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1. Executive Summary

Opioid agonist treatment (OAT) is a first-line treatment for people with opioid dependence[1]. A recent development in the treatment of opioid dependence is the introduction of long-acting injectable (LAI) formulations of buprenorphine[2]. Listed on the Pharmaceutical Benefit Scheme (PBS) in September 2019, LAI buprenorphine is administered via weekly[3] or monthly[4,5] subcutaneous injections, providing an alternative treatment option for opioid dependence that reduces the frequency of dosing visits and increases flexibility, compared to oral methadone and sublingual buprenorphine[6,7].

There have been reports of variation in the ability of LAI buprenorphine to maintain adequate symptom control between monthly doses[8]. The average dosing interval (i.e., the number of days between consecutive doses) for LAI buprenorphine in observational or real-world settings, is currently unknown. Quantifying variation in dosing intervals, as observed in clinical practice, will help inform both the management of clients and the cost effectiveness of LAI buprenorphine as a treatment option for opioid dependence.

This report assesses real-world dosing intervals for monthly LAI buprenorphine (Buvidal® Monthly and Sublocade®) using deidentified observational data collected from three service providers across three states (New South Wales, Victoria and South Australia) in Australia between October 2019 and July 2022.

Key Findings

- The study included 371 clients who each received two or more doses of monthly LAI buprenorphine, for a total of 3,765 dosing intervals.
- The median dosing interval for both Buvidal® Monthly and Sublocade® aligned with the recommended dosing interval of 28 days.
- Half (50%) of all dosing intervals were between 26 and 31 days for Buvidal® Monthly and 27 and 31 days for Sublocade®.

2. Background & Methods

2.1. Background

Opioid agonist treatment (OAT) is a first-line treatment for people with opioid dependence[1]. Involving regular and long-term pharmacotherapy with an opioid agonist or partial agonist, OAT has the broad goal of reducing harm due to non-medical use of opioids[9]. Methadone and buprenorphine are the most commonly available OAT medicines in most countries[10,11]. These medicines are listed on the Australian Government's Pharmaceutical Benefit Scheme (PBS), the national program that subsidises the cost of approved medicines.

A recent development in the treatment of opioid dependence has been the introduction of long-acting injectable (LAI) formulations of buprenorphine[2], including Buvidal® and Sublocade®. With PBS listing in September 2019, depending on the formulation, LAI buprenorphine is administered via weekly[3] or monthly[4,5] subcutaneous injections, providing an alternate treatment option to daily oral methadone and sublingual buprenorphine, reducing the frequency of dosing visits and improving the flexibility of treatment for clients[6,7].

A qualitative study in Australia showed that OAT clients reported variation in the efficacy of LAI buprenorphine in maintaining adequate symptom management throughout the prescribed dosing interval[8]. Guidelines[2,12] recommend:

- Sublocade® doses may be administered up to 2 days ahead of, or up to 14 days after the 28-day interval (i.e., between 26 to 42 days since the last injection).
- Buvidal® Monthly doses may be administered up to 1 week before or after the monthly time point (i.e., between 21 to 35 days since the last injection),
- Buvidal® Weekly doses may be administered up to 2 days before or after the weekly time point (i.e., between 5 to 9 days since the last injection), and
- Supplemental, or 'top-up', Buvidal® Weekly 8mg doses may be used if clinically indicated.

The extent to which LAI buprenorphine dosing intervals (i.e., the number of days between consecutive doses) in real-world settings aligns with these guidelines is currently unknown. Quantifying the variation in dosing intervals observed in clinical practice will inform both the clinical management of clients and the cost effectiveness of LAI buprenorphine as a form of OAT. Patterns of dosing intervals are of most interest for monthly formulations of LAI buprenorphine, which are

used more frequently in Australia[13,14] and likely to have more variability compared with weekly formulations.

2.2. Aims

This report aims to estimate real-world dosing intervals for monthly LAI buprenorphine in Australia, by brand (Buvidal® Monthly and Sublocade®).

2.3. Methods

2.3.1. Study design and time period

This was an observational descriptive study based on a chart review of data collected between October 2019 to July 2022 (inclusive).

2.3.2. Data source

This report is an extension of the CoLAB trial, a prospective single-arm, open-label trial of Sublocade® among 100 clients with opioid dependence attending six general practitioner and specialist drug treatment service providers. The primary objective of CoLAB was to assess treatment retention at 48 weeks after initiation of Sublocade; a secondary objective was to evaluate dosing schedule variations[12].

Deidentified dosing data were collected on clients attending three of the six service providers participating in the Community Long-Acting Buprenorphine (CoLAB) study[12]. Participating OAT providers were in the Australian states of New South Wales (NSW), Victoria (VIC) and South Australia (SA) and included a hospital outpatient clinic, drug and alcohol service, and general practice. Information on the product, dose and date of administration were collected. No client (sociodemographic or clinical) information was provided. All doses of Buvidal® Monthly and Sublocade® administered to the study population at the participating sites over the observation period were included.

2.3.3. Study population

The study cohort included clients administered at least two monthly LAI buprenorphine products at a participating service provider between October 2019 and July 2022, including, but not limited to, clients in the COLAB single-arm cohort. Clients were excluded if they only had one dose of monthly LAI buprenorphine, only weekly LAI buprenorphine, or were administered both Buvidal® Monthly and Sublocade® during the study period.

2.3.4. Medicines

Available monthly LAI buprenorphine formulations included in this report are presented in Table 1.

Table 1. Monthly long-acting injectable buprenorphine formulations available in Australia for opioid agonist treatment

Active Ingredient	Brand name	Strength (mg)	Entry to market†
Buprenorphine	Buvidal monthly	64	September 2019[15]
Buprenorphine	Buvidal monthly	96, 128	September 2019[15]
Buprenorphine	Buvidal monthly	160	May 2022[15]
Buprenorphine	Sublocade	100	May 2020[15]
Buprenorphine	Sublocade	300	May 2020[15]

†Entry to market based on PBS listing as part of the Australian Opioid Dependence Treatment Program

2.3.5. Dosing intervals

Dosing intervals were calculated by counting the days between consecutive doses. More than 56 days between injections was considered non-adherence[12] (i.e., a gap in treatment). Rarely, two injections were administered on the same day to the same client, resulting in a dosing interval of '0 days'. For example, when the Sublocade® 300mg injection was out of stock some clients received two Sublocade® 100mg injections on the same day, and before Buvidal® Monthly 160mg became available, some clients received Buvidal® Monthly 96mg and 64mg on the same day.

2.3.6. Statistical Analysis

Data from the three service providers were pooled to estimate an average dosing interval, in days, for monthly LAI buprenorphine, stratified by brand. Analysis was undertaken at both the person-level and pack-level. Analyses at the person-level excluded dosing intervals of '0 days' when calculating the average, to help estimate real-world dosing intervals in general terms. Analyses at the pack-level included dosing intervals of '0 days' when calculating the average, to produce estimates specifically relevant to converting data on packs sold into an estimate of the number of clients treated with LAI buprenorphine. For example, if a client was given two doses of Buvidal® Monthly on the same day and then one dose of Buvidal® Monthly 28 days later, the average dosing interval for the person-level analysis would be 28 days (28 days ÷ 1 dosing interval) and 14 days ([0 + 28 days] ÷ 2 dosing intervals) for the pack-level analysis.

Summary statistics, including medians, interquartile ranges and means were produced. The 95% confidence intervals of the mean were adjusted for clustering, taking into account the within-subject and -site nature of the data.

Analyses were conducted using SAS Enterprise Guide 9.4 (SAS Institute Inc., Cary, NC, USA) and Microsoft Excel for Microsoft 365 (Microsoft, Seattle, WA, USA).

Ethics approval

The study received ethics approval from the St Vincent's Hospital Sydney Human Research Ethics Committee (Ref. HREC/18/SVH/221 amendment).

3. Guide to interpretation of results

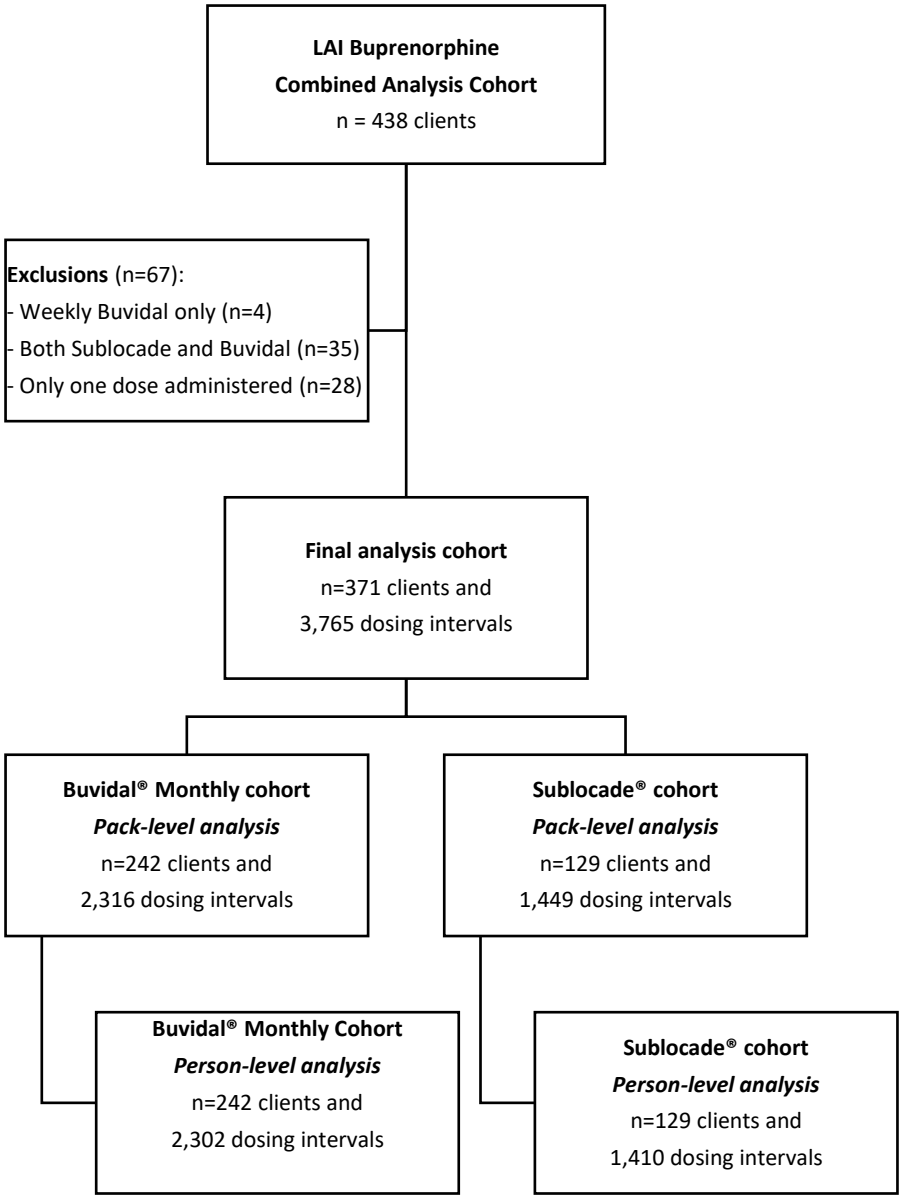
- Results from the person-level analysis estimate the average number of days before another dose of LAI buprenorphine is required.
- Supplemental or 'top up' doses with weekly LAI buprenorphine were not included in these analyses.
- Dosing intervals may reflect the time between scheduled appointments, often every 4 weeks, rather than the client's actual requirement for another dose. Doses may be administered opportunistically ahead of the 4-week mark if the client presents early, for another reason, and it's deemed clinically appropriate.
- Some clients were receiving Sublocade under the CoLAB trial conditions[12] but most clients (and all those on Buvidal® Monthly) were receiving LAI buprenorphine as part of routine clinical care.
- The pack-level analysis estimates the average number of days before another dose is required, allowing for same day doses with 0 days between them. These results will only be relevant in certain contexts, particularly when converting the number of packs sold into an estimate of the number of clients treated.
- The estimates provided in this report are based on data from clients attending one of three providers across NSW, VIC and SA. Doses administered by other providers are not captured in this analysis.
- These findings may not be representative of all clients and OAT provider types in Australia. While not nationally representative, the included sites are representative of a range of common treatment service models in Australia.

4. Findings

4.1. Dosing intervals

From a total of 438 clients, 371 clients met inclusion criteria, the majority (65%) of whom were on Buvidal® Monthly (see **Figure 1**). Clients had between 2 to 32 doses of LAI buprenorphine during the study period with a median and mean of 9 and 11 doses, respectively.

Figure 1. Study selection flowchart



Person-level analysis

The median and mean dosing intervals for Buvidal monthly were 28 and 29.0 days respectively, based on 2,302 individual dosing intervals. For Sublocade®, the median and mean dosing intervals were 28 and 29.2 days, respectively, based on 1,410 dosing intervals (see **Table 2**). There were 14 dosing intervals of '0 days' excluded from the Buvidal® Monthly person-level analysis (0.6% of 2,316 dosing Buvidal® Monthly dosing intervals) and 39 dosing intervals of '0 days' excluded from the Sublocade® person-level analysis (2.3% of 1668 Sublocade® dosing intervals) (**Figure 1**).

Fifity percent (50%) of dosing intervals were between 26 and 31 days for Buvidal® monthly and 27 and 31 days for Sublocade® (see **Table 2**: Q1-Q3). **Figure 2** displays the frequency of dosing intervals with the most common value, or major mode, at 4 weeks (28 days) and smaller peaks (minor modes) at 3 weeks, for Buvidal® Monthly, and 5 weeks for both brands.

Pack-level analysis

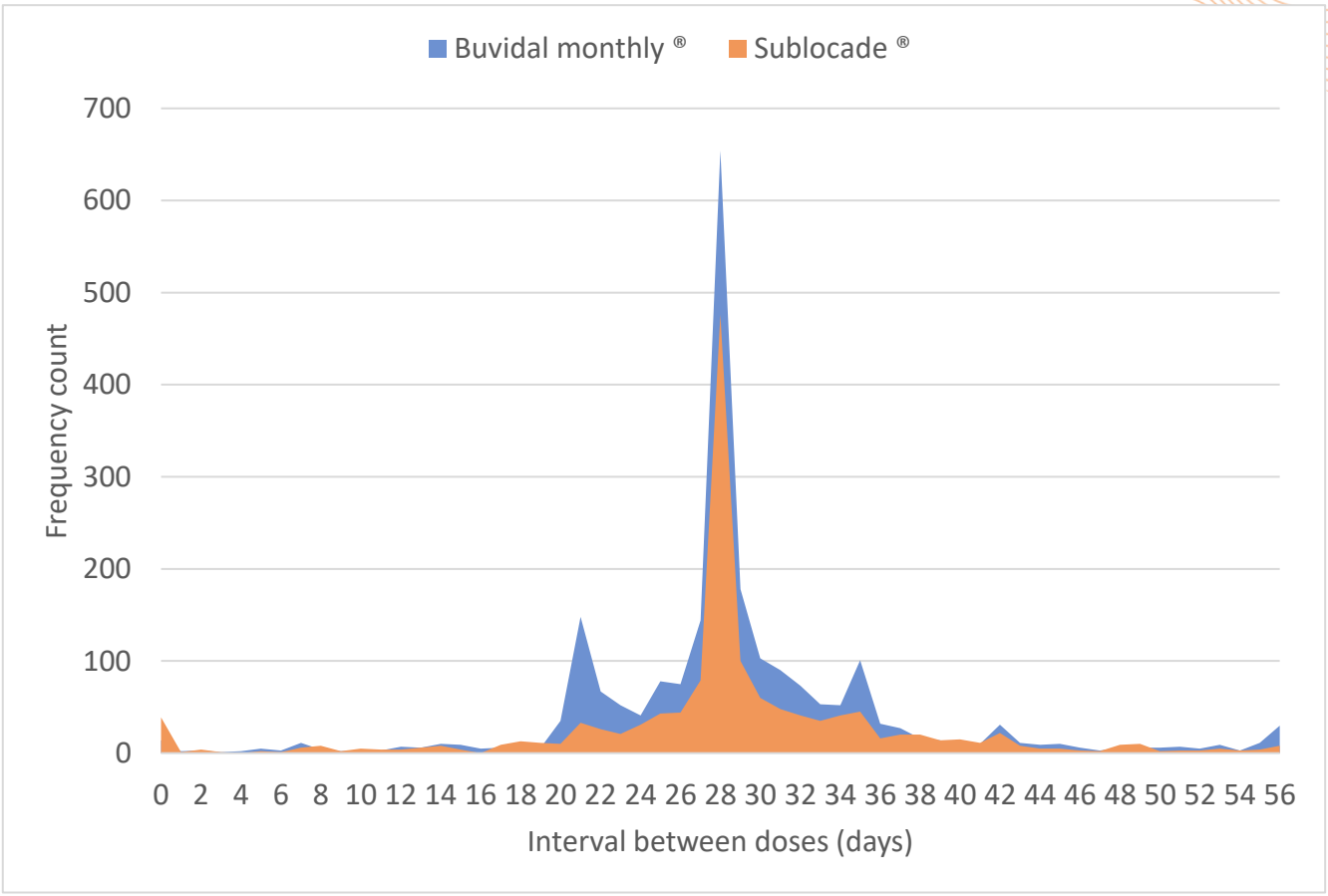
The median and mean dosing intervals for Buvidal® Monthly were 28 and 28.8 days respectively, based on 2,316 individual dosing intervals. For Sublocade®, the median and mean dosing intervals were 28 and 28.4 days, respectively, based on 1,449 dosing intervals (**Table 2**).

Table 2. Summary statistics of dosing intervals for Buvidal® Monthly and Sublocade® from observational Australian data (2019 to 2022)

Brand	Analysis	Dosing interval (days)						
		Number	Range	Median	Q1-Q3	Mean	Standard Deviation	Mean 95%CI
Buvidal® monthly (n=242 clients)	Person-level†	2,316	1-56	28.0	26-31	29.0	7.6	28.4 - 29.5
	Pack-level‡	2,302	0-56	28.0	26-31	28.8	7.9	28.2 - 29.4
Sublocade® (n=129 clients)	Person-level†	1,410	1-56	28.0	27-31	29.2	7.5	28.5 - 29.9
	Pack-level‡	1,449	0-56	28.0	27-31	28.4	8.8	27.5 - 29.3

† The person-level analysis excluded dosing intervals of 0 days. ‡ The pack-level analysis included dosing intervals of 0 days.

Figure 2. Distribution of dosing intervals for Buvidal® Monthly (n=2,728 doses) and Sublocade® (n=1,668 doses) from observational Australian data (2019 to 2022)



5. Discussion

To estimate real-world dosing intervals for monthly LAI buprenorphine (Buvidal® Monthly and Sublocade®) in the Australian context, analysis of data collected from three service providers (a hospital outpatient clinic, drug and alcohol service and specialist GP practice) was conducted. Among 371 clients the median dosing interval for both Buvidal® Monthly and Sublocade® aligned with the recommended dosing interval of 28 days[4,5] (based on 3,765 dosing intervals). Fifty (50%) of all dosing intervals were between 26 and 31 days for Buvidal® Monthly and 27 to 31 days for Sublocade®.

Despite differences in guidelines for administering Buvidal® and Sublocade®, the distribution of dosing intervals for both brands were similar. It is recommended that Buvidal® Monthly be administered up to 1 week before or after the 28-day interval and this was evident in the frequency distribution graph (Figure 2), with the most frequent dosing interval, or major mode, at 28 days, a smaller peak (minor mode) at 21 days and a third peak at 35 days. It is recommended that Sublocade® be administered between 2 days before, to 2 weeks after, the 28-day interval – as such we might have expected to see a 'left skewed' frequency distribution with a greater proportion of dosing intervals above the 28-day interval than below, but this was not evident. Like Buvidal® Monthly, the most frequent dosing interval for Sublocade® was 28 days, with a relatively even spread of dosing intervals from 21 to 35 days (Figure 2).

Among this study cohort, dosing intervals are likely to be influenced by the time between scheduled appointments, often every 4 weeks. It is possible that OAT services providing treatment to clients on a 'drop-in' basis may show greater variation in dosing intervals than OAT clinics with scheduled appointments. Conversely, settings with less flexibility in OAT provision, such as prisons, might show less variation.

Quantifying the extent of dosing schedule variations, as observed in clinical practice, will help inform both the management of clients and the cost effectiveness of LAI buprenorphine as a treatment option for opioid dependence.

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