

## CLOMIPHENE SHORTAGE

Clomiphene citrate is marketed under two different names in Canada: Clomid® by Sanofi Canada and Serophene® by EMD Serono.<sup>1</sup> Neither of these products is on the Saskatchewan Drug Plan & Extended Benefits Formulary.<sup>2</sup>

### Health Canada approved indications<sup>3</sup>

- Induction of ovulation in patients with persistent ovulatory dysfunction who desire pregnancy.

### Options to handle shortage:

- **Extemporaneous Compounding**

- Clomiphene bulk powder is not available at compounding suppliers available to community pharmacies (Xenex, Medisca), but can be ordered by PCCA pharmacies. PCCA pharmacies available in Saskatchewan: <http://www.pccarx.com/contact-us/find-a-compounder/>

- **Therapeutic alternatives:**

- Clomiphene is useful for women with **WHO class 2** anovulation.<sup>4</sup>
  - **WHO class 1:** hypogonadotropic hypogonadal anovulation (usually amenorrheic, low serum follicle-stimulating hormone (FSH) and low serum estradiol)
  - **WHO class 2:** normogonadotropic normoestrogenic anovulation (most have polycystic ovary syndrome (PCOS) and normal FSH and estradiol; luteinizing hormone (LH) is often high.)
  - **WHO class 3:** hypergonadotropic hypoestrogenic anovulation (many amenorrheic, often don't respond to ovulation induction therapies)
- Options for ovulation induction In women with **class 2 anovulation:**
  - Weight loss<sup>5</sup>
  - Tamoxifen and raloxifene are also selective estrogen modulators.<sup>6</sup> Not nearly as much data is available for either of these drugs concerning ovulation induction. Tamoxifen 20 mg to 60 mg daily starting on either cycle day three<sup>7,8</sup> or five<sup>9</sup> for five days has been studied.<sup>7-9</sup> Results have been mixed when compared to clomiphene when looking at pregnancy rates. One study found tamoxifen to be inferior to clomiphene<sup>7</sup>, while another found both had similar results.<sup>8,9</sup> A Cochrane review on the subject notes there was no difference found between clomiphene and tamoxifen but that the dearth of evidence regarding live births (outcomes often ovulation rates, sometimes pregnancy rates) limits the applicability of any of the results.<sup>10</sup>
  - Aromatase inhibitors (letrozole, anastrozole): off-label; perhaps more effective than clomiphene in obese women (BMI  $\geq 30\text{kg/m}^2$ )?<sup>5</sup> A Cochrane Review has concluded letrozole may be more effective than clomiphene in terms of live births and pregnancy rates (based on 15 RCTs) and that its effectiveness seems

to be similar to laparoscopic drilling (based on three RCTs). Two RCTs comparing letrozole to anastrozole found no difference in pregnancy rate.<sup>11</sup> A question of teratogenic effects prompted Health Canada to issue a “Physician Warning Letter” in 2005 about off-label use for ovulatory induction. Recent data suggests no teratogenic effects.<sup>5</sup> *Letrozole is contraindicated in premenopausal women.*<sup>3</sup> *Anastrozole is not recommended in pre-menopausal women (Serious Warnings and Precautions)*<sup>3</sup>

*Adverse events:* no difference in rates of ovarian hyperstimulation syndrome in clomiphene vs. letrozole.<sup>12</sup>

*Dosage letrozole:* ideal duration of protocol not established. Five days has been compared with 10 days with no differences reported in efficacy or adverse events.<sup>12</sup> Concern raised is that a 5 day protocol may not allow enough time for clearance of the letrozole prior to implantation, thereby potentially increasing the risk of teratogenic effects. Also unknown is ideal dose. One small study comparing 5 mg daily to 7.5 mg daily found no difference in efficacy or adverse events.<sup>13</sup>

*Dosage anastrozole:* only two studies have looked at anastrozole where it was compared with letrozole. In these studies, the dose used was 1 mg daily for five days starting on cycle day three.<sup>14,15</sup>

- Gonadotropin:<sup>4,5</sup> associated with higher costs, greater monitoring requirements, and multiple pregnancy
- Laparoscopic surgery<sup>4,6</sup>
- In vitro fertilization<sup>4</sup>
- Note: metformin in combination with clomiphene may result in higher pregnancy rates than either drug on its own; however, metformin on its own has not demonstrated statistically significant greater pregnancy rates compared to placebo.

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