublingual form. Sublocade® is a one-month-long depot formulation that is indicated in switch from sublingual buprenorphine, and which proposes only two dose schemes, i.e., 100 and 300 mg monthly. Buvidal®/Brixadi® is a one-week- or one-month-long depot formulation with multiple dosages, which can be used in initiation or in switched from sublingual formulations. While opioid users report some concerns with a risk of coercive use of long-acting forms of buprenorphine, both users and professionals deem that these new specialties could be particularly appreciated in stabilized patients bothered with the daily intake of the treatments, or specific situations at risk of treatment dropout (e.g., following hospital discharge or prison release).

KEYWORDS

Buprenorphine; Prolonged-release; Opioid dependence; Opiates; Substitution

Abbreviations

ADR: adverse drug reaction

OAT: opioid agonist treatment

OUD: opioid use disorder

PRB: prolonged-release buprenorphine

SmPCs: summary of product characteristics

Introduction

Opioids constitute a category of substances that act on receptors of the same name. Opioids are widely used in medicine, in particular because of their powerful analgesic effects. Depending on the dose used and the mode of action, opioids also induce and calm though intense euphoria, and they can thereby be used with a recreative purpose, or in self-medication of different types of symptoms. In both cases, this corresponds to what is called 'misuse' [1]. In practice, all opioids can be associated with misuse, but medical opioids are commonly distinguished from illicit opioids, for example heroin, or fentanyl derivatives such as ocfentanil or carfentanil. By way of illustration, it is estimated that a few more than 500,000 people in France have ever used heroin [2].

The main risk of opioid misuse is the occurrence of overdose. The effects of sedation and respiratory depression are very strong with opioids, and the risk of death is serious in case of overdose [1]. For example, each year in France, between 400 and 500 people die from opioid overdose [3]. When opioids are injected, their use is also associated with a great risk of viral or bacterial infection, in particular regarding the human immunodeficiency virus (HIV), and the hepatitis B and C viruses (HBV and HCV) [1]. Furthermore, opioid misuse may lead to opioid use disorder (OUD), which correspond to developing criteria for addiction [1]. Regular use of opioids rapidly leads to neuroadaptation processes, which induce the occurrence of tolerance and withdrawal symptoms, thus impeding the ability of the subject to stop or reduce opioid use [1]. Moreover, progressive processes of behavioral

habituation settle down, strengthening the need for using opioids and the occurrence of craving and loss of control over the substance. Such processes are met both with illicit and prescription opioids [4, 5].

OUD is associated with moderate to severe psychosocial consequences, which thus requires a specialized treatment [1]. This treatment is based both on an individualized psychosocial support and on the use of an opioid agonist treatment (OAT) [1]. OATs are maintenance drugs that have no recreative effects in therapeutic use, while they allow to restrain withdrawal symptoms and craving, and that reduce the psychosocial consequences of OUD. For these reasons, they are now considered as the gold standard pharmacotherapy of OUD [4, 6].

In France, two OATs are labeled for OUD: 1) methadone, and 2) high dose buprenorphine. Methadone was the first drug to be used in this indication, as soon as the 1960s [7]. Methadone is a full-agonist of the mu opioid receptor, and is has a very long pharmacological action, with an average half-life of 25 hours [1]. Methadone is more effective than placebo for supporting the cessation of heroin use and the associated aftermaths of heroin use, but in practice, methadone can also expose patients to an increased risk of overdose, and patients treated with methadone should thus be strictly supervised [8]. However, the overdose risk in patients under medical supervision is probably less important than in untreated heroin users, and the risk/benefit ratio of methadone in OUD is frequently considered as favorable by the experts of the field [4, 9].

Buprenorphine is the alternative OAT that has been marketed in France. Until recently, the galenic forms of buprenorphine have consisted of sublingual tablets, which allow to avoid the hepatic first-pass effects. By contrast with methadone, buprenorphine is a partial agonist of the mu receptor. Consequently, the risk of overdose, and thus the risk of death related to overdose, is very limited with buprenorphine [10]. However, much more than methadone, buprenorphine can be diverted by injection or intranasal use. Such buprenorphine misuses can lead to medical consequences, such as viral infections or distal microvascular infringements [11].

In France, the use of OAT has started in the mid1990s. A clear public health preference has been made on access to treatment, in particular with regard to buprenorphine [12]. Initiating buprenorphine treatment has been permitted to any physician, including office-based general practitioners. Moreover, buprenorphine can be prescribed for 28 days, whereas methadone syrup can be prescribed only for 14 days. For these reasons, buprenorphine has been the most prescribed OAT in France, while the rate of treatment coverage among opioid users has been very high, as it has been

estimated that between 70 and 80% of them receive more or less frequent prescriptions of OAT, essentially of buprenorphine [13].

Despite the relative success of the 'French way' of managing the public health strategy of OUD treatment, many issues remain with regard to this population. Many patients are not sufficiently treated as they do not receive adequate doses or are not correctly educated on how to use buprenorphine. Buprenorphine tablets remain too frequently swallowed by patients, which dramatically restrain the bioavailability of the drug [14]. Meanwhile, sublingual tablet use may require up to ten minutes to be dissolved under the tongue, which can be tedious and may cause underdosing, and thus foster the injection or intranasal misuse of buprenorphine [15], even if a lyophilizate of buprenorphine has recently been commercialized in France, which substantially reduces the sublingual dissolve time, and enhances the bioavailability of the drug [16].

Furthermore, treatment dropouts remain frequent in this population. Release from prison or hospitalization are at risk situations, in which treatment follow-up and continued access to OAT prescriptions can be difficult to ensure. Such situations expose patients to resuming illicit opioid use, or purchasing OATs on the black market, with increased risks of overdose, in particular with methadone. A last major concern in France is that buprenorphine misuse remains frequent, as it might concern 20% of patients at the international level [11], and up to 50% of them in French specialized addiction centers [17].

In this context, new galenic forms of 'prolonged-release' buprenorphine are becoming available in Western countries. These new treatments consist either of subcutaneous depot forms, or in implants. They allow for a very long treatment coverage, i.e., between one week to six months. In France, at least one of these specialties should be available very soon. This article aims to describe the main characteristics of these new medicines, the main evidence regarding efficacy and safety features, and the different expectancies and possible concerns of opioid users and professionals regarding the use of prolonged-release buprenorphine (PRB).

Characteristics of the different formulations of prolonged-release buprenorphine

PRB can be divided in two main formulations: 1) subcutaneous implant, and 2) subcutaneous injection depot. Three medical specialties are currently available at the internal level: one implant (Probuphine® / Sixmo®) and two depot formulations (Sublocade® and Brixadi® / Buvidal®) [Table 1].

The main features of the three different specialties can be found in Table 2, and will be detailed below.

Sixmo® / Probuphine®: the six-month implant by Titan Pharmaceuticals®

Characteristics of the product

This product is the first implant of buprenorphine. It consists of four white / light yellow implants (Ethylene vinyl acetate copolymer) that are 26.5 mm long and have a 2.4 mm diameter. Each of them delivers 74.2 mg buprenorphine over a six-month period for a total amount of 296.8 mg, even if the packaging of the drug only specifies the amount of dose per implant. The implants are to be implanted in the internal part of the higher part of the patient's arm, beneath the shoulder, using a local anesthesia. The implants must be surgically removed after six months. This surgical procedures of placing and removing the implant has to be undertaken by a trained physician.

This specialty is already commercialized in the USA, and a European labeling has recently been granted (brand name: Sixmo®) [18]. Sixmo® will be indicated for "clinically stabilized" (i.e., at least 30 days without heroin use) adults, in whom buprenorphine oral daily dose does not exceed 8 mg. The treatment duration is limited to two successive implants, that is, 12 months. After that, is planned to switch back to oral form. Moreover, in some circumstances (e.g., stress, craving, withdrawal symptoms), an adjunctive treatment of sublingual buprenorphine can be prescribed. In this respect, the summary of product characteristics (SmPCs) specify as follows: "*Although some patients may require occasional supplemental dosing with buprenorphine, patients should not be provided with prescriptions for sublingual buprenorphine-containing products for as needed use. Instead, patients*

who feel the need for supplemental dosing should be seen and evaluated promptly" [18]. In the clinical trials, 22.5% patients received additional doses of sublingual buprenorphine, and 21.9% of them required a 5th implant [19].

Efficacy / safety data

Three efficacy studies were conducted among 627 subjects [19-21]. The first two studies [19, 20] were double blind randomized placebo-controlled trials. Efficacy was defined as a negative urine screen at the end of the study period, i.e., 24 weeks for 287 patients (31 % for Sixmo® versus 13 % placebo versus 33 % for sublingual buprenorphine) and 16 weeks for 163 patients (40 % versus 28 % placebo). Participants should not be treated with buprenorphine or another OAT before the inclusion in the study. The third trial [21] was also a double-blind double-dummy randomized trial, but the control group consisted of subjects treated with sublingual buprenorphine. This trial enrolled 177 subjects who were already treated with sublingual buprenorphine before inclusion, with a maximum daily dose of 8 mg, which certainly explain why this is the maximum dose required as the indication of the final approval. After 6 months of treatment, approximately 96% were negative for heroin in the group receiving the active implant, versus 88% in the group receiving active sublingual buprenorphine, which confirmed the non-inferiority of Sixmo®, compared to the sublingual galenic form.

No concerning safety issue was reported in these three trials. The most frequent adverse events were those of buprenorphine, whatever be the galenic formulation. Specific adverse events related to the implant form were reported, but they were not serious. They essentially consisted of local pain, itching, bleeding, or reddening at the implantation site. Such minor symptoms affected approximately one quarter of participants, which is not a negligible figure.

Sublocade®: Indivior's prolonged-release depot formulation (unknown European trade name)

Characteristics of the product

This specialty is planned for 2021 in the EU. By contrast with Sixmo®, Sublocade® is not an implant but a depot formulation. Buprenorphine is encapsulated in a biodegradable polymeric gel (50:50 poly(DL-lactide-co-glycolide) polymer and a biocompatible solvent, N-methyl-2-pyrrolidone) named Atrigel®. Sublocade® has to be subcutaneously injected. This procedure does not require a specific previous training. Moreover, the gel spontaneously dissolves and no removal procedure is required. Sublocade® depot has a therapeutic action of one month. Two dosages exist: 1) 100 mg (in 0.5 mL solution); and 2) 300 mg (in a 1.5 mL solution). Two successive injections must be separated by at least 26 days of delay. Sublocade® has to be stored in a refrigerator (at between +2 and +8°C), as its stability does not exceed 7 days at room temperature. Kits are displayed as pre-filled syringes which a secure needle has only to be fixed on. Injection is performed in the abdominal area, remotely from the umbilicus.

In the US, Sublocade® is approved for subjects with OUD that have been "stabilized" for at least 7 days with a sublingual form of buprenorphine, using a dose ranging from 8 to 24 mg per day [22]. The dosing scheme consists of delivering a 300 mg monthly formulation during the first two months, followed by a maintenance period based on a monthly 100 mg dosing. However, the American SmPCs provide for the possibility of maintaining a monthly 300 mg regimens in patients that would not wish to receive 100 mg, while they specify that the controlled trials have not demonstrated the superiority of using 300 mg monthly versus using 100 mg (see below).

In France, the drug circuit and the dispensing procedure (i.e., take-home, or restricted to treatment settings) is still unknown, as the French drug agency has not stated on this point.

Efficacy / safety data

The efficacy study that was conducted in view of obtaining the approval was a 6-month long, 489-subject, randomized controlled trial [23]. Participants were separated into three groups that received: 1) a monthly 300 mg Sublocade® injection during 6 months; 2) 300 mg per month during two months, followed by 100 mg monthly during the four following months; and 3) placebo during six months, respectively. The main assessment criterion was reporting no opioid use and displaying a negative urine screen at the end of the study period (41.3% with 300 mg monthly were abstinent versus 42.7% with 300 mg then 100 mg versus 5.0% with placebo). Important differences were found, between the two Sublocade® and the placebo group, but there was no difference between the two schemes of Sublocade® use. Though this study design was previously approved by the Food and Drugs Administration (FDA), and certainly discussed with Indivior® before the conductance of the trial, it is very unlikely that this kind of design will be accepted by the European Medicines Agency. In Europe, it is generally required to compare a new drug, or a new galenic form, with the standards of care, that is, here, with sublingual buprenorphine. Nevertheless, clinical studies comparing Sublocade® with actives comparators (buprenorphine without naloxone which is the most used form in our country and methadone) are announced (EudraCT Number: 2018-004460-63), as well as studies exploring the efficacy initiating Sublocade® in subjects that were not previously treated with sublingual buprenorphine (NCT03993392).

Moreover, a study conducted among 39 patients explored the PK and pharmacodynamics features of Sublocade® [24]. A peak concentration is reached 24 hours after administration. Blood concentrations of buprenorphine were of 5.0 ng per mL and was slightly higher after the second injection (6.6 ng per mL). Sublocade® could block the effects of 6 and 18 mg of hydromorphone (i.m), which is a mu-receptor agonist. As a partial mu-receptor agonist exhibiting a very high affinity for this receptor, buprenorphine is able to block the effects of many full agonists. Sublocade® have allowed for a significant reduction in the reinforcing effects of hydromorphone. This test using hydromorphone is an efficacy criterion requested by the Food and Drug Administration. Based on these results, it shows that the buprenorphine contained in Sublocade® is effective for targeting the mu-opioid receptors of patients.

Overall, the tolerability of Sublocade® was acceptable. Local adverse drug reactions affected 16.5% of participants versus 9.0% of those with placebo [22], and consisted of local pain, itching, or erythema. Other adverse drug reactions comprised the common effects of buprenorphine, e.g.,

constipation, nausea, vomiting, headache, or sedation. After commercialization, and according to a recent financial report issued by Indivior [25], 10,630 people had received at least one Sublocade® injection in mid2019. 74% of them had a second administration, while 56% had received three injections, 39% had five injections, and 21% ten injections. This may point out a substantial rate of dropouts, but, meanwhile, the commercialization is also recent, and a limited number of subjects were able to receive an important number of injections at this stage.

A multi-center, open-label, long term clinical study was conducted with the aim to assess the effectiveness and safety up to 12 months of Sublocade® [26]. Different measures were collected during the study (EQ-5D-5L, SF-36v2, treatment effectiveness assessment (TEA), addiction severity index-lite (ASI-Lite), employment/insurance status questionnaire and medication satisfaction questionnaire (MSQ). 402 patients were included and 50% have been lost to follow-up. Regarding quality of life, EQ-5D-L remained stable, but SF-36v2 increased with a significant mental improvement. Improvement was noted for all treatment effectiveness assessment domain score. For the addiction severity index-lite, significant improvements were seen for all problem areas except for alcohol use from baseline to end of study. The proportion of participants employed increased 7% from base-line to end of study (44.2% vs 51.2%) whereas the proportion with health insurance was stable from baseline to end of study. At end of study, 88.8% of participants stated they were satisfied with treatment.

Buvidal®: Camurus®' weekly or monthly prolonged-release depot formulation

Characteristics of the product

Buvidal® is the first prolonged release buprenorphine depot formulation that has received a European labeling. The encapsulation of buprenorphine is made into a lipid-based liquid named FluidCrystal® (soybean phosphatidylcholine and glycerol dioleate). Like for Sublocade®, the depot form spontaneously dissolves in the body, and does not require a removal procedure. In France, this specialty should be commercialized in 2020. Buvidal® is displayed either with weekly forms, with four different

dosages of 8, 16, 24, or 32 mg, or monthly forms of 64, 96, or 128 mg. Buvidal® galenic aspect consists of a secure pre-charged syringe, which only requires the piston to be screened on. The injected volume is between 0.16 and 0.64 mL for the weekly form, and 0.18 and 0.36 mL for the monthly form. Injection can be delivered in the buttock, the leg, the arm, or the abdomen.

The correspondence between Buvidal® dosing and the daily sublingual doses of buprenorphine is not linear a requires using an equivalence table that is displayed in the SmPCs (Table 3) [27].

This equivalence table is based on "classical" sublingual forms of buprenorphine with limited bioavailability, while more recent galenics (lyophilisates form) may have a higher bioavailability [28], which should be considered when using the correspondence table. Moreover, no equivalence table between Buvidal® and Sublocade® dosages is currently available, and there is thus no indication yet, on how to proceed the switch from one form to the other.

Buvidal® has been approved for treating OUD in adults as well as in adolescents aged 16 years or more. Setting up an adjunctive psychosocial support is required in the SmPCs. Contraindications are similar to those of the sublingual form.

Similarly to Sublocade®, the dispensing process of Buvidal® is unknown at this stage, as the regulatory procedure is still ongoing.

Efficacy / safety data

The efficacy of Buvidal® has been explored one multicenter double-blind double-dummy randomized clinical trial in which Buvidal® was compared with sublingual buprenorphine / naloxone during 24 weeks among 428 subjects [29]. First group was treated with daily sublingual placebo and weekly (first 12 weeks; phase 1, up to 32 mg/week) and monthly (last 12 weeks; phase 2, up to 160 mg/month) Buvidal® versus daily active sublingual buprenorphine (up to 24 mg/day) with naloxone (24 weeks) with matched weekly and monthly placebo injections for the second group. The main assessment criterion was the use of illicit opioid at the end the study, based on self-report and urine screen. Participants should not be treated with buprenorphine during the 60 days prior to inclusion. This study found that Buvidal® was not inferior to sublingual formulation for supporting the cessation of non-

therapeutic opioid use. During the 24-week trial, 35.1% subjects in the Buvidal® active group, versus 28.4% in the sublingual buprenorphine / naloxone active group, displayed continuous negative urine screens. When combined with self-reports, these proportions fell at 17.4% and 14.4%, respectively.

A long-term safety study was conducted [30]. It was a 48-week-long multicenter trial conducted among 227 subjects. Participants received individualized doses, and could be treated using either the weekly or monthly formulation. 37 participants started buprenorphine with the depot form, whereas 190 switched from sublingual to depot form. One third of the sample received only weekly depot injections, whereas one other third received only monthly injections, and the other third received weekly and then subsequently monthly injection formulations. Approximately 83% of the participants ended the study. When taken together, urine screens and self-reports found that 63% of the participants initiated with Buvidal®, and 82.8% of the participants who had switched from sublingual buprenorphine to Buvidal®, maintained cessation of non-therapeutic use of opioids.

A study conducted among 47 patients explored the pharmacokinetic and pharmacodynamics features of Buvidal® weekly forms (24 mg and 32 mg) [31]. A peak concentration is reached after 24 hours, with a half-life of 4 to 5 days. Four hours after administration, blood concentrations of buprenorphine were of 1.25 ng per mL or more, while it is stated that between 2 and 3 ng per mL are required to block the majority of the mu receptors. On a clinical ground, all withdrawal symptoms disappeared within the first 24 hours. Moreover, Buvidal® could block the effects of 6 and 18 mg of hydromorphone, which is a mu-receptor agonist. As a partial mu-receptor agonist exhibiting a very high affinity for this receptor, buprenorphine is able to block the effects of many full agonists. With these results, it shows that the buprenorphine contained in Buvidal® is effective.

Regarding the safety aspects, the 24-week-long trial [29] found that 31.3% reported adverse drug reactions, both groups combined. The tolerability features related to the injections were essentially light to moderate pain (8.4%), itching (6.1%), or erythema (5.6%), at the injection site. Other adverse drug reactions consisted of headache (7.7%), constipation (7.5%), or nausea (7.5%). Five cases of overdose were reported, all of them in the active sublingual arm. The observational study [30] found that 63% of the participants reported at least one adverse event, among which 26.4% of them could be related with Buvidal®. These were local pain (15.4%), swelling (11.9%), and erythema (9.3%) at the site of injection. Other general adverse drug reactions were headache (7.9%), nausea (7.0%), and vomiting (5.3%). Surprisingly, patients switched from sublingual to depot form reported two-fold more

adverse drug reactions than those directly treated with Buvidal®. Five participants (2.2%) were withdrawn from the study because of a safety issue. The third study [31] found relatively similar figures.

Prolonged-release buprenorphine: expectancies and concerns of users and professionals

Opioid users

International surveys

So far, only four surveys have investigated the expectancies and preferences regarding prolonged-release buprenorphine among people who use opioid drugs.

In the UK, a qualitative survey was conducted in 2018 among 44 opioid users who had received a prolonged-release buprenorphine treatment (implant or depot form) [32]. Surveyed participants expressed some apprehensions regarding the possible coercive risk of these new galenic formulations that are difficult to stop overnight, compared to sublingual form. Such remarks are in line with some frequent concerns expressed by opioid users, who commonly worry about the risk of social and /or medical control upon their behaviors of drug use [33]. In this context, any treatment scheme that is deemed as too rigid or abstinence-focused can be perceived as a constraint. Nevertheless, the people interviewed in this survey also raised a relative interest for prolonged-release buprenorphine formulations. In particular, they pointed out that these new galenic forms could break the daily ritual of taking buprenorphine or another OAT, which could help some subjects to feel more easily away from an identity of “addicted”, and thereby more swiftly fit into a recovery trajectory.

A second British qualitative survey has explored the perceptions on prolonged-release buprenorphine of 36 subjects receiving daily oral OAT [34]. In this sample, the perceptions on such

new formulations were quite favorable. Participants deemed that these new formulations will be useful to put distance with other opioid users and medical settings, and thus to recover a more “normal” life.

Conversely, they thought that these new specialties would not attract people who are not willing to completely stop opioid use, and /or would not want to completely cut themselves from a users’ environment. Ethical concerns were also raised, in particular the same risk of coercion addressed in the first survey.

In Australia, a recently-published quantitative survey conducted among 402 users of opioids found that the overall acceptation of prolonged-release buprenorphine was correct [35]. More than two third of the participants considered that these new forms constituted an interesting therapeutic option for them. Compared to uninterested subjects, those who reported an interest in these long-acting forms were younger, more frequently females, and had a lower level of education. They were more recent opioid users. A clear preference was reported for monthly formulations, compared to weekly regimens. The issue of how far to go to access buprenorphine was also a major factor in adherence to PRB.

Last, preliminary results of the French study ‘AMBRE’ were recently published [36]. This was a multicenter quantitative survey conducted among 366 French opioid users treated with an OAT, between February and July 2019. 55% of the participants (probably those with split deliveries) reported that the main constraint with their oral OAT was the need to frequently have to meet a prescriber and/or a delivery pharmacist. If weekly injections will not change this feeling, for these patients, the monthly version might give them more flexibility. The need to take an OAT every day was also an issue for 40% of them. One third of participants reported more or less frequent problems with the intake of current forms, e.g., intimacy, professional constraints, or travelling issues. Approximately a half of the interviewed sample was ready to try a prolonged-release buprenorphine formulation. The main cause of interest for these subjects was the weekly or monthly aspect of the treatment (86.7% of the interested subjects), and the expected reduction in craving (81.2%) or withdrawal symptoms (80.3%). They also considered these new treatment forms as more discreet than sublingual tablets (73.3%).

Opinions on opioid users’ online forums

Opioid users already debate on prolonged-release formulations of buprenorphine on community online forums (for example, in France, [37-39]). For some of them, injection OATs should not be long-acting, but more immediate-release buprenorphine, for people who inject themselves their sublingual buprenorphine treatment. Some opinions expressed on forums are in line with what was found in the qualitative surveys, i.e., that the subjects with OUD that will be the most interested in prolonged-release buprenorphine would those that wish to completely stop recreative opioid use and aim for a complete social reinsertion. Some interesting concerns were also raised about the risk of feeling bad at the end of the injection action, i.e., that blood levels of buprenorphine would be low and induce withdrawal symptoms and / or craving.

Professionals involved in the treatment of opioid use disorder

Overall, most of the specialists deem that the treatment coverage of OUD is insufficient, and that new galenic forms are thus required [1, 4, 40]. A recent expert opinion article, which only pertained to Buvidal®, but could easily apply to other formulations, listed several types of specific publics for prolonged-release buprenorphine (Table 4) [33]. However, they also stated that these new formulations should always be proposed, and never imposed to patients with OUD, with respect to the apprehensions addressed above.

The reception that general practitioners already have, or will have in France, with regard to prolonged-release buprenorphine formulations remain largely unknown. In France, this question is important, because general practitioners are by far the most frequent prescribers of OATs, as it has been explained in the Introduction section. However, in France as abroad, an insufficient rate of general practitioners accepts to be involved in the prescribing of OATs [5, 33]. They might fear to prescribe a treatment such as sublingual buprenorphine, which can lead to traffic or diversion. In such case, they will maybe feel more at ease with prolonged-release buprenorphine formulations, which theoretically have no risk of misuse. By contrast, they may also feel uncomfortable with injecting constraints associated to these specialties. Surveys among general practitioners would be helpful to better address their knowledge and representations on these new treatments. In France, the drug circuit of the long-

acting forms has not been specified at this stage. Two options are supposed: 1) a wide outpatient-based access to the medicine, which is administered by a health professional (i.e., a doctor or a nurse), with the risk that the product may be diverted after delivery in pharmacies; or 2) a restricted access to addiction settings, which reduces the likelihood of misuse, but which will also greatly restrict the access to this galenic forms. In this second option, the financial coverage of these drugs will impact the budgets of many addiction units, which will further restrict the access to these new types of drugs. A final possible option would that training community pharmacists would perform the injection, as they already do for influenza vaccination. This option would allow a wider access while avoiding misuse, but it is unsure that pharmacists are ready for this.

If the French High Authory for Health (HAS) has still not decided which place these new galenics will have in the country, the NICE (British agency) has stated as follows [41]: "Buprenorphine prolonged-release injection may be an option where there is a risk of diversion of opioid substitution medicines or concerns about the safety of medicines stored at home. It may also be an option for people who have difficulties adhering to daily supervised opioid substitution medication, such as for people who are working or in education.

Buprenorphine prolonged-release injection may have a place in treating opioid dependence in people in custodial settings, where the risk of diversion and time needed for supervised consumption currently leads to challenges in supplying supervised medicines safely.

However, the higher drug acquisition cost of buprenorphine prolonged-release injection compared with other treatments for opioid dependence will need to be taken into account". In the United Kingdom, a monthly supply of buprenorphine prolonged-release injection costs £239.70 (excluding VAT about 275€) either approximatively the price of buprenorphine high dosage whereas methadone is much cheaper (£15 to £30). In France, we do not know the price expected by pharmaceutical companies.

Conclusions and perspectives

Prolonged-release buprenorphine will soon be available in France. Buvidal® has been approved and should arrive on the market in 2020. Sublocade® should follow quite quickly. These two specialties have many similarities, in particular in terms of tolerability and easiness of use, even if Buvidal® has the advantage to be stored at ambient temperature. These two products have also some differences (see Table 2). Only Buvidal® has a weekly formulation, though in practice, the monthly injection seems to be more expected by opioid users. Buvidal® has also a wider range of dosages, which can be swifter for clinical practice. Concerning Sixmo®, though the possibility of a six-month-acting product can be very appealing for some subjects, it can also be repelling for some others. But the authorization of only two treatments before returning to the sublingual form is very odd and difficult operationalize in current practice. Moreover, the constraints related to placing and removing the implants may refrain many physicians and many patients from using this product. All put together, these products may attract a very heterogeneous public of patients, from those living in places with difficult access to delivery pharmacies or prescribers from those bothered by the need to take a drug daily.

Some unknown questions will also need to be addressed with these new formulations. For example, the practical management of an acute and severe pain is likely to occasionally lead to pitfalls or issues. The potential of misuse and diversion of these products is theoretically very low, but this remains to be confirmed such cases will have to be declared to the regional addictovigilance center (For France: [42] in order to monitor this potential for post-market abuse. On a more general ground, post-marketing data of phase IV and pharmacovigilance follow-up will be necessary to guarantee the safe use of these products on the long run. Furthermore, the dose correspondence between the three specialties would need to be assessed, even if, for other long-acting treatment, e.g., antipsychotics, such correspondence were never established without too many practical issues.

Disclosure of interest

MC: ATHS Congress (2017): invitation by Indivior® as a participant (inscription fees, travelling and housing costs). ATHS Congress (2019): invitation by Ethypharm® as a participant.

JB: conflicts of interests with Camurus®, Indivior®, Bouchara-Recordati®, HAC® and Shire®

GB: conflicts of interests with Indivior®, Bouchara- Recordati®, Lundbeck®, Janssen-Cilag®, Sanofi® and AstraZeneca®.

BR: conflicts of interests with Ethypharm®, Camurus®, Indivior®, Bouchara-Recordati®, Lundbeck®, Otsuka®, Grunenthal®, HAC® and Shire®.

BT: Encephale Congress (2020) and ATHS Congress (2019): invitation by Camurus® as a participant (inscription fees, travelling and housing costs). ECNP Congress (2019) invitation by Jansen-Cilag® as a participant (inscription fees, travelling and housing costs).

PB: conflicts of interests with Indivior®, Ethypharm®, ATHS Congress (2019): invitation by Abbvie® as a participant (inscription fees, travelling and housing costs). Albatros (2019) and Encephale Congress (2020): invitation by Camurus® as a participant, Clinical survey (Ambre) participation for Camurus®.

PN: did not report competing interest with this manuscript.

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Table 1. Currently-existing prolonged-release buprenorphine formulation in the World

	Localization		
Company	USA	EU	Australia
Titan Pharmaceuticals®	**Probuphine®** *Commercialized*	**Sixmo®** *Labeled (Jun 2019) but not commercialized*	*No data*
Indivior®	**Sublocade®** *Commercialized*	**Unknown trade name** *Labeling application planned in 2020*	**Sublocade®** *Commercialized*
Camurus®	**Brixadi®** *Tentatively approved, but not commercialized due to an exclusivity for Sublocade® up to Dec 2020*	**Buvidal®** *Labeled in the EU and currently commercialized in the UK, in Denmark, Germany, Sweden, Norway, and Finland. Commercialization planned in 2020 in France*	**Buvidal®** *Commercialized*

Table 2. Main features of the different prolonged-release formulations of buprenorphine approved or planned to be approved in the European Union.

	Sixmo® Titan Pharmaceuticals®	**Sublocade®** *(unknown European trade name)* Indivior®	**Buvidal®** Camurus®
Type	Implant	Subcutaneous depot	Subcutaneous depot
Duration of action	6 months	One month	One week or one month
Dosage(s)	74.2 mg	300 mg (first two doses) then 100 mg or 300 mg	8, 16, 24 or 32 mg (weekly) 64, 96 or 128 mg (monthly)
Storage	Room temperature	Refrigerator (7 days at room temperature)	Room temperature
Demonstrated non-inferiority vs. sublingual form	Yes	No (2020)	Yes
Indication	No opioid use for ≥ 30 days Relay from sublingual form	No opioid use for ≥ 7 days Relay from sublingual form	Relay from sublingual form or initiation
Duration of treatment	No more than 12 months	Unlimited	Unlimited
Frequency of ADRs related to injection	27.2 %	16.5 %	10 to 20 %
Advantages *(authors' viewpoint)*	Duration of action	Easy administration	Easy administration Two-duration forms Wide range of dosages Possible initiation
Disadvantages *(authors' viewpoint)*	Administration constraints Indication limitations (not applicable if sublingual buprenorphine dosing exceeds 8 mg per day) Limited to 12 months May require adjunctive sublingual treatment	No compared efficacy vs. sublingual form (early 2020) Pharmacy : Required being kept cold Limited range of doses	Possible confusion between sublingual dosage (daily) and injectable (weekly)

Table 3. Correspondence between Buvidal® injection dosages and the daily doses of sublingual buprenorphine [27].

Daily dose of sublingual buprenorphine	Weekly Buvidal® injection	Monthly Buvidal® injection
2-6 mg	8 mg	
8-10 mg	16 mg	64 mg
12-16 mg	24 mg	96 mg
18-24 mg	32 mg	128 mg

Table 4. Situations and publics for which prolonged-release buprenorphine could be particularly fitted (expert opinion [33])

Situations	**Examples**
People concerned with avoiding daily OAT intake (practical aspects and stigma)	- living in the parental home, in a reintegration home, in incarceration - frequent travelers, especially abroad - reinserted subject wishing to limit their contacts with the drug consumer environment and the healthcare environment (pharmacy and doctor), and no longer take daily medication
People having difficulty ensuring daily buprenorphine taking and **motivated to do it**.	- precarious social situation, entourage consumer of recreational opioids
Take care relay with risk of interruption	- out of prison, from reintegration home, from psychiatric hospitalization - a move out
People with diversion their OAT or selling a part of them and **wishing to stop**	