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META-OPINION

What place for prolonged-release buprenorphine depot-formulation Buvidal® in the treatment arsenal of opioid dependence? Insights from the French experience on buprenorphine

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ABSTRACT

Introduction: Since the 1990s, opioid maintenance treatments (OMTs), i.e. mostly methadone and buprenorphine, have represented the therapeutic cornerstone of opioid dependence. In France, the public health strategy on opioid dependence, identified here as the 'French model', has consisted of offering a facilitated access to buprenorphine, to reach a large treatment coverage and reduce opioid-related mortality.

Areas covered: Recently, a new formulation of subcutaneous buprenorphine depot (Buvidal®) has been approved in Europe for treatment of opioid dependence. The place of Buvidal® among the pre-existing arsenal of OMTs is discussed in the light of the pharmacological specificities of this new formulation, and with the particular standpoint of the French model on opioid dependence.

Expert opinion: Buvidal® could constitute a promising treatment option mainly in case of: 1) OMT initiation, including in non-specialized addiction medicine care; 2) Discharge from prison or hospital; Diversion/misuse of 3) buprenorphine or 4) methadone; 5) Clinically stabilized patients wishing to avoid daily oral taking of the medication. As such, this new formulation should be highly accessible, which will require specific pathways through care as the product is intended to be administered by a healthcare professional.

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Buprenorphine; opioid dependence; opioid-related disorders long-acting treatments; delivery of health care; France

1. Introduction

Opioid dependence, as officially defined by the ICD-10, is a severe addictive disorder associated with a heavy health and social burden of disease, and with increased risks of death and disabilities due to several consequences of opioid dependence, including overdose, HIV or HCV infection, suicide, and the concurrent use and misuse of several other pharmacological treatments and illicit drugs [1]. Indeed, North American countries are currently facing an opioid public health crisis, that has not only been restrained to the recent prescription opioid problem that most clinicians are aware of [2]. Indeed, this huge problem started with a sub-epidemic associated with a significant increase in heroin-related deaths, i.e. a 2-fold increase between 2010 and 2013 in the United States (US) [3]. The heroin-related deaths were accompanied by a series of significant increases in deaths related to prescription opioids, i.e. a 5-fold increase in overdoses between 2000 and 2010 in the US [4], and thereafter a 45% additional increase between 2015 and 2017, mostly driven by illicitly manufactured fentanyl and its derivates, such as carfentanil or sufentanil [5]. Stakeholders and health professionals in the US and other developed countries have called for political, research and organizational healthcare measures to fight the epidemic [6]. In this perspective, enlarging treatment accessibility, with or without medical insurance coverage, and increasing treatment retention for patients with opioid dependence seems crucial [7].

1.1. Current best treatments for opioid dependence

Pharmacotherapeutic options for opioid dependence should be integrated within a global therapeutic approach, which includes psychosocial support, and which should focus on the individual's functional recovery. In this respect, Opioid maintenance treatments (OMTs) are the gold standard medication for opioid dependence. While opioid medications are

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commonly indicated for treating pain [8], when used as OMTs, they have their specific indication and their specific rules of use. Maintenance antagonist treatments, such as long-acting naltrexone, have also proven some efficacy [9], but are regarded as second-choice treatment, that is, if OMTs have been ineffective or were not available. Retention rates with long-acting antagonists are supposed to be lower to those of OMTs, even if results have been somewhat contradictory on this issue [10,11]. Regardless, maintenance antagonist treatments are mostly prescribed in case of unavailability of OMTs or patient preference for non-OMT treatment [12]. Patients with good retention in antagonist treatment programs were described as opioid-dependent subjects with less mental health issues, higher education, and were less likely to report recent drug use at baseline [13]. Finally, some countries such as Great Britain, Swiss, or the Netherlands, have also authorized the dispensation of heroin under medical supervision, including through self-intravenous administration in specific care centers, or oral morphine, usually in specific care centers, for patients defined as non-responders to classical OMTs.

Methadone was the first-approved among the classical OMTs. It has been prescribed for heroin dependence for more than four decades, with a marked improvement in health and social condition of patients noted already in 1965 in the US [14]. Moreover, methadone has also been used in European countries such as France since the 1970s [15,16]. It is still the most frequently prescribed treatment for opioid dependence in the US, where around 300 000 patients are being treated [17], as well as in Western Europe, where it is prescribed to around 400 000 patients (i.e. two-thirds of the 628 000 opioid dependence patients undergoing OMT [18]). Because it is a full mu-opioid receptor agonist, methadone is usually thought to be more efficacious than buprenorphine in patients with severe opioid dependence, and associated with higher retention rates [19]. However, this statement is still under debate [20], as some studies found that that buprenorphine maintenance treatment had similar retention and favorable outcome rates, compared to methadone [21].

Buprenorphine has more recently appeared as an efficacious treatment for opioid dependence. It has been marketed only since the 1990s for this purpose. In 2018, it was prescribed to 220 000 patients in Europe [18], and it was the most frequently prescribed treatment in 8 countries, including, France, Sweden, Norway, Finland, and Greece.

As OMTs, buprenorphine and methadone are designed to be used as long-term maintenance medications, and usually using oral formulations intended to be taken once a day. As such, they have constituted a cornerstone of opioid dependence treatment since the increase of their access in the mid-1990s [22], in association with appropriate psychosocial support. OMTs were found to foster the cessation of opioid use, and they reduce the risks of viral transmission, as well as the overall risk of mortality [23]. Moreover, OMTs improve the overall functioning of opioid dependence patients [22,24,25], and have thus allowed improving the recovery trajectory of many opioid users. At a societal level, methadone and buprenorphine have even been shown to lower the rate of crimes committed by subjects with opioid dependence [26]. Methadone and buprenorphine have also demonstrated a good cost-effectiveness ratio in the context of developed countries [27,28].

1.2. Unmet needs in treatment of opioid dependence

1.2.1. Risk and harms of existing treatments

Despite their benefits, the use of OMTs also conveys specific risks and harms. Methadone is a full mu-opioid receptor agonist that can increase the risk of overdose in specific situations, in particular during the initiation phase of the treatment, and/or in case of insufficient supervision [29,30]. Furthermore, optimizing the methadone dose requires several weeks or a few months of progressive dosage increase [31], as the optimal dose for each patient is highly variable, is associated with several clinical and very likely several genetic factors [32,33], and cannot be predicted *a priori*. Despite the difficulties and the time required, achieving an adequate methadone dosage is a key factor to increase the retention rate in methadone programs [34]. While the risk of overdose is much reduced with the partial mu-opioid receptor agonist buprenorphine [35], using this alternative OMT also has drawbacks. In particular, it has been estimated that approximately 20% of buprenorphine-treated opioid dependence subjects display injection or intranasal misuse behaviors with buprenorphine [36]. Buprenorphine misuse can contribute to disseminating viral or bacterial infections, in particular in case of unsafe injection practices [37].

Nevertheless, buprenorphine has several advantages over methadone. The therapeutic dose range is much smaller than for methadone, with most patients being responders between 8 and 24 mg per day, only a 3-fold interval. This makes it easier to target the optimal dose compared to methadone, which has no maximum approved dose. Thus, patients avoid the possible need of several weeks of dose adjustments. Furthermore, in contrast to methadone, buprenorphine is not associated with weight gain or QT prolongation, which is not negligible considering that this is a chronic treatment. But, of course, the major advantage of using a partial receptor agonist is its ceiling effect, associated with a lower risk of treatment-induced overdoses, during treatment initiation but also in case of treatment misuse, associated with heroin, alcohol or other sedative drugs, or even suicide attempt. This last advantage is crucial as the number of deaths involving an opioid receptor agonist in combination with other drugs is also an increasing concern [38].

1.2.2. Improving the generalization of treatment access

In the light of these different elements, national public health policies on OMT access strategy are based on complex equations and strong choices. A strategy of large access to OMT, for example based on general practitioners' (GPs') prescription, has been advocated by some experts [39]. This strategy allows for a more widespread treatment coverage for the population with opioid dependence, at least for those who benefit from a social security coverage. The choice to limit the prescription in specific care centers such as 'open access' or low-threshold care facilities also has some advantages if those clinics offer integrated care and treatment, as they can reach out patients without any social insurance coverage [40]. In parallel,

a facilitated access to OMT is commonly associated with a reduced treatment supervision, which may expose the patients to increased OMT-related risks, including a possible risk of increases in opioid overdose deaths in case of facilitated access to methadone without supervision (i.e. regular clinical assessment and slow dose increase). While some countries have restrained this access with the aim to better control OMT-related risks, other countries have made the choice to open a wide access to OMT through a large access to buprenorphine for example France [40] and Portugal [41].

1.3. The example of french health policy regarding opioid dependence treatment strategy

In France, since the mid-1990s, it has been decided to facilitate the specific access to buprenorphine for subjects with opioid dependence [42]. While the initial prescription and dispensing of methadone remains restrained to specialized addiction settings, buprenorphine can be started by any physician, including GPs, with no need for a prior training or waiver. Similarly, buprenorphine dispensing can be performed by community pharmacists, under the coordination of the prescribing physician. Twenty-four mg per day of buprenorphine is the maximum dose approved. During the first treatment year, the maximum prescription duration is longer for buprenorphine (i.e. 28 days) than for methadone (i.e. 14 days), while urine screens are compulsory only for methadone [42,43]. All of this has contributed to durably shaping the French landscape of opioid dependence treatment, which has been largely dominated by GP-based prescription of buprenorphine. Still, the large access to treatment prescription by GPs and dispensation by community pharmacists does not mean an absence of treatment supervision, as the pharmacist has to be chosen in advance and is the only one that can deliver the drug, and that several safeguards are used to ensure the reality of the prescription. This has resulted in a low rate of doctor shopping for buprenorphine, defined as overlapping prescriptions by different physicians, estimated to be 12.6% [44]. The facilitated access to buprenorphine has been accompanied by other harm reduction measures, including syringe-exchange campaigns [45], and, more recently, the early steps of a national plan to develop take-home naloxone education programs [46,47]. Methadone initiation remains limited to specialized addiction care facilities, with a dose chosen by the prescriber, and the possibility to either dispense the treatment in the care center or at the local pharmacist, with a maximum take-home of 14 days during the first year of treatment, and up to 28 days if the physician estimates that the patient has reached a clinical 'steady-state' or stabilization. GPs can only renew the prescription. Methadone initiation remains limited to specialized addiction care facilities, with a dose chosen by the prescriber, and the possibility to either dispense the treatment in the care center or at the local pharmacist, with a maximum take-home of 14 days during the first year of treatment, and up to 28 days if the physician estimates that the patient has reached a clinical 'steady-state' or stabilization. GPs can only renew the prescription. The implementation of this bold public health strategy in France since the mid-1990s resulted in an 80%-reduction in overdose-related between 1994 and 2002 [42,45], and the incidence of acquired immune deficiency syndrome in intravenous drug users fell from 25% in the mid-1990s to 6% in 2010 [45]. Despite the wide availability of buprenorphine among subjects with opioid dependence, the estimated rate of buprenorphine misuse remained stable at around 20% of the illicit opioid users [43], which is similar to the average of the international data. Overall, it is estimated that 80% to 90% of the illicit opioid users in France have had access to OMT prescriptions in the preceding year, which corresponds to one of the highest rates of treatment coverage across Europe [48].

1.4. Buvidal®: the first long acting medication for opioid dependence approved in Europe

Recently, several new prolonged-release formulations of buprenorphine have been developed and approved as OMT [49]. In the US, an implantable, six-month formulation (Probuphine®) and a once-monthly subcutaneous polymer-based injection formulation (Sublocade®; also called RBP-6000) are approved and marketed, while in Europe and Australia, a once-weekly and once-monthly subcutaneous lipid-based injection formulation (Buvidal®; also called CAM2038) has recently been approved [50]. This new type of galenics might reshape the landscape of opioid dependence treatment, in a similar way as long-acting antipsychotics have modified the treatment of several psychiatric disorders, or insulin pumps have been a new solution for some people with diabetes mellitus. This article aims to present the main features and scientific data on Buvidal®, and to conceptualize how this new type of long-acting formulation can be integrated into a 'high access' public health strategy with respect to OMTs, in the light of the French experience on the matter.

2. Main features and scientific data on Buvidal®

Buvidal® is a new galenic preparation of buprenorphine, specifically designed to give a prolonged release following injection, so that therapeutic blood levels comparable to those of daily sublingual buprenorphine are achieved [50]. Two forms of Buvidal® are available, one providing buprenorphine exposure for one week following a single subcutaneous injection, and one providing buprenorphine exposure for one month following a single subcutaneous injection [51]. The indications and contra-indications of Buvidal® are similar to those of sublingual buprenorphine [50].

The prolonged release is obtained by a drug delivery technology called FluidCrystal®, which is based on two natural lipids; phosphatidylcholine and glycerol dioleate. The lipids encapsulate the active drug buprenorphine in a crystal matrix, which is formed upon contact with aqueous environment and which then slowly biodegrades. The crystal matrix is forming a highly viscous gel that is normally not visible or palpable after injection into the subcutaneous tissue, as the injected volume is low (0.16–0.64 mL depending on dose). Below are the available scientific data that caught the attention of the authors in order to anticipate what can be expected from this product and its place in the therapeutic arsenal in a country

with an already high access to OMT, and high insurance coverage of subjects with opioid dependence.

2.1. Efficacy

The pivotal efficacy study with Buvidal® was a phase 3, randomized, double-blind, double-dummy, active-controlled, flexible-dose, 24-week study in patients with moderate to severe opioid dependence [52]. The study included 428 participants who had not received OMT for 60 days and therefore were inducted directly on Buvidal®. The study met its primary outcome, with different primary endpoints between the US and Europe due to regulatory requirements, and demonstrated non-inferiority in the use of illicit opioids after treatment with Buvidal® in comparison to treatment with daily sublingual buprenorphine/naloxone. As the primary endpoints were met, a secondary superiority comparison between the treatment arms could be conducted according to the pre-specified statistical test order. This comparison demonstrated that Buvidal® was superior on the cumulative distribution function (CDF) for percentage of opioid-negative urine samples (determined using GCMS and LCMS analysis methods) during treatment weeks 4 to 24 (missing urine samples were imputed as positive; only urine sample results and not subjects self-reported opioid use) with a treatment difference of 20% (26.7% vs 6.7%; P = 0.008). The CDF shows the full range of patient responses, from complete abstinence to no abstinence and thereby provides an overall picture of drug-use behavior across the study population. Buvidal® showed improved drug use behavior in the majority of patients, except in those achieving complete or nearly complete abstinence and in those showing no or nearly no abstinence.

A long-term, open-label, multicenter, phase 3 safety study with flexible dosing of weekly and monthly Buvidal® for 48 weeks was conducted in 227 patients that were both new to treatment (n = 37) or switched from sublingual buprenorphine to Buvidal® (n = 190) [53]. The study treatment period was completed by 167/227 (73.6%) participants. At the end of study, the percentage of opioid-negative urine tests combined with self-reports was 63.0% (17/37) in new-to-treatment participants and 82.8% (111/190) for participants switched from sublingual buprenorphine. The study allowed testing of individualized dosing as the Investigators could titrate doses and adjust dosing intervals (weekly or monthly) as needed for each participant. During the study, approximately 33% of patients received only weekly Buvidal®, 34% only monthly Buvidal® and 33% were initially treated with weekly Buvidal® and were later switched to monthly treatment. The study extended the efficacy findings to include also patients switched from sublingual buprenorphine, in addition to the new-to-treatment patients in the previous phase-3 efficacy study.

2.2. Time to reach efficacy and efficacy maintenance over time

The opinion in our group of experts that Buvidal® could be used as first-line treatment for patients with opioid dependence. The experts based their opinion on the fact that Buvidal® suppresses all types of withdrawal symptoms from day 1 and that blocks both the desire of using an opioid, as well as the effects of injected hydromorphone (18 mg; intramuscular), a euphorigenic opioid, was achieved after the first injection of either 24 mg or 32 mg of the weekly formulation at a plasma concentration of 1.25 ng/mL, reached after 4 hours in a laboratory setting study with 47 opioid-dependent subjects [54]. However, it should be noted that no study has demonstrated the potential of Buvidal® to block the effects of heroin or fentanyl and derivatives .

Buprenorphine plasma concentration data derived from the Phase I and 2 trials with Buvidal® were used to build a pharmacokinetic model estimating the plasma exposure for once-weekly and once-monthly Buvidal® formulations [50,54]. The dosages of Buvidal® indicated by the manufacturer to reach plasma concentrations of buprenorphine that are comparable to those obtained from the daily sublingual formulation and provide adequate exposure for the expected duration of one week and four weeks [51]. Reading those oral – subcutaneous equivalence curves, some of the experts hypothesized from the simulated data that buprenorphine concentrations over time would be more stable after treatment with Buvidal® than during repeated treatment with sublingual buprenorphine.

2.3. Safety profile

In the 48-week long-term safety study 167/227 (73.6%) participants completed the treatment period and five participants (2.2%) discontinued study drug due to a treatment-emergent adverse events [53]. Among those five patients, two discontinued the drug because of injection site side effects. In total 45/227 participants (20.3%) reported mild to moderate injection site reactions at some point of the study, such as pain, swelling, or erythema at the injection site. The other most common adverse events, occurring in ≥5% of participants, were mainly systemic opioid related events such as headache, nausea and vomiting. These events reminded the experts of some commonly reported opioid withdrawal symptoms after treatment initiation with sublingual buprenorphine, especially in patients who are too close from their last full mu-agonist intake. It should be noted that the impact of licit and illicit substance use on safety features was not assessed in this study.

Of course, considering that patients who will receive Buvidal® will be under a long-lasting mu-opioid partial agonist, the need for full mu-opioid agonists, in case of anesthesia for a surgical procedure for example, will have to be anticipated during a planned anesthesiology assessment, with the aim go back to oral buprenorphine during the days prior to the act. In case of emergency, Buvidal® partial agonist effect can still be overcome by '*an adequately titrated dosage of a combination highly potent mu agonists such as fentanyl, non-opioid analgesics and anesthetic compounds. Titration of oral or intravenous short-acting opioid pain medicinal products (immediate release morphine, oxycodone or fentanyl) to the desired analgesic effect in patients treated with Buvidal® might require higher doses. Patients should be monitored during treatment*' [50], and for the time period of remaining Buvidal® in their system.

2.4. Patients' view of depot formulations

There are at least two published qualitative studies on patients under OMT or heroin users on their views of what could be the advantages or disadvantages of weekly or monthly, and administration of depot buprenorphine formulations [55,56]. Participants expressed fears about coercive treatment using those formulations, and about reduced choice and control of their lives [56]. On the other hand, heroin users and patients also expected that long-lasting formulations would fit patients who wanted to avoid thinking about drugs and drug-using associates, or wished to evade the stigma of substance use, or desired 'normality' and 'recovery' [55]. They also expected that weekly-lasting depot formulations would fit patients who are new to OMT, who worry about the safety and reliability/effectiveness of OMT, who want a 'break' from street opioids, or who need contact with services to monitor/support them.

3. Conclusion

The results of the open-label extension trial on Buvidal®found a roughly equal distribution of patients who received only (1) once-weekly, (2) once-monthly, or (3). once-weekly then once-monthly injections The expert opinion provided here on Buvidal® was based on the clinician and researcher expertise of the author group, in the light of the specific experience and model on OMT in the French context. This national treatment policy has been characterized by a facilitated access, mainly through GPs, to reimbursed or free OMT for almost all subjects with opioid dependence in the French population.

As the first available long-lasting buprenorphine formulation, Buvidal® would present several advantages as a new treatment option, either as a first- or a second-line treatment, based on patient preference or specific medical indications.

Compared to oral forms of buprenorphine, Buvidal® might reduce the risk of buprenorphine diversion, such as intranasal use or injection [49]. Buprenorphine misuse has been described in around 20% of buprenorphine-treated opioid dependence patients [36], and is associated with an increased risk of disseminating viral infections [37], in particular in case of use of unclean injecting equipment. Buvidal® could, if prescribed to a substantial number of subjects, reduce those risks at a population level.

The active component of Buvidal® is buprenorphine. As such, Buvidal® should allow for a short time needed to achieve treatment 'steady state', i.e. clinical stabilization, and would not have the large between-subject unpredictable variability of optimal dose that characterizes methadone as an OMT [57]. Furthermore, Buvidal® would provide the treated patients with a prolonged partial agonist effect in case of abrupt treatment cessation, for example if the patients drop out from care programs, are unexpectedly released from prison due to a reduced sentence, or are discharged from a hospital. Those situations constitute a high risk of heroin-related overdoses, due to the loss of previous tolerance to respiratory depression effects. Here the patients would be under buprenorphine treatment for up to one month, or even a little bit longer in some individuals as expected from the reading of the pharmacokinetic simulation studies, so that resuming to illicit opioid use would not necessarily carry the same overdose risk.

Although this new buprenorphine formulation is not without risks, e.g. the risk of inducing withdrawal symptoms if it is administered too closely to the last full opioid receptor agonist dose, or the subcutaneous site reactions observed in 20% of the treated patients in the safety study [46], Buvidal® may improve the overall effectiveness of OMT in several situations. In particular, we have emphasized possible advantages in four clinical situations, i.e. 1) OMT initiation, including in non-specialized addiction medicine care; 2) Discharge from prison or hospital; Diversion/misuse of 3) buprenorphine or 4) methadone; 5) Steady state patients wishing to avoid daily oral taking of the medication. The interest of Buvidal® in these five types of situations should warrant specific assessment in the future. Above all, providing patients with another treatment option will enlarge the proportion of those suffering from opioid dependence to enter a treatment matching their expectations.

4. Expert view on Buvidal® in the light of the French model on buprenorphine

4.1. Context

Taking all those results into account, a group of French experts in opioid dependence treatment management, authors of the present article, wanted to express their own expectations regarding what could be the place for subcutaneous buprenorphine depot formulations such as Buvidal® in the treatment arsenal for opioid dependence. They based their opinion on published evidence and on their previous experience from clinical practice and research. Their reflections were influenced by the French model of OMT: a large-scale, mainly GP-prescribed, use of buprenorphine to treat the majority of patients with opioid dependence disorder in France. They addressed four questions.

(i) what advantages could patients gain by being prescribed Buvidal® rather than a classical high dosage of buprenorphine medication or generic medication?
(ii) what current or innovative prescription rules could ensure the best safety/treatment access ratio for a specialty like Buvidal®?
(iii) what type of patients would specifically benefit from a Buvidal® prescription?
(iv) what pathway through care or care organization would be needed in every day clinical practice to implement Buvidal® prescription in the therapeutic arsenal in a country with an already high access to OMT like France?

5. Expert opinion

5.1. What advantages could patients gain by being prescribed Buvidal® rather than a classical high dosage buprenorphine medication or generic medication?

Regarding the advantages that patients could gain by being prescribed Buvidal® rather than a classical high dosage of buprenorphine medication or generic medication, the group

stated first that some patients may choose subcutaneous Buvidal® because they want to be relieved of the once-daily oral intake of the drug. This group could include: patients with little privacy such as young patients living with their parents; homeless patients housed in collective housing; prisoners who do not want their inmates to see them go to the prison infirmary every day to take a medication; sailors or mobile workers; or stable patients on chronic OMT who are just bored of their daily oral treatment.

Second, the group stated that unstable patients who are not fully compliant with their current sublingual buprenorphine prescription conditions (at least monthly encounters with their physician and pharmacist, or more frequently if required) could take advantages of a depot formulation. Indeed, looking at the pharmacokinetic curves derived from Buvidal® studies [49,53], some of the experts (FV, BR) suggested that the plasma concentrations of buprenorphine may not still reach therapeutic levels in the days following the supposed end of the first dosing interval, which would suggest that unstable patients who are not able to attend fixed appointment could avoid withdrawal symptoms even if they come a few days late.

5.2. What current or innovative prescription rules could ensure the best safety/treatment access ratio for a specialty like Buvidal®?

The group stated that ensuring safety in the administration of this new product was of high importance, because there might be a risk that a thrombus composed of the gel intended to slowly be reabsorbed in the subcutaneous tissue would occlude a small vessel, resulting in damages, if diverted and injected intravenously. It is recommended to ensure that Buvidal® is delivered and administrated subcutaneously only by a healthcare professional (who could be a pharmacist, a nurse or an MD who have received appropriate teaching) so that the opioid-dependent patient, possibly with a past/current history of intravenous use of illicit opioids, would not be tempted to divert Buvidal®. Furthermore, this would be in accordance with the Risk Management Plan (RMP) of the drug as validated by the EMA, saying that Buvidal® is '*intended to be administrated by healthcare professionals only*'.

5.3. What type of patients would specifically benefit from a Buvidal® prescription?

First, considering their clinical practice expertise, the group stated that Buvidal® could be regarded as a good option for OMT initiation in patients actively using illicit opioids during their first encounter with the care system. This could in particular be relevant for regions with lower medical coverage, where everyday visits to ensure an oral supervised delivery in the first days of treatment, if needed, would be difficult to provide. This would also be relevant for patients asking for first OMT initiation at emergency rooms, knowing that there would be at least several days of delay for them to be referred to a specialized addiction care facility. After having received the first Buvidal® injection (preceded by an oral dose of 4 mg buprenorphine and observation for one hour before the Buvidal® injection to ensure tolerability to buprenorphine), the patient can be discharged from the clinic or emergency room with a robust OMT coverage lasting for 7 days.

Second, the group stated that Buvidal® could be regarded as a good treatment option in the specific case of patients with opioid dependence under OMT when they leave prison or inpatient hospital heroin cessation attempts. Those two specific conditions are known to be associated with a high risk of opioid-related deaths by overdose in case of relapse to illicit opioid use in patients with loss of previous tolerance to respiratory depression effects. Because of the partial agonist properties of buprenorphine, a patient who is discharged from prison or hospital after having received a 1-month Buvidal® subcutaneous injection would be expected by the experts to be protected from opioid-related overdose in case of relapse, up to 1 month after the last injection, or even a little bit more in some individuals according to the reading they made of the pharmacokinetic profile of the drug, as suggested by FV and BR [54].

Third, Buvidal® could be regarded as a good second-line treatment option for patients who divert sublingual buprenorphine by snorting or injecting it. Indeed, with Buvidal®, the treatment would be given by healthcare professionals, which would limit the possibility to misuse it. Furthermore, it would ensure long lasting partial agonist coverage so that patients would not feel opioid craving or withdrawal, and at the same time, in case of extra-administration of a pure opioid receptor agonist such as heroin on top of their OMT, would not feel the high. In that way, their risk of changing a slip to a full-blown relapse could be lowered.

Fourth, Buvidal® could be regarded as a good second-line treatment option for patients who divert oral methadone by using illicit opioids at the same time, patients who mix methadone and alcohol to potentiate the effects, and patients who inject oral capsules of methadone for the same reasons. Indeed, indirect evidence suggest that methadone, but not buprenorphine, could potentiate the effect of alcohol use [58]. Furthermore, Buvidal® would ensure long lasting mu-opioid receptor partial agonist coverage so that patients would not feel opioid craving or withdrawal and at the same time, in case of extra-administration of pure opioid agonists such as heroin, morphine, or codeine, would not feel the high, because of the occupancy of the mu-opioid receptors by buprenorphine given its high affinity, and because of its partial agonist properties. In this case, the risk of changing a slip to a full-blown relapse could be lowered. This opioid antagonist effect may nevertheless be insufficient to revert the effects of illicitly produced fentanyl and its derivates, as this agonist is much more potent and could displace buprenorphine from the mu-opioid receptors, the group feared.

Fifth, Buvidal® could be regarded as a good second-line treatment for very stable patients, who are completely abstinent from illicit opioid use and under stable buprenorphine dosage, who would prefer a once-monthly treatment administration at their GP or pharmacist over an everyday oral treatment that they have to remember taking themselves.

5.4. What pathway through care or care organization would be needed in every day clinical practice to implement Buvidal® prescription in the therapeutic arsenal in a country with an already high access to OMT like France?

The group emphasized their attachment to the French care system characterized by of free choice where patients are empowered to go to the physician of their choice for OMT prescription. The group stated that Buvidal® prescription should not be restrained to hospitals or specialized treatment centers, as some GPs could be interested in starting new patients on Buvidal® or switching their patients already on OMT with buprenorphine or methadone to Buvidal® without having to refer them to another facility.

The group insisted on the importance of ensuring a safe administration of the treatment by healthcare professionals, so that unstable patients would not be capable to divert Buvidal® and inject the treatment intravenously, which is a key point of the safety of the treatment.

Thirdly, because in France buprenorphine is mainly prescribed by GPs, and is almost 3-fold more frequently prescribed than methadone, and because access to new galenic formulations is warranted to bridge the gap of unmet needs, the high access rate of Buvidal® was seen as important by most experts in the group. High access to this new formulation could require innovative care pathways, such as administration by local pharmacists, storage and treatment administration by local GPs, or storage and treatment administration by local community nurses. It may also need innovative distribution, storage and administration pathways that are yet to be invented. The price of the product itself, which is unknown to date, as well as the retribution of the professionals involved in the product storage and administration, should be decided by the national social insurance system, keeping in mind the objective of allowing an as large as possible access to this new treatment.

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