TARGIN®: INTEGRATING AGONISTS AND ANTAGONISTS IN PAIN MANAGEMENT

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MEETING AGENDA

- Pain management principles

- Opioid-induced constipation (OIC)

- TARGIN® tablets
  - Mode of action
  - Pharmacokinetic studies
  - Clinical evidence
    - Analgesic efficacy
    - Bowel function benefits

- CASES STUDIES
  - Sovenor
  - Targin

- Questions and discussion
PAIN

IASP Definition (1979)

‘an unpleasant sensory and emotional experience, associated with actual or potential damage or described in terms of such damage’

• Pain is a complex process
  – Pain involves thoughts and feelings
  – Whatever the experiencing person says it is
  – Exists whenever the experiencing person says it does

• All pain is real
  – Regardless of whether the biological cause is known
PAIN SCALES

- Subjective experience - rely on self reporting

- Verbal Rating Scale
  - no pain, mild, moderate and severe (0-3)

- Visual Analogue Score
  - 10cm line from “no pain” to “worst pain”
CHRONIC (Persistent) PAIN

• Pain persists beyond expected recovery time
  – Pain continuous or recurrent beyond 3-6 months
  – Up to 33% persistent back pain at 1 year
  – 20% substantial limitations in activity

• Pain interferes with life
  – Pain affects self-esteem, well-being and relationships
  – Pain can lead to avoidance, depression and irritability
  – Physical disabilities, psychological distress
  – Unable to work
Effective pain management requires comprehensive assessment which incorporates:
- Biological – nociceptive or neuropathic
- Psychological – anxiety, depression, negative thoughts
- Social factors - litigation, cultural, financial, isolation
TYPES OF PAIN

Nociceptive pain

Mixed pain
(Both types of pain co-exist in many conditions)

Neuropathic pain
A sensory and emotional experience that occurs when specific peripheral sensory neurons (nociceptors) respond to noxious stimuli.

Painful region is typically localised at the site of injury:
- Throbbing, aching or stiffness
- Aggravated by movement

Usually time-limited and resolves when damaged tissue heals (e.g. bone fractures, burns and bruises).

Can be chronic (e.g. osteoarthritis).

Responds to conventional analgesics.
WHO ANALGESIC LADDER (GENERALLY FOR NOCICEPTIVE PAIN)

Non-opioids (paracetamol, NSAID’s, COX-2)

Persistent pain or increasing pain

Weak opioids (codeine, tramadol, buprenorphine, tapendatol) for mild-moderate pain +/− non opioids +/− adjuvants (TCA, AED)

Persistent pain or increasing pain

Strong opioids (oxycodone, Targin, morphine, fentanyl) for moderate-severe pain +/− non opioids +/− adjuvants

Supervised

Symptoms

Mild

Severe
NEUROPATHIC PAIN

- Pain initiated or caused by a primary lesion or dysfunction in the peripheral or central nervous system

- Pain often described as shooting, electric shock-like, burning – commonly associated with tingling or numbness

- Pain occurs in the neurological territory of the affected structure (nerve, root, spinal cord, brain) – typically distant from the site of injury

- Commonly a chronic condition (e.g. Post-herpetic neuralgia, post-stroke pain), but can occur with acute nerve injury (e.g. spinal cord injury, sciatica or surgery)

- Responds poorly to conventional analgesics
RECOGNITION OF NEUROPATHIC PAIN

Common descriptors
- Shooting
- Electric shock-like
- Burning
- Tingling
- Numbness

Post-stroke pain
Diabetic peripheral neuropathy
Lumbar radicular pain
Post-herpetic neuralgia
Chronic post-surgical pain
DIAGNOSING PAIN

LISTEN
Patient verbal descriptors, Q & A

LOCATE
Nervous system lesion/dysfunction

LOOK
Sensory abnormalities, pattern recognition

TARGIN®
OXYCODONE/NALOXONE
CONTROLLED RELEASE TABLETS
Carbamazepine (NNT to obtain 50% relief - 1.7)
Valproate, Phenytoin, Gabapentin, Lamotrigine, Topiramate, Oxcarbazepine
Pregabalin, Levetiracetam, Tiagabine
Lacosamide (Vimpat), Zonisamide
Clonazepam

Amitriptyline, Nortriptyline, Imipramine
Duloxetine

Opioids – Tramadol, Buprenorphine, Oxycodone (Targin), Tapendatol, Morphine, Fentanyl, Hydromorphone

Baclofen, Mexilitene, Clonidine
Capsaicin cream, Lignocaine 5% Dermal patch

N-methyl-D-aspartate (NMDA) blockers – Ketamine, Memantine

Botulinum Toxin
Vitamin B12
OPIOIDS PLACE IN PAIN MANAGEMENT

• Beneficial in some patients
  – Demonstrated good efficacy outcomes
  – Dose dependent response
  – Only moderate side effects
  – Low risk of abuse or addiction when used for pain

• Longer acting opioids are better than short-acting

• Patient selection and close follow-up important

• Most common side effects
  – Nausea and constipation - NNH was 4.2 (CI 3.2-5.6)
  – Followed by drowsiness, dizziness and vomiting
OXYCODONE ANALGESIC EFFICACY

- Cancer pain
  - Citron 1998
  - Bruera 1998
  - Hagen 1997
  - Mucci-LoRusso 1998
  - Riley 2008
  - Heiskanen 1997
  - Biancofiore 2006

- OA pain
  - Roth 2000
  - Zautra 2005
  - McCroskery 2000
  - Markenson 2005

- Neuropathic pain
  - Gatti 2009

- Post-herpetic neuralgia
  - Curtis 1999
  - Sunshine 1996
  - Ginsberg 2003
  - Cheville 2001
  - De Beer 2005
  - Wirz 2005

- Post-operative pain
  - Hanna 2008
  - Watson 2003
  - Gimbel 2003

OA=osteoarthritis
APPROPRIATE PATIENT SELECTION\textsuperscript{1–3}

- Patients with moderate-severe pain\textsuperscript{1,2}

- Other conservative methods of analgesia have been tried and failed\textsuperscript{1}

- Pain is having a significant impact on the patient’s quality of life\textsuperscript{1,3}

- There is no psychological contraindication, drug-seeking behaviour or history of prescription medicine, illicit drug or alcohol misuse.\textsuperscript{1}

OPIOID-RELATED SIDE EFFECTS

- **Common**\(^1,2\)
  - **Constipation**, nausea, anorexia
  - Sedation, dizziness, cognitive impairment
  - Postural hypotension
  - Pruritus, dry mouth, miosis

- **Less common**\(^1,2\)
  - Hormonal effects – reduced testosterone / oestrogen
  - Immunosuppression
  - Opioid-induced hyperalgesia
  - Respiratory depression

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OPIOID-INDUCED CONSTIPATION (OIC)

- OIC is common and experienced by 40–95% of opioid-treated patients and typically continues for the duration of opioid therapy.\(^1\)\(^–\)\(^3\)

OIC reduces health-related quality of life \((p<0.05)\)

OIC reduces ability to undertake work \((p<0.05)\)

OIC reduces ability to undertake daily activities \((p<0.05)\)

OIC COMPROMISES PAIN MANAGEMENT\(^4\)\(^–\)\(^6\)

- OIC is one of the most common reasons chronic, moderate to severe pain patients avoid using opioids.\(^5\),\(^7\)

- 1 in 3 patients with chronic pain* reduce or skip opioid doses specifically to facilitate a bowel movement.\(^5\)

*taking laxatives and daily oral opioids

CONSTIPATION: A VARIETY OF SYMPTOMS

- Straining
- Hard or lumpy stools
- Incomplete emptying
- Stool cannot be passed
- Abdominal bloating/distension
- Infrequent stools
- Manual pressure

Pare P et al. Am J Gastroenterol 2001;96:3130-7
OPIOID-INDUCED BOWEL DYSFUNCTION (OIBD) and OIC SYMPTOMS¹,²

Constipation (OIC)

- Anorexia
- Bloating
- Abdominal distension
- Nausea, vomiting
- Abdominal pain
- Flatulence

The primary cause of OIC is activation of opioid receptors in the gut\textsuperscript{1–3}

Normal bowel function requires co-ordinated motility, mucosal transport and defaecation reflexes

Opioid receptors lie within the enteric nervous system of the GI wall

Opioid molecule, binding to enteric opioid receptors to exert local effects

## PHARMACOLOGIC EFFECTS OF OPIOIDS BINDING IN THE GUT resulting in OIBD\(^1,2\)

<table>
<thead>
<tr>
<th>Site of action</th>
<th>Pharmacological action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>↓ gastric motility</td>
</tr>
<tr>
<td></td>
<td>↑ pyloric sphincter tone</td>
</tr>
<tr>
<td>Small intestine</td>
<td>↓ pancreatic, biliary and intestinal secretions</td>
</tr>
<tr>
<td></td>
<td>↓ intestinal secretion</td>
</tr>
<tr>
<td></td>
<td>↑ non-propulsive contractions</td>
</tr>
<tr>
<td></td>
<td>↑ fluid absorption</td>
</tr>
<tr>
<td>Large intestine</td>
<td>Above plus</td>
</tr>
<tr>
<td></td>
<td>↑ anal sphincter tone</td>
</tr>
</tbody>
</table>

PATHOGENESIS OF CHRONIC CONSTIPATION

PRIMARY CONSTIPATION

- Functional constipation (low fibre and fluid intake)\(^1\,^3\,^4\)
- Idiopathic (includes irritable bowel disease)\(^1\,^2\,^4\)

SECONDARY CONSTIPATION

- Iatrogenic → opioids, Ca\(^{2+}\) channel blockers, anti-cholinergics, TCA’s, antacids\(^1\,^3\)
- Metabolic & endocrine disorders → diabetes, thyroid disease, \(^1\,^3\)
- Psychological → depression\(^2\)
- Neurologic and myopathic disorder → Parkinson’s disease, multiple sclerosis, stroke\(^1\,^3\)
- Structural obstruction → colon cancer, stricture, anal fissures and stenosis\(^1\,^3\)

STOOL CONSISTENCY CORRELATES WITH TRANSIT TIME and WATER CONTENT

Bristol Stool Form Scale¹

Less water content

Type 1
Type 2
Type 3
Type 4
Type 5
Type 6
Type 7

More

Slower colon transit

Faster

# TRADITIONAL THERAPY: LAXATIVES

<table>
<thead>
<tr>
<th>Type</th>
<th>Mechanism of action</th>
<th>Treatment goal</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bulk laxatives</strong></td>
<td>Water absorbing</td>
<td>Improve stool frequency and consistency</td>
<td>Bloating, flatulence</td>
</tr>
<tr>
<td>Fybogel, Metamucil</td>
<td>↑ stool volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stimulant laxatives</strong></td>
<td>↑ intestinal motility ↑ secretions</td>
<td>Improve stool frequency</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Senakot, Movicol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Osmotic laxatives</strong></td>
<td>Osmotic gradient, draws water into lumen to stimulate peristalsis</td>
<td>Improve stool frequency, consistency and straining</td>
<td>Bloating, nausea, abdominal pain</td>
</tr>
<tr>
<td>Lactulose, Movicol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stool softeners</strong></td>
<td>Detergent, allows water to mix with stool to soften stool</td>
<td>Improve stool consistency</td>
<td>Inhibit fat-soluble vitamin absorption</td>
</tr>
<tr>
<td>Coloxyl, Agarol, Movicol</td>
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<td></td>
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</tr>
</tbody>
</table>

CURRENT THERAPIES DO NOT ADDRESS THE CAUSE OF OIC$^{1-3}$

- Recommending laxatives for opioid-treated patients is considered best practice, however laxatives:
  - fail to address the underlying cause of OIC$^{1,2}$
  - are commonly associated with side effects$^{1,3}$
  - add to treatment costs for patients$^{4}$

- OIC often persists despite laxative use$^{1,3}$

**What is required is the blocking of opioid action at receptors in the gut, to prevent or reverse OIC**$^{4,5}$
NOVEL THERAPIES FOR OIC

- **Methylnaltrexone injectable (Relistor) sub-cut**
  
  - Treatment of OIC in palliative care patients when response to laxatives has not been sufficient
  - Acts as a *mu opioid antagonist in gut*
  - Does not cross BBB (low lipid solubility)
  - **No analgesic effect**
  - Short term use
    - Less than 4 months
  - Side effects
    - Abdominal pain, flatulence, nausea, dizziness

OXYCODONE$^{1,2}$

- Semi-synthetic derivative of a morphine alkaloid, thebaine
- Full opioid receptor agonist
- Therapeutic action is analgesia
- Metabolised in the liver with no clinically significant metabolites
- Up to 87% oral bioavailability

Synthetic congener of oxymorphone\(^1\)

Pure antagonist at opioid receptors\(^2\)

Parenterally administered naloxone is used to reverse effects of opioids\(^1\)

Metabolised extensively in the liver\(^1\) during 1\(^{st}\) pass metabolism

Less than 2% oral bioavailability\(^1\)

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Oxycodone
Naloxone
preferentially binds to enteric opioid receptors, preventing oxycodone binding.

Intestinal wall

Gastrointestinal lumen

Opioid receptors within the enteric nervous system of the GI wall

Epithelium

- **Oxycodone**
- **Naloxone** preferentially binds to enteric opioid receptors, preventing oxycodone binding

**TARGIN® TABLETS**

**MODE OF ACTION**

1. **12-HOURLY OXYCODONE AND NALOXONE**
   - Oral TARGIN® tablets deliver oxycodone CR and naloxone CR

2. **NALOXONE BINDS COMPETITIVELY TO OPIOID RECEPTORS IN THE GUT**
   - Due to its high binding affinity, naloxone prevents or reverses the effects of oxycodone in the GI tract, reducing OIC

3. **NALOXONE IS METABOLISED DURING FIRST PASS**
   - During first pass, at least 97% of naloxone is metabolised in the healthy liver, (low oral bioavailability while up to 87% of oxycodone passes into the circulation unchanged)

4. **OXYCODONE REACHES THE CNS**
   - The oxycodone in TARGIN® tablets exerts a central analgesic effect equivalent to oxycodone administered alone

OIC=opioid-induced constipation. GI=gastrointestinal. CNS=central nervous system. CR=controlled release

1. TARGIN® tablets Product Information. April 2011.
TARGIN® TABLETS
INITIATION and TITRATION

Opioid therapy should only be used as part of a multimodal pain management plan

USUAL STARTING DOSE

- Patients uncontrolled on weaker opioids

12-hourly oral dosing

- TARGIN® tablets must be swallowed whole and must not be broken, chewed or crushed

- Titrate cautiously, to achieve pain relief and functional improvement, and to minimise the risk of adverse events

1. TARGIN® tablets Product Information. April 2011.
50% STARTING DOSE IN:¹

- Patients with mild hepatic impairment
  Bil to 45, Alb to 28, INR 2.3
- Patients with renal impairment
  Clcr <60mL/min
- Debilitated elderly patients

A maximum recommended dose exists due to limited exposure of patients receiving doses beyond 40/20 mg 12-hourly.

If longer-term treatment is anticipated, careful and regular assessment and monitoring is required to establish the clinical need for ongoing opioid treatment.

MAXIMUM RECOMMENDED DOSE¹

40/20 mg TARGIN®,
tablet 12-hourly

- A maximum recommended dose exists due to limited exposure of patients receiving doses beyond 40/20 mg 12-hourly

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1. TARGIN® tablets Product Information. April 2011.
Morning and evening doses can be adjusted individually to help manage day–night variations in pain severity.

- **ASYMMETRIC DOSING**
  - Gradually reduce dose to minimise withdrawal symptoms

- **DISCONTINUATION**
  - TARGIN® tablets should not be prescribed or taken for longer than absolutely necessary to manage pain
  - After complete discontinuation of TARGIN® tablets and a subsequent switch to another opioid, a worsening of bowel function can be expected

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1. TARGIN® tablets Product Information. April 2011.
TARGIN® TABLETS
BREAKTHROUGH PAIN or INCIDENT PAIN

- OxyNorm® capsules
  5-10 mg q4hr

- If clinically necessary, treat with oxycodone IR (OxyNorm / Endone) rescue medication

- If more than two doses of rescue medication are required per day reassess the patient and, if appropriate, adjust the dosage of TARGIN® tablets

- If incident pain can be predicted, consider rescue medication prior to activity causing pain

- If pain persists, consider neuropathic component to pain

- Reassess non-pharmacological treatment adjuncts such as pacing and coping techniques, physical exercise and TENS

A consensus exists for a clinically appropriate daily dose range in most patients with chronic non-cancer pain in general practice\(^1\)–\(^3\)

Below 120 mg of oral morphine or equivalent per day
ie 80 mg of oxycodone

- Before increasing the daily opioid dose above this range, consider:
  - if pain is opioid-responsive
  - if the patient has demonstrated sustained improvements in both function and pain
  - the possible risks/benefits of higher opioid doses\(^3\),\(^4\)

- If daily doses exceed the equivalent of 120 mg morphine (oxycodone 2:3 morphine), it is strongly recommended that the treating doctor considers discussion with or referral to a pain specialist \(^1\)–\(^3\),\(^5\)

Beyond the TARGIN® tablets maximum recommended daily dose of 40/20 mg 12-hourly, administer OXYCONTIN at the same time interval.

The beneficial effect of naloxone in TARGIN® tablets on bowel function may be impaired by supplemental oxycodone dosing.
CONTRAINDICATIONS (similar to OXYCONTIN):

- Moderate to severe hepatic impairment
  - Bil >45, Alb <28 and INR >2.3
- Patients with moderate to severe renal impairment
  - Clcr <20mL/min
- Severe respiratory depression
- Pregnancy and lactation

Please review Product Information for complete details of Adverse Reactions, Contraindications and Precautions.
CLINICAL TRIALS

TARGIN®: THE ONLY OPIOID ANALGESIC THAT HELPS PREVENT OPIOID-INDUCED CONSTIPATION (OIC)¹-³

A/Professor Arun Aggarwal

Will naloxone interfere with the analgesic effect of oxycodone?

Will TARGIN demonstrate significant bowel function benefits regarding opioid-induced constipation (OIC) vs oxycodone alone?\(^1\)

What is the effect of naloxone on analgesia and bowel function, long-term?\(^2\)

PHARMACOKINETIC STUDIES – Phase 1

- Single-dose and absolute bioavailability of naloxone¹

- Single-dose²,³ and steady-state pharmacokinetic²,⁴ comparison of TARGIN® tablets with oxycodone CR and naloxone CR

SINGLE DOSE
MEAN NALOXONE PLASMA CONCENTRATIONS\textsuperscript{1}

<table>
<thead>
<tr>
<th>Dose naloxone CR</th>
<th>Mean absolute bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg</td>
<td>0.9%</td>
</tr>
<tr>
<td>20 mg</td>
<td>1.8%</td>
</tr>
<tr>
<td>40 mg</td>
<td>2.0%</td>
</tr>
<tr>
<td>80 mg</td>
<td>2.0%</td>
</tr>
<tr>
<td>120 mg</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

DISINTEGRATION OF TARGIN® TABLETS

Deconvolution results for the 20/10 mg TARGIN® tablet.

SINGLE DOSE
MEAN OXYCODONE PLASMA CONCENTRATIONS\textsuperscript{1,2}

\begin{itemize}
\item 2 x 20 mg oxycodone CR plus 2 x 10 mg naloxone CR
\item 2 x 20/10 mg TARGIN\textsuperscript{®} tablets
\item 4 x 10/5 mg TARGIN\textsuperscript{®} tablets
\item 1 x 40/20 mg TARGIN\textsuperscript{®} tablets
\end{itemize}

\textit{n=28 healthy volunteers}

MULTIPLE DOSE (7 consecutive doses)
MEAN PLASMA OXYCODONE CONCENTRATIONS\textsuperscript{1,2}

\textbf{Graph:}
- Orange line: 40/20 mg TARGIN\textsuperscript{\textregistered} tablet 12 hourly
- Blue line: 40 mg oxycodone CR tablets 12 hourly

\textit{n=34 healthy volunteers}

**STUDY DESIGN**

**ANALGESIC EFFICACY and BOWEL FUNCTION**

### Pre-randomisation

- **Screening**
- **Run-in**

### Double-blind

- **20–80 mg/day**

### Extension

- All on TARGIN® tablets
- **20–80 mg/day**

<table>
<thead>
<tr>
<th>Pre-randomisation</th>
<th>Double-blind</th>
<th>Extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2 weeks</td>
<td>12 weeks</td>
<td>12 months</td>
</tr>
</tbody>
</table>

Oxycodone CR

Oxycodone/naloxone CR (TARGIN)

Oxycodone/naloxone CR

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CR=controlled release. IR=immediate release. *Oxycodone dose, administered as either oxycodone CR or TARGIN® tablets.

- 86% of patients experienced pain associated with musculoskeletal & connective tissue disorders. 34% of patients reported neuropathic pain.
- There was no statistically significant difference in mean daily use of rescue medication between the two groups.

EFFECTIVE LONGER-TERM ANALGESIA

MEAN PAIN SCORES STABLE OVER 12 MONTHS (379 patients)

- The majority of patients remained on a TARGIN® tablets dose that was comparable with the dose they received during the double-blind phase

Mean oxycodone dose:
- 35.6 mg/day at week 2
- 40.9 mg/day for weeks 1-52

BOWEL FUNCTION INDEX (BFI)$^{1,2}$

- Evaluates constipation from the patient’s perspective$^{1,2}$
- Clinician-administered, patient-reported, 3-item questionnaire$^{1,2}$

- The items measured by the BFI are:$^{1,2}$
  - Ease of defaecation
  - Feeling of incomplete bowel evacuation
  - Personal judgement of constipation

- The patient assesses the severity of each item using a 0–100 numerical analogue scale (NAS) where 0=no problems, 100=most severe problems and the 3 scores are averaged$^{1,2}$

A SCORE OF $\leq 30$ IS CONSIDERED NORMAL BOWEL FUNCTION WITH RESPECT TO OIC$^{1–4}$

BFI SCORE CHANGE OF $\geq 12$ POINTS IS CLINICALLY MEANINGFUL

# THE BOWEL FUNCTION INDEX (BFI)

<table>
<thead>
<tr>
<th>ITEM</th>
<th>PATIENT QUESTION</th>
<th>SCORE</th>
</tr>
</thead>
</table>
| 1. EASE OF DEFECATION during the last 7 days according to patient assessment | **ASK YOUR PATIENT:**  
*During the last 7 days, how would you rate your ease of defecation on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?*  
**IF THE PATIENT NEEDS CLARIFICATION, ASK:**  
*During the last 7 days, how easy or difficult was it to have a bowel movement on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?* | 0 = easy / no difficulty  
100 = severe difficulty |
| 2. FEELING OF INCOMPLETE BOWEL EVACUATION during the last 7 days according to patient assessment | **ASK YOUR PATIENT:**  
*During the last 7 days, how would you rate your feeling of incomplete bowel evacuation on a scale from 0 to 100, where 0 = no feeling of incomplete evacuation and 100 = a very strong feeling of incomplete evacuation?*  
**IF THE PATIENT NEEDS CLARIFICATION, ASK:**  
*During the last 7 days, how strongly did you feel that you did not empty your bowels completely? Please indicate how strong this feeling was on a scale from 0 to 100, where 0 = not at all and 100 = very strong.* | 0 = not at all  
100 = very strong |
| 3. PERSONAL JUDGEMENT REGARDING CONSTIPATION during the last 7 days according to patient assessment | **ASK YOUR PATIENT:**  
*During the last 7 days, how would you rate your constipation on a scale from 0 to 100, where 0 = not at all and 100 = very strong?*  
**IF THE PATIENT NEEDS CLARIFICATION, ASK:**  
*During the last 7 days, how would you rate how constipated you felt on a scale from 0 to 100, where 0 = not at all and 100 = very strong?* | 0 = not at all  
100 = very strong |

**BFI**  
Calculate the BFI by finding the average of scores for items 1 to 3  
\[
\text{BFI} = \frac{\text{Score 1} + \text{Score 2} + \text{Score 3}}{3}
\]

\[
\leq 30 = \text{normal bowel function}^*\]
**TARGIN® TABLETS**
**IMPROVED BOWEL FUNCTION FROM WEEK 1**

**BOWEL FUNCTION INDEX (BFI) SCORE OVER TIME**

- **TARGIN® tablets**
  20/10 to 80/40 mg/day
- **oxycodone CR**
  20 to 80 mg/day

**A score of ≤30 is considered normal bowel function with respect to OIC.**

**A change of ≥12 points indicates a clinically relevant change in bowel function.**

**Laxatives used in fewer patients on TARGIN during 1st 4 weeks**

**Significantly fewer patients on TARGIN® tablets required laxatives during the first 4 weeks of treatment (p<0.0001 vs. oxycodone CR)**

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LONGER-TERM IMPROVEMENT IN BOWEL FUNCTION¹

Mean oxycodone dose:

- 32.8 mg/day with TARGIN® tablets in double-blind phase
- 34.0 mg/day with oxycodone CR in double-blind phase
- 38.3 mg/day with TARGIN® tablets in extension phase

A score of ≤30 is considered normal bowel function with respect to OIC.²⁻⁵

A change of ≥12 points indicates a clinically relevant change in bowel function.²⁻⁵

MAINTAINED IMPROVEMENT IN OIC OVER 12 MONTHS OF THERAPY¹

8.5% of patients reported regular laxative intake after the first week of the 12-month extension study¹

ANALGESIC EFFICACY

- Analgesic efficacy equivalent to oxycodone CR\textsuperscript{1,2}

- Mean pain scores remained low and stable throughout the 12-month extension with minimal dose escalations\textsuperscript{3}

BOWEL BENEFITS

- Significant improvements in OIC were apparent after only 1 week\textsuperscript{2}

- Significant improvements in OIC were maintained for the 12-week study period\textsuperscript{2} compared with oxycodone CR\textsuperscript{2}

- Improvements in OIC were maintained throughout the 12-month extension study\textsuperscript{3}

- Fewer patients required laxatives compared with oxycodone CR\textsuperscript{2}

TARGIN®: THE ONLY OPIOID ANALGESIC THAT HELPS PREVENT OPIOID-INDUCED CONSTIPATION (OIC)1-3

A/Professor Arun Aggarwal

CASE STUDIES

76 yo carpenter,
  - now manager at carpentry firm
  - also likes working in garden
History of right knee pain
Currently on maximum dose paracetamol/codeine (30 mg)
  - NSAID for breakthrough pain
Has regular physiotherapy
  - home-based exercise programme
  - heat packs
PRESENTATION

- Complains of worsening knee pain
  - pain assessment NRS 8/10 = moderate to severe pain

- Complains of impaired daily function
  - unable to work a full day due to knee pain
  - trouble with light household and gardening tasks
  - reduced tolerance for standing
  - disturbed sleep

- Experiences dyspepsia due to NSAID use

NRS = Numerical rating scale
WHAT IS YOUR TREATMENT PLAN FOR JOHN?

John may be a candidate for knee surgery.

How would you manage John’s moderate to severe chronic pain between now and surgery?
OPIOIDS

Discussion point: Which opioid would you trial for John’s moderate to severe chronic pain and why?

- Buprenorphine 7-day patch (Sovenor)
- Tramadol / Tapendatol
- Oxycodone/naloxone CR (Targin)
- Oxycodone CR (Oxycontin)
- Fentanyl 3-day patch
- Morphine CR (MS Contin)
- Hydromorphone (modified release)

INITIATING OPIOID THERAPY

- **Opioid risk assessment** (Next slide)
- Set treatment goals, including increased participation in an exercise program
- Obtain patient consent and written or verbal treatment agreement
- Initiate 4–6 week strong opioid trial with weekly reviews
  - Discuss side effects
- Monthly review as per the **6 A’s of pain medicine** (Next slide)
  - If pain opioid responsive, continue with monthly reviews for 3–6 mths
  - if there is reduction in pain and improvement in function, consider longer-term (until surgery)
  - Taper dose and cease opioid post surgery
## OPIOID RISK ASSESSMENT TOOL (ORT)\(^1–2\)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of substance abuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Alcohol</td>
<td>3 points</td>
<td>1 point</td>
</tr>
<tr>
<td>- Illicit drugs</td>
<td>3 points</td>
<td>2 points</td>
</tr>
<tr>
<td>- Prescription drugs</td>
<td>4 points</td>
<td>4 points</td>
</tr>
<tr>
<td>Personal history of substance abuse</td>
<td></td>
<td></td>
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<tr>
<td>- Alcohol</td>
<td>3 points</td>
<td>3 points</td>
</tr>
<tr>
<td>- Illicit drugs</td>
<td>4 points</td>
<td>4 points</td>
</tr>
<tr>
<td>- Prescription drugs</td>
<td>5 points</td>
<td>5 points</td>
</tr>
<tr>
<td>Aged between 16 and 45</td>
<td>1 point</td>
<td>1 point</td>
</tr>
<tr>
<td>History of preadolescent sexual abuse</td>
<td>0 points</td>
<td>3 points</td>
</tr>
<tr>
<td>Psychiatric disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Attention deficit disorder, obsessive-compulsive disorder, bipolar disorder, schizophrenia</td>
<td>2 points</td>
<td>2 points</td>
</tr>
<tr>
<td>Depression</td>
<td>1 point</td>
<td>1 point</td>
</tr>
</tbody>
</table>

# THE 6 As OF PAIN MEDICINE

<table>
<thead>
<tr>
<th>Activity</th>
<th>What progress has been made in the patient’s functional goals?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia</td>
<td>How does the patient rate their average and worst pain over the last 24 hours? How much relief have pain medications provided?</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Has the patient experienced any adverse effects from medication?</td>
</tr>
<tr>
<td>Aberrant behaviour</td>
<td>Has the patient been taking medication as prescribed? Has the patient exhibited any signs of medication misuse/abuse?</td>
</tr>
<tr>
<td>Affect</td>
<td>Have there been any changes to the way the patient has been feeling? Is pain impacting on the patient’s mood? Depressed? Anxious?</td>
</tr>
<tr>
<td>Accurate records</td>
<td>Document the initial evaluation and each follow-up, including current pain medication and any changes to the management plan.</td>
</tr>
</tbody>
</table>

PROGRESS

• Commence **Buprenorphine 5 mcg/hr weekly patch (Sovenor)**

• Pain improved from **NRS 8/10 to 4/10**
  – Ceased regular paracetamol/codeine, but needs paracetamol 8/day
  – Able to work all day, without being limited by pain
  – Stand for as long as needed
  – Sleeping well at night

• Review in 4 weeks, **Sovenor increased to 10 mcg/hr weekly**

• Pain **improved to 2/10**
  – No additional analgesia required and functioning very well
Mrs PK

- 86 year old widow
- Lives alone

- Lumbar laminectomy 20 years ago
- Bleeding gastric ulcer 5 years ago

- Clinical and radiological diagnosis indicate:
  - Symptomatic osteoarthritis of knees
  - Lumbar spondylosis with central canal stenosis

- Independent ADL but difficulty walking up steps
CURRENT MEDICATIONS

• Consultation for repeat prescriptions for *pain killers*
  – “Not that they do a lot for me these days”

• Analgesics
  – Paracetamol 1000 mg 4/day
  – Tramadol 50 mg tds

• Other medications
  – Doxepin
  – Amiloride/Hydrochlorothiazide (5 mg/50 mg) mane
  – Glucosamine sulphate 500mg tds
  – Antioxidant supplement for macular degeneration
**PAIN ASSESSMENT**

- Both knees are painful and stiff
  - Increasingly difficult to walk up stairs and hills (knee pain)

- Low back pain, radiating to her legs (no paraesthesiae)
  - Walking is limited to 10 minutes or 50 metres (back pain)
  - Prolonged sitting and standing are difficult
  - Able to sit for 10 minutes only

- Sleep interrupted by pain

- Background pain level is **6/10**
- Worst pain is **9/10**, which occurs with prolonged walking or walking up stairs
MANAGEMENT

- Tramadol providing short-term benefit

- Replace with:
  - Slow release Tramadol – SR or XR
  - Stronger opioid – Transdermal buprenorphine (Sovenor) due to potential compliance benefit

- Glucosamine discontinued

- Continue paracetamol as opioid sparer, but standard formulation replaced by modified release tablets to aid compliance
  - Panadol Osteo 2 tablets tds
PROGRESS

• Buprenorphine patch **5 mcg/hr weekly:**
  – Background pain **6/10 to 4-5/10**
  – Sleep has improved, not waking in pain
  – No change on pain during walking (rating 9/10)
  – No adverse effects reported

• Buprenorphine patch dose increased to **10 mcg/hr**

• Pain relief improved
  • Background pain reduced further to **3/10**
  • Incident pain improved with worst pain 5/10
  • Walking tolerance increased to 30 minutes
  • Buprenorphine is well tolerated

• Continue buprenorphine patch at **10 mcg/h**
BUPRENORHINE (Sovenor)

- A potent partial agonist with a long duration of action
  - 30x as potent as morphine

- Low dose patches very useful in elderly patients with musculoskeletal degenerative disease

- Ceiling agonist effect at approximately 12mg/day in most adults
  - Full $\mu$ agonists are antagonised beyond this dose
  - Non-opiate analgesics will be required, eg amitriptyline
Mrs MW

- 54 yo
- 8 year history of lower lumbar back pain
- Constant sharp shooting pain radiating down right leg 9/10
- CT Lumbar spine – severe degenerative facet joint disease and moderate disc bulge L4/5

- **Amitriptyline 10 mg nocte**
  - Improved sharp pain
- Ongoing dull ache 5-6/10

- **Add Tramadol SR 100 mg mane**
  - Improved pain and able to return to work
Mrs MW

- Constant dull ache 5/10
- Increased Tramadol to 200 mg bd

**Bone Scan**
  - Moderate facet joint uptake at multiple levels

**Started Oxycontin 10 mg bd**
  - Excessive daytime drowsiness
  - 5 mg bd improved pain from 8/10 to 5/10
  - Drowsy during the day
  - “Sick of taking pills”
Mrs MW

- **Fentanyl patch**
  - 12 – 25 – 37 mcg every 3 days but lasts only 2 days
  - Drowsy throughout the day
  - Constant pain - dull ache - **5/10**

- **Constipation**
  - Opening her bowels about once a week
    - Drinking 2 litres of water a day
    - Tony Ferguson high fibre diet

- **Targin 10/5 mg bd** increasing to **20/10 mg bd**
  - Pain manageable and tolerable **2/10**
  - Less drowsy during the day
  - Less constipation – bowels opening **2-3 times a week**
Mrs PS

- 58 yo
- Self employed Occupational Therapist

- 2 year history of chronic generalised pain
- Lower lumbar pain radiating down both legs
- Constant dull ache with no sharp stabbing pain – 8/10

- MRI- degenerative disease or cervical and lumbar spine

- Responded initially to Tramadol SR 50 mg nocte
  - Improved pain on 100mg bd 8/10 to 2/10
Mrs PS

• 12 months later pain increased back to 8/10
  – Increased use of Mersyndol

• Increased Tramadol SR to 200 mg bd
  – Constipation – Movicol

• Changed to Buprenorphine (Sovenor)
  – Increased pain despite increasing patch to 20 mcg weekly – 8/10

• Targin 10/5 mg bd increased to 20/10 bd
  – Pain improved 8/10 – 2/10
  – No constipation

• Back to work as OT
Pain is the Most Common Treatable Symptom of Cancer

- Early/Intermediate: ~25-30% experience severe pain
- Advanced: 75%

Mr RW

- 80 years old
- Diagnosed with prostate cancer 6 years ago
- Treated with radical radiotherapy with satisfactory results
- 2 years ago, increased prostate specific antigen
  - Hormone treatment
- History of renal impairment and cardiac failure
- Developed bone pain in several different sites
  - Pain levels generally 8-9/10
- Bone scan shows multiple bony metastases
Analgesia for Bone Pain

• NSAID
  – Good for bone pain, but this patient’s age and cardiac failure may preclude use

• Paracetamol
  – Probable central action, good for superficial pain but may not provide sufficient relief

• Opioid
  – Effective, manageable risks and easily titrated
  – Morphine has traditionally been the preferred agent for cancer pain
  – But morphine is far from ideal:
    • Oral bioavailability is highly variable
    • Pharmacologically active metabolites (morphine-6-glucuronide)
ALTERNATIVES to MORPHINE

• Oxycodone
  – Available in short and long-acting formulations
  – Quick onset of action
  – No significant active metabolites

• Fentanyl
  – Transdermal fentanyl is a good analgesic choice for patients with stable and infrequent episodes of breakthrough pain

• Methadone
  – Useful if pain is poorly controlled with standard opioids, but is difficult to titrate

PROGRESS

• Commenced **Targin 5/2.5mg twice a day**
• Regular Paracetamol 1000mg qid
  – No improvement in pain, but well tolerated

• **Targin** increased to **10/5mg twice a day**
  – Pain improved from 8-9/10 to 6/10

• **Targin** increased to **20/10mg twice a day**
  – Pain improved further to 3/10
  – Sleeping better
  – Walking longer distances

• **Targin** increased to **40/20mg twice a day**
  – Virtually pain free 0-1/10
  – No problems with constipation
SUMMARY

- There are many causes of constipation: one of these is opioid-induced constipation (OIC), which is common and can be debilitating\(^1,^2\)

- OIC can have a significant impact on health-related QoL\(^2\)

- Laxatives fail to address the underlying cause of OIC\(^3^–^5\)

- When administered orally, naloxone undergoes extensive first-pass metabolism resulting in negligible (<2%) systemic bioavailability\(^6,^7\)

- TARGIN\(^\text{®}\) tablets offer a specific mode of action in PAIN MANAGEMENT to help prevent OIC\(^6\)

---

Opioids can be an important component of a multimodal pain management plan\(^1\)

Pharmacokinetic properties of oxycodone in TARGIN® tablets are bioequivalent to oxycodone CR tablets\(^6,7\)

Oxycodone in TARGIN® tablets is **bioequivalent** to oxycodone CR tablets\(^3\)

Effective in patients with **chronic moderate - severe osteoarthritis, back, neuropathic and cancer pain**\(^5-7\)

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WHO ANALGESIC LADDER (GENERALLY FOR NOCICEPTIVE PAIN)

- **Non-opioids (paracetamol, NSAID’s, COX-2)**
  - Persistent pain or increasing pain
  - **Weak opioids (codeine, tramadol, buprenorphine, tapentadol)**
    - for mild-moderate pain
    - +/- non opioids +/- adjuvants (TCA, AED)
  - Persistent pain or increasing pain
  - **Strong opioids (oxycodone, Targin, morphine, fentanyl)**
    - for moderate-severe pain
    - +/- non opioids +/- adjuvants
- Symptoms
  - Supervised
  - Severe
  - Mild
THANK YOU
Common side effects are typical of those expected with other strong opioids and include:\(^1\)

- Nausea
- Constipation
- Dry mouth
- Dizziness
- Vomiting
- Diarrhoea
- Pruritus
- Headache

**GI TOLERABILITY**

- Fewer GI side effects such as constipation, nausea, vomiting, abdominal pain compared with oxycodone CR administered alone\(^2,3\)
- Diarrhoea may be a possible effect of naloxone, especially at the beginning of treatment, but tends to be transient\(^1\)

Please review Product Information for complete details of Adverse Reactions, Contraindications and Precautions.

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OPIOID WITHDRAWAL

- When taken orally, the naloxone component in TARGIN® tablets is unlikely to result in a clinically relevant systemic effect due to naloxone’s pronounced first-pass metabolism and low oral bioavailability (<3%)\(^1\).

ABUSE

- If abused parenterally or intranasally by individuals dependent on opioid agonists, TARGIN® tablets are expected to produce marked withdrawal symptoms due to the opioid receptor antagonist characteristics of naloxone\(^1\).

Please review Product Information for complete details of Adverse Reactions, Contraindications and Precautions.

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1. TARGIN® tablets Product Information. April 2011.
UNIVERSAL PRECAUTIONS IN PAIN MEDICINE

As with all opioid analgesics, the following universal precautions must be applied when considering initiating TARGIN® tablets in chronic non-cancer pain patients:

- Undertake a comprehensive personal and family risk assessment of past and current substance and alcohol abuse

- All other conservative treatment options, including the non-pharmacological, must have been tried and failed before considering a trial of a strong opioid. Opioids should not be used in isolation but as part of a multimodal pain management plan

- Set clear treatment goals and consider a written or verbal treatment agreement or contract for initiation, continuation and termination of treatment

- Initiate an opioid trial of 4 to 6 weeks for first-time patients

- If longer-term pain treatment is anticipated, regularly assess the 4+2As of pain medicine

- Prepare a protocol to be implemented for eventual opioid treatment discontinuation

Please refer to the Mundipharma Opioid Prescribing Requirements and participant’s workbooks for more information and list of references, available from Mundipharma.
PBS Information: Restricted benefit. Chronic severe disabling pain not responding to non-narcotic analgesics. Authority required for increased maximum quantities and/or repeats. Refer to PBS schedule for full restricted benefit and authority information.

Before prescribing any product mentioned in this presentation, please refer to Product Information and to State and Federal regulations.

**OPIOID THERAPY SHOULD ONLY BE USED AS PART OF A MULTIMODAL PAIN MANAGEMENT PLAN. TARGIN® tablets MINIMUM PRODUCT INFORMATION. INDICATIONS** The management of moderate to severe chronic pain unresponsive to non-narcotic analgesics. The naloxone component in a fixed combination with oxycodone is indicated for the therapy and/or prophylaxis of opioid-induced constipation. **CONTRAINDICATIONS** Hypersensitivity to opioids, naloxone and any of the excipients or any situation where opioids are contraindicated; moderate to severe hepatic impairment; severe respiratory depression with hypoxia; elevated carbon dioxide levels in the blood; cor pulmonale; cardiac arrhythmias; uncontrolled bronchial asthma; severe chronic obstructive pulmonary disease; non-opioid induced paralytic ileus; pregnancy; lactation; severe CNS depression; increased cerebrospinal or intracranial pressure; brain tumour or head injury (due to the risk of increased intracranial pressure); uncontrolled convulsive disorders; suspected surgical abdomen; delayed gastric emptying; alcoholism; delirium tremens; concurrent administration of MAO-inhibitors and for 2 weeks after their cessation. **PRECAUTIONS** Most important hazard of opioid preparations is respiratory depression; occurs most frequently in overdose situations, the elderly, the debilitated and in those suffering from conditions accompanied by hypoxia when even moderate doses may be dangerous. Use with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, chronic obstructive pulmonary disease. Use with caution in hypothyroidism (may need to reduce dose); elderly, infirm or debilitated patients; mild hepatic impairment; renal impairment; severely impaired pulmonary function; opioid dependence; hypotension; hypertension; hypovolaemia; biliary tract disease; pancreatitis; inflammatory bowel disorders; prostatic hypertrophy; avoided in patients with peritoneal carcinomatosis or sub-occlusive syndrome in advanced stages of digestive and pelvic cancers. Tolerance and physical dependence tend to develop upon repeated administration. Withdraw gradually. Parenteral or intranasal abuse in opioid-dependent individuals is expected to produce marked withdrawal symptoms. Parenteral venous administration may be fatal. Reduce dosage to 1/3 to 1/2 of the usual dose in elderly patients who are infirm or debilitated and in patients with renal failure or mild hepatic impairment. May impair ability to drive and operate machinery. May produce positive results in sports agency drug testing procedures. Not recommended for immediate pre-operative use and post-operative for 24 hours after surgery. Do not use within 24 hours of cordotomy or other pain-relieving surgery. **INTERACTIONS** Anticholinergic agents, antihypertensives, CNS depressants (antidepressants, sedatives, hypnotics, general anaesthetics, phenothiazines or other tranquillizers, alcohol, other opioids, anti-histamines, anti-emetics, neuroleptics etc), coumarin derivatives, metoclopramide, non-selective MAOIs or within 14 days of stopping treatment (caution is advised with selective MAOIs), neuromuscular blocking agents, opioid agonist analgesics and mixed agonist/antagonist analgesics, drugs that affect the P450 enzyme system (CYP3A4, CYP2D6). **ADVERSE EFFECTS** Typical of full opioid agonists and tend to reduce with time. Common side effects (incidence ≥1%) include agitation, anorexia, asthenic conditions, abdominal pain, bronchospasm, chills, constipation, diarrhoea, dizziness, drug withdrawal syndrome, dry mouth, dyspepsia, faintness, fever, gastritis, headache, hepatic enzymes increased, hiccup, hyperhidrosis, hypotension, mood changes, muscle spasms, muscle twitching, myalgia, nausea, orthostatic hypotension, pharyngitis, pruritus, rash, uréteric spasm, urinary abnormalities, urinary tract infection, vertigo, voice alteration, vomiting. **DOSAGE AND ADMINISTRATION** Must be swallowed whole and not broken, chewed or crushed. Taking broken, chewed or crushed TARGIN® tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone that could be fatal. **Adults:** Usual starting dose (opioid-naive patients, or patients with moderate to severe chronic pain uncontrolled by weaker opioids): one TARGIN® 10/5 mg tablet T2-hourly. Patients with renal or mild hepatic impairment: one TARGIN® 5/2.5 mg tablet 12-hourly. Titrate cautiously (every 1–2 days if necessary) to achieve pain relief. Maximum recommended daily dose: 80/40 mg (TARGIN® 40/20 mg tablets 12-hourly). **Children:** Not recommended in patients below 12 years of age. **DATE OF MOST RECENT AMENDMENT** 14 April 2011. **DATE OF FIRST INCLUSION ON ARTG** 12 May 2010.
**OxyContin® TABLETS**

**PRODUCT INFORMATION**

**PBS Information:** OxyContin® tablets.

**Restricted Benefit:** Chronic severe disabling pain not responding to non-narcotic analgesics. Authority Required (increased maximum quantities and/or repeats).

Refer to PBS Schedule for full restricted benefit and authority required information.

Before prescribing any product mentioned in this presentation, please refer to Product Information and to State and Federal regulations.

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**OxyContin® tablets (5mg, 10mg, 15mg, 20mg, 30mg, 40mg, 80mg) MINIMUM PRODUCT INFORMATION. INDICATIONS** The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia. **CONTRAINDICATIONS** Hypersensitivity to opioids or to any constituents of OxyContin® tablets. acute respiratory depression, **cor pulmonale**, cardiac arrhythmias, acute asthma or other obstructive airways disease, paralytic ileus, suspected surgical abdomen, severe renal impairment (creatinine clearance <10 mL/min), severe hepatic impairment, delayed gastric emptying, acute alcoholism, brain tumour, increased cerebrospinal or intracranial pressure, head injury (due to risk of raised intracranial pressure), severe CNS depression, convulsive disorders, delirium tremens, hypercarbia, concurrent administration of monoamine oxidase inhibitors (MAOIs) or within 2 weeks of discontinuation of their use, pregnancy. Not recommended for pre-operative use or for the first 24 hours post-operatively. **PRECAUTIONS** The major risk of opioid excess is respiratory depression. Use with caution in patients with hypothyroidism (may need to reduce dose), debilitated elderly or infirm patients, opioid-dependent patients, hypotension, hypovolaemia, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency (Addison’s disease), toxic psychosis, chronic pulmonary, renal or hepatic disease, myxoedema, following abdominal surgery (discontinue use if paralytic ileus is suspected or occurs), chronic, non-malignant pain, a prior history of substance abuse. Oxycodone should not be used during pregnancy or lactation unless clearly needed (Category C). Tolerance and physical dependence tend to develop upon repeated administration. Withdraw gradually. Parenteral venous injection of the tablet constituents may be fatal. Reduce dosage in elderly, debilitated patients and in patients with renal impairment or hepatic impairment (one-third to one-half of usual starting dose). May affect driving or operating machinery. Do not use in immediate pre-operative period, or within 24 hours of cordotomy or other pain-relieving surgery. **INTERACTIONS** Anticholinergic agents, antihypertensives, CNS depressants (sedatives, hypnotics, general anaesthetics, phenothiazines, other tranquilisers, alcohol, other opioids, neuroleptic drugs, etc), coumarin derivatives, metoclopramide, non-selective MAOIs or within 14 days of stopping treatment (caution is advised with selective MAOIs), neuromuscular blocking agents, opioid agonist analgesics and mixed agonist/antagonist analgesics, drugs that affect the P450 enzyme system (CYP3A4, CYP2D6). **ADVERSE REACTIONS** Typical of full opioid agonists and tend to reduce with time, except constipation. Common side effects (incidence ≥1%) include abdominal pain, abnormal dreams, anxiety, asthenic conditions, bronchospasm, chills, confusion, state, constipation, diarrhoea, dizziness, dry mouth, dyspepsia, dysphoria, faintness, fever, gastritis, headache, hiccups, hyperhidrosis, insomnia, nausea, nervousness, orthostatic hypotension, pharyngitis, pruritus, rash, sedation, somnolence, thinking abnormal, twitching, voice alteration, vomiting. **DOSAGE AND ADMINISTRATION** Must be swallowed whole and not broken, chewed or crushed. Taking broken, chewed or crushed OxyContin® tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone. Alcohol should be avoided while the patient is being treated with OxyContin® tablets. **Adults, elderly and children over 12 years:** Dose at 12-hourly intervals. Usual starting dose (opioid-naïve patients or patients with severe pain uncontrolled by weaker opioids): one OxyContin® 10 mg tablet 12-hourly. Patients with renal or hepatic impairment: one OxyContin® 5 mg tablet 12-hourly. Titrate carefully (as frequently as once a day if necessary) to achieve pain relief. 10 mg oral oxycodone is equivalent to 20 mg oral morphine. OxyContin® 80 mg tablets should only be used in opioid-tolerant patients. In opioid-naïve patients, this tablet strength may cause fatal respiratory depression. **Children:** Not recommended in patients under 12 years of age. **TGA APPROVAL DATE** 15 July 1999. **DATE OF MOST RECENT AMENDMENT** 17 Feb 2011. ®: OXYCONTIN is a Registered Trademark. Product Information and further information are available from Mundipharma Pty Limited ABN 87 081 322 509, 50 Bridge Street, Sydney, NSW 2000. Phone 1800 188 009.
**OxyNorm®** CAPSULES and LIQUID  
PRODUCT INFORMATION

**PBS Information:** **OxyNorm®** Capsules, **OxyNorm®** Liquid  
**Restricted** Benefit: Severe disabling pain not responding to non-narcotic analgesics.  
Authority Required (increased maximum quantities and/or repeats).  
Refer to PBS schedule for full restricted benefit and authority required information.

**Before prescribing any product mentioned in this presentation, please refer to Product Information and to State and Federal regulations.**

**OxyNorm®** Capsules (5mg, 10mg, 20mg), **OxyNorm®** Liquid (5mg/5mL)  
**MINIMUM PRODUCT INFORMATION. INDICATIONS** The management of opioid responsive, moderate to severe pain.  
**CONTRAINDICATIONS** Hypersensitivity to opioids or constituents of **OxyNorm®** capsules or liquid; acute respiratory depression; *cor pulmonale*; cardiac arrhythmias; acute asthma or other obstructive airways disease; paralytic ileus; suspected surgical abdomen; severe renal impairment (creatinine clearance < 10 mL/min); severe hepatic impairment; delayed gastric emptying; acute alcoholism; brain tumour; increased cerebrospinal or intracranial pressure; head injury; severe CNS depression; convulsive disorders; *delirium tremens*; hypercarbia; pregnancy; concurrent administration of monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping treatment of their use. Not recommended for pre-operative use.  
**PRECAUTIONS** The major risk of opioid excess is respiratory depression. Use with caution in patients with hypothyroidism (may need to reduce dose); opioid dependence; hypotension; hypovolaemia; diseases of the biliary tract; pancreatitis; inflammatory bowel disorders; prostatic hypertrophy; adrenocortical insufficiency; toxic psychosis; chronic pulmonary, renal or hepatic disease; myxoedema; following abdominal surgery; debilitated elderly or infirm patients; non-malignant pain; a prior history of substance abuse. Not recommended in pregnancy (Category C); lactation. As with other opioids, tolerance and physical dependence tend to develop upon repeated administration of oxycodone. There is potential for abuse of the drug and for development of strong psychological dependence. **OxyNorm®** capsules or liquid should therefore be prescribed and handled with a high degree of caution appropriate to the use of a drug with strong abuse potential. Withdraw gradually. Discontinue use if paralytic ileus is suspected or occurs. Parenteral venous administration may be fatal. Reduce dosage in elderly, debilitated patients and in patients with renal or hepatic impairment (one-third to one-half of usual starting dose). May affect driving or operating machinery. Do not use 6 hours prior to cordotomy or other pain relieving surgery.  
**INTERACTIONS** Anticholinergic agents, antihypertensives, CNS depressants (sedatives, hypnotics, general anaesthetics, phenothiazines or other tranquilizers, alcohol, other opioids, neuroleptics etc), coumarin derivatives, metoclopramide, non-selective MAOIs or within 14 days of stopping treatment (caution is advised with selective MAOIs), neuromuscular blocking agents, opioid agonist analgesics and mixed opioid agonist/antagonist analgesics, drugs that affect the P450 enzyme system (CYP3A4, CYP2D6).  
**ADVERSE REACTIONS** Typical of full opioid agonists and tend to reduce with time, except constipation. Immediate release formulations such as **OxyNorm®** capsules or liquid may have a higher incidence of some adverse reactions than controlled release formulations. The most frequently observed side effects with an incidence ≥ 1% include abdominal pain, abnormal dreams, anorexia, anxiety, asthenic conditions, bronchospasm, chills, confusion, constipation, diarrhea, dizziness, dry mouth, dyspepsia, dyspnoea, faintness, fever, gastritis, headache, hiccup, hyperhidrosis, increased hepatic enzymes, insomnia, miosis, nausea, nervousness, orthostatic hypotension, pharyngitis, pruritis, rash, sedation, somnolence, thinking abnormal, twitching, vertigo, visual impairment, voice alteration, vomiting.  
**DOSAGE AND ADMINISTRATION** **OxyNorm®** capsules must be swallowed whole and not opened, chewed or crushed. Alcohol should be avoided while the patient is being treated with **OxyNorm®** capsules or liquid. **OxyNorm®** oral dosage forms are not interchangeable with Endone tablets.  
**Usual starting dose (opioid naïve patients or patients presenting with severe pain uncontrolled by weaker opioids):** 5 mg 4-6 hourly.  
**Titrated carefully (once a day if required) to achieve pain relief.**  
10 mg oral oxycodone is equivalent to 20 mg oral morphine. Dose conservatively in mild to moderate renal impairment and mild hepatic impairment. Absorption of oxycodone from an oral solution may be significantly increased by food.  
**Children:** Not recommended in patients under 18 years of age.  
**TGA APPROVAL DATE** 13 November 2001  
**DATE OF MOST RECENT AMENDMENT** Feb 2010.  
**OXYNORM is a Registered Trademark. Product Information and further information are available from Mundipharma Pty Limited ABN 87 081 322 509, 50 Bridge Street, Sydney, NSW 2000. Phone 1800 188 009.**