# Propranolol Long-Acting Oral Capsules (Inderal®-LA)

Supplier of long-acting propranolol capsules marketed* in Canada[1]

| Product | Strength | DIN | Manufacturer |
|---|---|---|---|
| Inderal®-LA | 60 mg | 02042231 | Pfizer Canada ULC |
| | 80 mg | 02042258 | |
| | 120 mg | 02042266 | |
| | 160 mg | 02042274 | |

*Lupin-Propranolol LA capsules have been approved in Canada[1] but are not expected to be available until June 2022.[2]

### Inderal®-LA Indications[3]

- hypertension
- prophylaxis of angina pectoris

Note that immediate-release propranolol has several additional Health Canada approved indications, including cardiac arrhythmias, migraine prophylaxis, hypertrophic subaortic stenosis, and pheochromocytoma.[4] Inderal®-LA is used off-label for some of these and other indications.

### Background[5]

All lots of all strengths of Inderal®-LA capsules have been recalled in Canada due to a nitrosamine impurity.

Nitrosamine impurities have been detected in several other medications, including angiotensin receptor blockers and histamine$_2$-receptor blockers. Nitrosamines are unavoidable in our environment as they are found in some foods and drinking water. While classified as a probable human carcinogen, low levels are not concerning. The concern is with long-term exposure; daily exposure to levels exceeding the acceptable level for 70 years may increase the risk of cancer. As such, there is no immediate risk and patients should continue taking any supply of Inderal®-LA they have on hand unless otherwise directed by their health care provider.

### General Considerations

- The information in this document is general and resources such as CPS and RxFiles should be consulted for specific cases.
- Dosages of long-acting propranolol vary according to indication and there are no direct conversions (or 'equivalent' doses) to immediate-release propranolol or other beta-blockers.
- When choosing a dosage of an alternative agent (including immediate-release propranolol), the risk of symptom/condition exacerbation with lower doses needs to be weighed against the risk of adverse effects with higher doses.
  - In most cases, starting with a lower dosage and titrating up as tolerated is prudent.
  - Immediate-release propranolol may be administered two to four times daily, depending on the indication.[4] While titrating, more frequent dosing may help avoid excessive plasma concentrations and associated adverse effects; once stabilized on a daily dose, reducing frequencies (to no less than twice daily) may be attempted if desired and appropriate for the indication.

### Pharmaceutical Alternatives

Immediate-release propranolol tablets are available, though it is plausible this stock will be depleted.

#### *Switching from Long-Acting Propranolol to Immediate-Release Propranolol*

Switching information is generally available for switching *from* immediate-release *to* long-acting. Little information is available regarding the reverse switch.

When switching to long-acting propranolol, the same total daily dose is used and titrated as required.[3]

However, **when switching from long-acting to immediate-release propranolol**, lower total daily doses may be required due to greater bioavailability of the immediate-release tablets compared to long-acting capsules.

- At equivalent total daily doses, the bioavailability of long-acting propranolol is ~60-65% that of immediate-release.[3]
- Propranolol dose frequency depends on the patient and condition and is between two and four times daily.
- Presumably the patient had been stabilized on immediate-release tablets before switching to Inderal®-LA. If so, use the dosage at the time of switch as a guide, if known. Account for any dose titrations of the Inderal®-LA.
- Depending on the patient and condition, consider switching to a total daily dose of immediate-release that is 50–75% of the current long-acting dose. Consider the current control of the condition and patient's ability to tolerate adverse effects.
  - E.g., if the daily dose of Inderal®-LA for a patient treated for angina pectoris is 160 mg once daily, consider switching to a daily dose of 80 mg to 120 mg of immediate-release propranolol as:
    - 40 mg BID, or
    - 60 mg BID, or
    - 40 mg TID
      - Starting with 40 mg BID allows for titration up to 40 mg TID if needed; depending on the indication, once the daily dose is stabilized, the frequency can be reduced (e.g., if stabilized on 40 mg TID, switch to 60 mg BID if desired).
- Monitor patient for:
  - exacerbation of symptoms/condition(s)
  - adverse effects such as bradycardia, hypotension, dizziness[6]
- Be prepared to titrate dose; adjustments every 3–7 days is appropriate for most indications (see information for specific condition).
- Ensure patient has rescue medication available if appropriate during the titration (e.g. nitroglycerin in the case of angina pectoris; triptans in the case of migraine prophylaxis).
- See CPS and RxFiles for usual dosing of immediate-release propranolol by indication.

**Alternative Beta-Blockers**

- Choose alternative beta-blocker based on indication, patient comorbidities, availability, and price.
  - See CPS and RxFiles for alternative beta-blockers and their dosing for specific indications, including those that are off-label.
- Select dosages of the alternative beta-blocker based on usual dosages/dosage ranges for the particular indication.
  - If the patient's Inderal®-LA dosage is at the lower end of the range, start with a low (starting) dosage of the alternative beta-blocker.
  - If the patient's Inderal® LA dosage is in the middle or at the higher end of the range, start with a dosage at a similar place or somewhat lower in the dosage range of the alternative beta-blocker.
    - E.g., if the patient's daily dose of Inderal®-LA for treatment of angina pectoris is 160 mg once daily and the patient is being switched to bisoprolol:
      - the dosage range of long-acting propranolol for stable angina is 60–320 mg daily[7] making 160 mg mid-range
      - the dosage range of bisoprolol for stable angina is 2.5–20 mg daily[7]
      - a mid-range dosage of bisoprolol is 10 mg daily; consider starting with 5 mg daily (which can be easily titrated up)
  - Monitor patient for:
    - exacerbation of symptoms/condition(s)
    - adverse effects such as bradycardia, hypotension, dizziness[6]
  - Be prepared to titrate dose.
  - Ensure patient has rescue medication available if appropriate during the titration (e.g., nitroglycerin in the case of angina pectoris; triptans in the case of migraine prophylaxis).

Health Canada Approved Indications of Oral Beta-Blockers*

| | HTN, mild to moderate | Heart Failure | Angina Pectoris | Post-MI | Supraventricular Arrhythmias | Ventricular Arrhythmias | Migraine Prophylaxis | Pheochromocytoma |
|---|---|---|---|---|---|---|---|---|
| Acebutolol | √ | – | √ | – | – | – | – | – |
| Atenolol | √ | – | √ | – | – | – | – | – |
| Bisoprolol | √ | – | – | – | – | – | – | – |
| Carvedilol | – | √ | – | – | – | – | – | – |
| Labetalol | √ | – | – | – | – | – | – | – |
| Metoprolol | √ | – | √ | √ | – | – | – | – |
| Nadolol | √ | – | √ | – | – | – | – | – |
| Nebivolol | √ | – | – | – | – | – | – | – |
| Pindolol | √ | – | √ | – | – | – | – | – |
| Propranolol IR | √ | – | √ | √ | √ | √ | √ | √ |
| Propranolol LA | √ | – | √ | – | – | – | – | – |
| Sotalol | – | – | -– | – | – | √ | – | – |
| Timolol | √ | – | √ | √ | – | – | √ | – |

HTN = hypertension; IR = immediate-release; LA = long-acting; MI= myocardial infarction
*See CPS and RxFiles for dosages as well as the beta-blockers that are used off-label for various indications.

Reproduced in part with permission from CPS [Internet]. Ottawa (ON): Canadian Pharmacists Association; c2022 [updated 2018 Jun 01; cited 2022 Mar 02]. Beta-Adrenergic Blocking Agents [CPhA monograph]. Available from: https://cps.pharmacists.ca. Also available in paper copy from the publisher.

### Therapeutic Alternatives

- Switching to a therapeutic alternative is only recommended if beta-blocker therapy can be tapered.
  - If there is a compelling reason to discontinue beta-blocker therapy, switch to a beta-blocker (immediate-release propranolol or another immediate-release beta-blocker) to taper, then initiate the alternative therapy.
    - Abrupt discontinuation of beta-blocker therapy may result in withdrawal and rebound symptoms such as[8,9]:
      - Angina, anxiety, headache, hyperthyroidism, myocardial infarction, rebound hypertension/hypertensive urgency, rebound tachycardia, tremor, ventricular arrhythmia.
        - Myocardial infarction and arrhythmias are rare[8]
      - Risk factors (especially for the cardiovascular symptoms) include hypertension and coronary artery disease.[9]
    - Taper the beta-blocker over 1 to 2 weeks[8,10] or even up to 4 weeks[11,12]
      - consider longer tapering regimens for more frail patients and/or those with coronary artery disease
      - adjust taper schedule based on presence/absence of withdrawal symptoms
- Choose alternative agent based on indication, patient comorbidities, potential drug interactions, availability, and price.
  - See CPS and RxFiles for therapeutic alternatives and their dosing for specific indications, including those that are off-label.
- When to initiate therapeutic alternatives will depend on the agent chosen, the indication, and patient factors. Possible strategies to switch include:
  - cross-taper
    - start the new agent at a low dose when the beta-blocker dose is 25–50% of original dose and titrate the new agent as the beta-blocker dose decreases and is discontinued
  - straight switch
    - start the new agent after the beta-blocker is discontinued and titrate
- Monitor patient for:
  - exacerbation of symptoms/condition(s)
  - adverse effects as appropriate for the chosen agent
- Ensure patient has rescue medication available if appropriate during the titration (e.g., nitroglycerin in the case of angina pectoris; triptans in the case of migraine prophylaxis).

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