10th January 2022

Dear Colleague,

Implementation of Buvidal (buprenorphine prolonged release solution for injection) at We Are With You in Cornwall

We are currently implementing Buvidal in our We Are With You Cornwall service. We will be prescribing this in a small number of suitable patients. If an individual is transferred to your service and is receiving treatment from We Are With You, please contact the relevant We Are With You service to confirm their current treatment - service details can be found at the bottom of this letter. Where an individual is prescribed Buvidal one of our Clinicians will provide the appropriate clinical advice and support to ensure safe and effective continued care of that individual.

Below is some information to make you aware of features of the medication.

Pharmaceutical form, posology and indication

Buvidal is a flexible-dose buprenorphine prolonged-release solution for subcutaneous injection in a pre-filled syringe administered by healthcare professionals only. It is provided in weekly or monthly dose durations at a range of strengths corresponding to existing daily oral doses of buprenorphine. Buvidal is indicated for the treatment of opioid dependence within a framework of medical, social and psychological treatment in adults and adolescents aged 16 years or over and may be prescribed for patients who are switching from daily oral buprenorphine, re-entering treatment, new to treatment or switching from low doses of methadone (30 mg/day or less).

Table 1. Conventional sublingual buprenorphine daily treatment doses and recommended corresponding doses of weekly and monthly Buvidal

Dose of daily SL buprenorphine (mg)	Dose of weekly Buvidal (mg)	Dose of monthly Buvidal (mg)
2 - 6	8	-
8 - 10	16	64
12 - 16	24	96
18 - 24	32	128

SL=sublingual

Table 2. Calculated conversion between Espranor and Buvidal based on difference in bioavailability between Espranor and sublingual Subutex

Dose of daily OM Espranor [a] (mg)	Dose of weekly Buvidal (mg)	Dose of monthly Buvidal (mg)
2 - 4	8	-
6 - 8	16	64
10 - 12	24	96
14 - 18	32	128

OM=oromucosal

[a] 25-30% higher bioavailability for Espranor than for SL Subutex tablet (MHRA Public Assessment Report Decentralized Procedure Espranor 2 mg and 8 mg lyophilizate)

Note that the dose of buprenorphine in mg can differ between products, which needs to be taken into consideration on a product-by-product basis.

Pharmacokinetic properties

After Buvidal injection, the buprenorphine plasma concentration increases with a median time to maximum plasma concentration (T_{max}) of about 24 hours for the weekly injection and 6 – 10 hours for the monthly injection. Elimination of buprenorphine from Buvidal is release-rate limited with a terminal half life ranging from 3-5 days for the weekly injection and 19 – 25 days for the monthly injection.

Safety profile

With the exception of injection site reactions (generally of mild-to-moderate intensity), the safety profile observed with Buvidal in clinical studies was generally consistent with the known safety profile of oral buprenorphine formulations (EPAR 2018, European Medicines Agency 2018. Assessment Report: Buvidal). The adverse reactions most frequently reported for buprenorphine are headache, nausea, hyperhidrosis, insomnia, drug withdrawal syndrome and pain (Buvidal Summary of Product Characteristics).

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events can also be reported to the manufacturer, Camurus AB, by phone: +800 2577 2577

Interactions with other medications and other forms of interactions

No specific interaction studies have been performed with Buvidal. Co-administration of the following products with buprenorphine formulations should be used cautiously:

- **Benzodiazepines:** this combination may result in death due to respiratory depression of central origin. Therefore, dosages must be closely monitored and this combination must be avoided in cases where there is a risk of misuse. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines whilst taking this product, and should also be

cautioned to use benzodiazepines concurrently with this product only as directed by their physician (see section 4.4).

- **Gabapentinoids:** this combination may result in death due to respiratory depression. Herefore, dosages must be closely monitored and this combination must be avoided in cases where there is a risk of misuse. Patients should be cautioned to use gabapentinoids (such as pregabalin and gabapentin) concurrently with this product only as directed by their physician (see section 4.4).
- **Alcoholic drinks or medicinal products containing alcohol** as alcohol increases the sedative effect of buprenorphine.
- **Other central nervous system depressants:** other opioid derivatives (e.g. methadone, analgesics and antitussives); certain antidepressants, sedative H_1-receptor antagonists, barbiturates, anxiolytics other than benzodiazepines, antipsychotics, clonidine and related substances. These combinations increase central nervous system depression. The reduced level of alertness can make driving and using machinery hazardous (see section 4.7).
- **Opioid analgesics:** adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving buprenorphine. The potential for overdose also exists with a full agonist, especially when attempting to overcome buprenorphine partial agonist effects, or when buprenorphine plasma levels are declining.
- **Naltrexone and nalmefene:** these are opioid antagonists that can block the pharmacological effects of buprenorphine. For opioid-dependent patients currently receiving buprenorphine treatment, naltrexone may precipitate a sudden onset of prolonged and intense opioid withdrawal symptoms. For patients currently receiving naltrexone treatment, the intended therapeutic effects of buprenorphine administration may be blocked by naltrexone.

- **CYP3A4 inhibitors:** may inhibit the metabolism of buprenorphine resulting in increased C_{max} and AUC of buprenorphine and norbuprenorphine. Buvidal avoids first-pass effects and CYP3A4 inhibitors (e.g. protease inhibitors like ritonavir, nelfinavir or indinavir, or azole antifungals such as ketoconazole or itraconazole, or macrolide antibiotics) are expected to have less effects on buprenorphine metabolism when co-administered with Buvidal as compared to when co-administered with sublingual buprenorphine. Patients already on Buvidal who start treatment with CYP3A4 inhibitors should be treated with weekly Buvidal and be monitored for signs and symptoms of overtreatment. Conversely, if a patient who is concomitantly treated with Buvidal and a CYP3A4 inhibitor stops treatment with the CYP3A4 inhibitor, the patient should be monitored for symptoms of withdrawal.
- **CYP3A4 inducers:** may induce the metabolism of buprenorphine resulting in decreased buprenorphine levels. Buvidal avoids first-pass effects and CYP3A4 inducers (e.g. phenobarbital, carbamazepine, phenytoin or rifampicin) are expected to have less effects on buprenorphine metabolism when co-administered with Buvidal as compared to when co-administered with sublingual buprenorphine. Patients already on Buvidal who start treatment with CYP3A4 inducers should be treated with weekly Buvidal and be monitored for

signs and symptoms of withdrawal. Conversely, if a patient who is concomitantly treated with Buvidal and a CYP3A4 inducer stops treatment with the CYP3A4 inducer, the patient should be monitored for symptoms of overtreatment.
- **UGT1A1 inhibitors:** may affect the systemic exposure of buprenorphine
- **Monoamine oxidase inhibitors (MAOI):** possible exacerbation of the opioids effects, based on experience with morphine

Management of overdose

General supportive measures should be instituted, including close monitoring of respiratory and cardiac status of the patient. Symptomatic treatment of respiratory depression, following standard intensive care measures, should be instituted. A patent airway and assisted or controlled ventilation must be assured. The patient should be transferred to an environment within which full resuscitation facilities are available. If the patient vomits, precautions must be taken to prevent aspiration. Use of an opioid antagonist (i.e. naloxone) is recommended, despite the modest effect it may have in reversing the respiratory symptoms of buprenorphine compared with its effects on full opioid agonists. The long duration of action of buprenorphine and the prolonged release of Buvidal (see **Pharmacokinetic properties** above) should be taken into consideration when determining the length of treatment needed to reverse the effects of an overdose. Naloxone can be cleared more rapidly than buprenorphine, allowing for a return of previously controlled buprenorphine overdose symptoms.

Management of acute pain

For management of acute pain during continued use of Buvidal, a combination of use of opioids with high mu-opioid receptor affinity (e.g. fentanyl), non-opioid analgesics and regional anaesthesia might be necessary. 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.

Further information on Buvidal can be found in the Summary of Product Characteristics available here:

https://www.medicines.org.uk/emc/product/9705/smpc (weekly)

https://www.medicines.org.uk/emc/product/9706/smpc (monthly)

Please do not hesitate to get in contact if you have any questions regarding the content of this letter.

Kind Regards

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February 2020: UK-BUV-2000016

Abbreviated Prescribing Information for Buvidal (buprenorphine) prolonged-release solution for injection

Please refer to the Summary of Product Characteristi (SmPC) before prescribing.

Presentations: Prolonged-release solution for injection pre-filled syringes containing buprenorphine for week injection (8 mg, 16 mg, 24 mg, 32 mg) or monthly injectic (64 mg, 96 mg, 128 mg). **Indication:** Treatment of opio dependence within a framework of medical, social ar psychological treatment. Treatment is intended for use adults and adolescents aged 16 years or ove **Dosage and Administration:** Administration of Buvidal® restricted to healthcare professionals. Appropriat precautions, such as to conduct patient follow-up visits wit clinical monitoring to the patient´s needs, should be take when prescribing and dispensing buprenorphine. Take-hom use or self-administration of the product by patients is n allowed. *Precautions to be taken before initiation treatment:* To avoid precipitating symptoms of withdrawa treatment with Buvidal® should be started when objectiv and clear signs of mild to moderate withdrawal are eviden For patients using heroin or short-acting opioids, the initi dose of Buvidal® must not be administered until at lea 6 hours after the patient last used opioids. For patien receiving methadone, the methadone dose should b reduced to a maximum of 30 mg/day before startir treatment with Buvidal® which should not be administere until at least 24 hours after the patient last received methadone dose. Buvidal® may trigger withdraw symptoms in methadone-dependent patients. *Initiation treatment in patients not already receiving buprenorphin* Patients not previously exposed to buprenorphine shou receive a sublingual buprenorphine 4 mg dose and b observed for an hour before the first administration weekly Buvidal® to confirm tolerability to buprenorphin The recommended starting dose of Buvidal® is 16 mg, wit one or two additional 8 mg doses at least 1 day apart, to target dose of 24 mg or 32 mg during the first treatmer week. The recommended dose for the second treatmer week is the total dose administered during the week initiation. Treatment with monthly Buvidal® can be starte after treatment initiation with weekly Buvidal®, accordance with the dose conversion in Table 2 of the fu SmPC and once patients have been stabilised on week treatment (four weeks or more, where practical). *Switchir from sublingual buprenorphine products to Buvidal* Patients treated with sublingual buprenorphine may b switched directly to weekly or monthly Buvidal®, starting c the day after the last daily buprenorphine sublingu treatment dose in accordance with the dosir recommendations in the full SmPC. *Maintenance treatmer and dose adjustments:* Buvidal® can be administered week or monthly. Doses may be increased or decreased an patients can be switched between weekly and monthly products according to individual patient's needs and treating physician's clinical judgement as per recommendations in the full SmPC. Following switching, patients may need closer monitoring. Assessment of long-term treatment is based on 48-week data. *Supplemental dosing:* A maximum of one supplemental Buvidal® 8 mg dose may be administered at an unscheduled visit between regular weekly and monthly doses, based on individual patient's temporary needs. The maximum dose per week for patients who are on weekly Buvidal® treatment is 32 mg with an additional 8 mg dose. The maximum dose per month for patients who are on monthly Buvidal® treatment is 128 mg with an additional 8 mg dose. *Missed doses*: To avoid missed doses, the weekly dose may be administered up to 2 days before or after the weekly time point, and the monthly dose may be administered up to 1 week before or after the monthly time point. If a dose is missed, the next dose should be administered as soon as practically possible. *Termination of treatment*: If Buvidal® treatment is discontinued, its prolonged-release characteristics and any withdrawal symptoms experienced by the patient must be considered. If the patient is switched to treatment with sublingual buprenorphine, this should be done one week after the last weekly dose or one month after the last monthly dose of Buvidal® according to the recommendations in the full SmPC. ***Method of administration**:* Buvidal® is intended for subcutaneous administration only. It should be injected slowly and completely into the subcutaneous tissue of different areas (buttock, thigh, abdomen, or upper arm), provided there is enough subcutaneous tissue. Each area can have multiple injection sites. A minimum of 8 weeks should be left before re-injecting a previously used injection site with the weekly dose.

Contraindications: Hypersensitivity to the active substance or to any of the excipients. Severe respiratory insufficiency. Severe hepatic impairment. Acute alcoholism or *delirium tremens.* **Special warnings and precautions for use:** Care must be taken to avoid inadvertent injection of Buvidal®. The dose must not be administered intravascularly (intravenously), intramuscularly or intradermally. Intravascular such as intravenous injection would present a risk of serious harm as Buvidal forms a solid mass upon contact with body fluids, which potentially could cause blood vessel injury, occlusion, or thromboembolic events. To minimise the risk of misuse, abuse or diversion, appropriate precautions should be taken when prescribing and dispensing buprenorphine. Healthcare professionals should administer Buvidal directly to the patient. Take-home use or self-administration of the product by patients is not allowed. Any attempts to remove the depot should be monitored throughout treatment. The prolonged-release properties of the product should be considered during treatment

including initiation and termination. In particular, patien with concomitant medicinal products and/or co-morbiditie should be monitored for signs and symptoms of toxicit overdose or withdrawal caused by increased or decrease levels of buprenorphine. Buprenorphine should be use with care in patients with respiratory insufficienc Buprenorphine may cause drowsiness particularly whe taken together with alcohol or central nervous syste depressants such as benzodiazepines, tranquiliser sedatives, gabapentinoids or hypnotics. Buprenorphine is partial agonist at the mu-opiate receptor and chron administration can produce opioid dependence. Baselin liver function tests and documentation of viral hepatit status are recommended prior to starting therap Buprenorphine products have caused precipitate withdrawal symptoms in opioid-dependent patients whe administered before the agonist effects resulting fro recent opioid use or misuse have subsided. Buprenorphin should be used with caution in patients with moderat hepatic impairment. Hepatic function should be monitore regularly whilst on treatment. The use of buprenorphine contraindicated in patients with severe hepatic impairmen Caution is recommended when dosing patients with seve renal impairment. Caution should be exercised whe co-administering Buvidal® with other medicinal produc that prolong the QT interval and in patients with a history long QT syndrome or other risk factors for QT prolongatio For management of acute pain during continued use Buvidal®, a combination of use of opioids with hig mu-opioid receptor affinity (e.g. fentanyl), non-opio analgesics and regional anaesthesia might be necessar Titration of oral or intravenous short-acting opioid pai medicinal products (immediate-release morphin oxycodone or fentanyl) to the desired analgesic effect patients treated with Buvidal® might require higher dose Patients should be monitored during treatmen *Interactions*: No interaction studies have been performe with Buvidal®. See SmPC for precautions whe co-administering buprenorphine with other drugs. *Fertilit pregnancy and lactation*: Buprenorphine should be use during pregnancy only if the potential benefit outweighs th potential risk to the foetus. Towards the end of pregnanc buprenorphine may induce respiratory depression in th newborn infant even after a short period of administratio Buprenorphine and its metabolites are excreted in huma breast milk and Buvidal® should be used with caution durir breast-feeding. There are no or limited data on effects buprenorphine on human fertility. *Driving and operatir machines:* Buprenorphine has minor to moderate influence on the ability to drive and use machines when administered to opioid-dependent patients. The patient should be cautioned not to drive or operate hazardous machinery whilst taking this medicine until it is known how the patient is affected by the medicine.

Undesirable effects: The adverse reactions most frequently reported for buprenorphine are headache, nausea, hyperhidrosis, insomnia, drug withdrawal syndrome and pain. *Very common (≥ 1/10):* insomnia, headache, nausea, hyperhidrosis, drug withdrawal syndrome, pain. *Injection site reactions:* in the double-blind, phase 3 efficacy trial, injection site-related adverse reactions were observed in 36 (16.9%) of the 213 patients (5% of the administered injections) in the Buvidal® treatment group. The most common adverse reactions were injection site pain (8.9%), injection site pruritus (6.1%) and injection site erythema (4.7%). The injection site reactions were all mild or moderate in severity and most events were transient. See full SmPC for further details of adverse reactions. **Overdose:** General supportive measures should be instituted, including close monitoring of respiratory and cardiac status of the patient. Symptomatic treatment of respiratory depression, following standard intensive care measures, should be instituted. The long duration of action of buprenorphine and the prolonged release from Buvidal®, should be taken into consideration when determining length of treatment needed to reverse the effects of an overdose.

Package quantities and price: Pack contains 1 pre-filled syringe with stopper, needle, needle shield, safety device and 1 plunger rod. Pre-filled syringes for weekly injection (8 mg, 16 mg, 24 mg, 32 mg): £55.93. Pre-filled syringes for monthly injection (64 mg, 96 mg, 128 mg): £239.70. **Marketing authorisation numbers:** EU/1/18/1336/001, EU/1/18/1336/002, EU/1/18/1336/003, EU/1/18/1336/004, EU/1/18/1336/005, EU/1/18/1336/006, EU/1/18/1336/007. **Legal category:** Prescription-only medicine. Further information is available from the **Marketing Authorisation Holder:** Camurus AB, Ideon Science Park, SE-223 70 Lund, Sweden. Phone: +800 2577 2577. **Date of preparation:** January 2019 REF-00003

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events can also be reported to Camurus AB by phone: +800 2577 2577.