

## Long-acting formulations: a paradigm shift in treatment?

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## Disclosures

- Funded to participate in studies sponsored by Braeburn Inc. and Camurus AB
- Received consultation fees for participation in advisory boards and completing consultant's reports for Indivior PLC and Mundipharma International Ltd





## Disclaimer

• For ease of understanding, products mentioned in this presentation are referred to by their trade names. This content has been developed for CME use; i.e. the use of trade names is not intended to be for brand marketing purposes and the data complies with CME principles of fair balance.





## Learning objectives

After this talk participants should be able to:

- Distinguish between buprenorphine (BPN) depot products
- Discuss the role of depot BPN in clinical practice



## **BPN** overview

- Pharmacology
  - $\circ$  High affinity but limited intrinsic activity at the  $\mu\text{-receptor}$
  - $\circ$   $\,$  Slow rate of dissociation
  - $\circ$   $\,$  Low potential for overdose
  - Low toxicity
  - Reduces exogenous opioid binding
- Clinical use in opioid dependence
  - Available since the 1990s in Europe
  - Available in combination formulation with naloxone (NX)
  - o Available as a sublingual (SL) tablet and film

#### Long-acting (depot) formulations have recently become available



EMCDDA. Annual report: 2005 Buprenorphine – treatment, misuse and prescription practices. <u>http://www.emcdda.europa.eu/system/files/publications/365/sel2005\_3-en\_69710.pdf</u> [Accessed May 2019] Rosenthal RN and Goradia VV. Drug Des Devel Ther. 2017;11:2493–505



### Overview of BPN depot products

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## Depot BPN

Depot BPN is becoming available as weekly or monthly subcutaneous (SC) injections

#### Rationale for the development of depot BPN

- Reduce **frequency** of clinic/pharmacy visits
- Reduce **costs**
- Increase convenience
- Improve adherence (fewer missed doses) and therefore outcomes
- Less diversion of medication
- Less risk of injecting BPN designed for SL use (safety and community perceptions)





## Depot BPN as Buvidal® (CAM2038)

#### Weekly and monthly dose options

- Weekly: 8 mg, 16 mg, 24 mg and 32 mg
- Monthly: 64 mg, 96 mg and 128 mg



- Ready-for-use in prefilled syringe (0.16–0.67 ml)
- **SC injection** by healthcare professional (HCP) (not to be dispensed to patient)
- Approved in Europe and Australia
- Stored at room temperature
- Injections rotated between multiple sites (buttock, abdomen, arm, thigh)

Camurus AB. Summary of product characteristics: Buvidal 64/96/128 mg prolonged-release solution for injection. <a href="https://www.medicines.org.uk/emc/product/9706/smpc">https://www.medicines.org.uk/emc/product/9706/smpc</a> [Accessed May 2019] Camurus AB. Summary of product characteristics: Buvidal 8/16/24/32 mg prolonged-release solution for injection. <a href="https://www.medicines.org.uk/emc/product/9705/smpc">https://www.medicines.org.uk/emc/product/9706/smpc</a> [Accessed May 2019] Camurus AB. Summary of product characteristics: Buvidal 8/16/24/32 mg prolonged-release solution for injection. <a href="https://www.medicines.org.uk/emc/product/9705/smpc">https://www.medicines.org.uk/emc/product/9705/smpc</a> [Accessed May 2019] Camurus Pty Ltd. Australian product information: Buvidal weekly. <a href="https://www.medicines.org.au/files/capbuviw.pdf">https://www.medicines.org.au/files/capbuviw.pdf</a> [Accessed May 2019] Camurus Pty Ltd. Australian product information: Buvidal monthly. <a href="https://www.medicines.org.au/files/capbuvim.pdf">http://www.medicines.org.au/files/capbuvim.pdf</a> [Accessed May 2019] Camurus Pty Ltd. Australian product information: Buvidal monthly. <a href="https://www.medicines.org.au/files/capbuvim.pdf">http://www.medicines.org.au/files/capbuvim.pdf</a> [Accessed May 2019] Camurus Pty Ltd. Australian product information: Buvidal monthly. <a href="https://www.medicines.org.au/files/capbuvim.pdf">http://www.medicines.org.au/files/capbuvim.pdf</a> [Accessed May 2019] Tiberg F. Presented at SSA Annual Meeting 2018, Newcastle, UK, 8–9 November





## Buvidal® PK profile



- Population pharmacokinetic (PK) analysis and modelling based on data from four clinical studies (N = 236)
- Diagnostic testing demonstrated predictive BPN concentrations and good agreement between observed and predicted data percentiles

#### Weekly Buvidal® versus daily SL BPN



Tiberg F and Johnsson M. J Drug Delivery Science Techn. 2011;21(1):101–9 Tiberg F. Presented at SSA Annual Meeting 2018, Newcastle, UK, 8–9 November





## Buvidal<sup>®</sup>: active-control RCT evidence

- Double-blind, double-dummy
- SC depot BPN (Buvidal<sup>®</sup>) versus SL BPN+NX
- Treatment-seeking adults with moderate-to-severe opioid use disorder
- Flexible dosing according to patient needs and clinical judgment







## Buvidal<sup>®</sup>: active-control RCT evidence



Buvidal<sup>®</sup> was **non-inferior** to SL BPN+NX





## Buvidal<sup>®</sup>: long-term safety evidence

- Open-label, observational, 48-week trial
- 227 patients with opioid use disorder in > 30 centres across Europe, the US and Australia



#### Urine analysis







## Buvidal®: patient satisfaction

• Patient-reported satisfaction with Buvidal® versus SL BPN







## Buvidal<sup>®</sup>: clinical considerations

#### Initiation and dosing

- Patients stabilised on SL BPN treatment can be switched directly to Buvidal<sup>®</sup> (in line with SL dose)
- BPN-naïve: initiate with Buvidal<sup>®</sup> after confirming tolerance with SL BPN 4 mg test dose Fixed dosing schedule: 16 mg with 1 or 2 additional 8 mg doses (at least 1-day apart) up to 24 mg or 32 mg

#### Pharmacology

- Peak effects seen within 6–24 hours of dose
- Accumulation of BPN plasma levels with time (steady state after 3–4 injections)
- Weekly dose every 5–9 days ( $t_{1/2}$  = 3–5 days)
- $_{\odot}$  Monthly dose every 3–5 weeks (t<sub>1/2</sub> = 19–25 days)

#### Supplemental BPN doses

- Top-up Buvidal<sup>®</sup> 8 mg doses (up to 24 hours apart)
- SL BPN if necessary

#### Adverse events

 Local site reactions (redness, pain) generally mild and transient in about 10–15% patients

#### Dose conversion table

Daily SL BPN	Buvidal® weekly	Buvidal® monthly
≤ 6mg	8 mg	No equivalent
8–10 mg	16 mg	64 mg
12–16 mg	24 mg	96 mg
18–24 mg	32 mg	128 mg

Camurus AB. Summary of product characteristics: Buvidal 64/96/128 mg prolonged-release solution for injection. <u>https://www.medicines.org.uk/emc/product/9706/smpc</u> [Accessed May 2019] Camurus AB. Summary of product characteristics: Buvidal 8/16/24/32 mg prolonged-release solution for injection. <u>https://www.medicines.org.uk/emc/product/9705/smpc</u> [Accessed May 2019] Lintzeris et al. NSW Health. Sydney. 2019 (in press)





## Depot BPN as SUBLOCADE™ (RBP-6000)

#### Monthly dose options

• 100 mg and 300 mg



- Ready-for-use in prefilled syringe
  - 0.5 ml or 1.5 ml
- Four-week SC injection by HCP (not to be dispensed to patient)
- **Cold-storage requirements** (4°C), can be stored at room temperature for 7 days
- Approved in **the US** and **Canada**; Australia and some EU countries submitted
- Single injection site (abdomen)





## SUBLOCADE<sup>TM</sup> PK profile







## SUBLOCADE<sup>TM</sup>: RCT evidence

- Double-blind, 6-month, placebo-controlled
- Treatment-seeking adults aged 18–65 years who had moderate or severe opioid use disorder







## SUBLOCADE<sup>TM</sup>: RCT evidence



- Abstinence was **significantly higher** with both doses of SUBLOCADE™
- No difference between SUBLOCADE<sup>™</sup> doses





## SUBLOCADE<sup>TM</sup>: clinical considerations

#### Initiation and dosing

- Must be on SL BPN ≥ 7 days before starting SUBLOCADE<sup>™</sup>
- Commence 300 mg monthly for first two doses

(2 x 4 weeks)

- Thereafter, choose between 100 mg or 300 mg injections
- Recommend no fewer than 26 days between doses, and up to 14 days 'late' without concerns (i.e. 4–6 week doses)

#### Pharmacology

- Peak effects seen within 24 hours post dose
- 4–8 weeks, depends on dose and duration;  $t_{1/2} = 43-60$  days
- $\circ$  Steady state equilibrium after 3–5 doses

#### Supplemental BPN doses

 Add low dose SL BPN (no 'top up' depot doses) if required

#### Adverse events

- Local site reactions (redness, pain) generally mild and transient in about 10–20% patients
- Small 'lump' common





## PK parameters

#### Steady state SL BPN, SUBLOCADE<sup>™</sup> and Buvidal<sup>®</sup> C<sub>min</sub>, C<sub>avg</sub> and C<sub>max</sub>



Lintzeris et al. NSW Health. Sydney. 2019 (in press)



### Implementation considerations

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## Availability of Buvidal®



Camurus AB. Summary of product characteristics: Buvidal 64/96/128 mg prolonged-release solution for injection. <a href="https://www.medicines.org.uk/emc/product/9706/smpc">https://www.medicines.org.uk/emc/product/9706/smpc</a> [Accessed May 2019] Camurus AB. Summary of product characteristics: Buvidal 8/16/24/32 mg prolonged-release solution for injection. <a href="https://www.medicines.org.uk/emc/product/9705/smpc">https://www.medicines.org.uk/emc/product/9706/smpc</a> [Accessed May 2019] Camurus AB. Summary of product characteristics: Buvidal 8/16/24/32 mg prolonged-release solution for injection. <a href="https://www.medicines.org.uk/emc/product/9705/smpc">https://www.medicines.org.uk/emc/product/9705/smpc</a> [Accessed May 2019] Camurus Pty Ltd. Australian product information: Buvidal weekly. <a href="https://www.medicines.org.au/files/capbuviw.pdf">https://www.medicines.org.au/files/capbuviw.pdf</a> [Accessed May 2019] Camurus Pty Ltd. Australian product information: Buvidal monthly. <a href="https://www.medicines.org.au/files/capbuvim.pdf">https://www.medicines.org.au/files/capbuvim.pdf</a> [Accessed May 2019]





## Availability of SUBLOCADE<sup>TM</sup>

- Not currently licensed in Europe: under review in some EU countries
- Approved in the US and Canada for the treatment of moderate-to-severe opioid use disorder in adult patients who have been inducted and clinically stabilized on a transmucosal BPN-containing product
  - Should be used as part of a complete treatment plan including counselling and psychosocial support
- Under review with regulators in Australia





## Depot BPN service delivery considerations

#### **Clinical guidelines**

'Best evidence' and consensus approach

#### **Regulatory** Which HCPs will be allowed to use depot BPN in your settings 'Permit' or 'patient authority' systems

#### **Consumer information**

Credentialing/training programmes for HCPs Training for prescribers and HCP administering medications

#### Drug handling

Consideration of handling outside of clinic settings (e.g. community pharmacies)





## Implications for patients, services and beyond

- Potential for large impact on medication-assisted treatment for opioid dependence (MATOD):
  - No need for supervised dosing or take-aways (consider the role of urine drug screening)
  - $\uparrow$  convenience for patients
  - ↓ costs
  - $\downarrow$  concerns regarding non-medical use of BPN medications
  - source of conflict between providers and patients (e.g. intoxicated presentations, urine testing, take-away restrictions)
- May change the balance between methadone and BPN
- May increase availability of treatment in prison settings
- May impact on upon how services operate:
  - Specialist opioid services could operate 'depot clinics' rather than 'methadone queues'
  - Improve relationship between specialist and primary care services
  - **Evolved role** of community pharmacies/co-located services
- May impact on how we do **research in opioid treatment programmes** (no longer 'captive audiences')





## Future research questions

Can we identify patients who 'do better' on depot than SL products? What is the experience of withdrawing from opioid agonist treatment? What are the outcomes?

What is their costeffectiveness? What do we know about use in prison settings?

> Transfer between depot BPN and methadone?

> > And then there are the 'unknown unknowns' ...

Environmental mobile

assessments and

interventions?





## Conclusions

- Depot BPN formulations may prevent misuse of BPN, reduce costs and resources in the clinic and be of greater convenience to the patient and service providers
- Data from clinical trials show that novel BPN depot injections are generally safe and efficacious in reducing unsanctioned opioid use and retaining patients in treatment, with high levels of patient satisfaction
- These formulations are novel and may face challenges in the clinical setting:
  - Informative guidelines, training programmes and consumer information are required