Danazol Shortage

Table 1: Suppliers of Danazol[1]

Product	Strength	DIN	MFR
Cyclomen	50 mg	02018144	AVT
	100 mg	02018152	
	200 mg	02018160	

Health Canada approved indications of danazol[2]:

- treatment of **endometriosis** associated symptoms and/or to reduce the extent of endometriotic foci.
- symptomatic relief of severe pain and tenderness associated with **fibrocystic breast disease**

Management Options

- Danazol powder is not available for compounding.[3]

Therapeutic Alternatives

Endometriosis

- Endometriosis may cause pain and/or infertility[4,5]
- Surgical options are available if pharmacological treatment is ineffective or contraindicated[4,5]
- Danazol[4]:
    - may be effective for dysmenorrhea (less effective for chronic pelvic pain) but has no effect on infertility
    - poor response if endometrioma diameter exceeds 1 cm
    - limited by adverse effects: androgenic adverse effects (voice deepening [irreversible], hirsutism, acne, dyslipidemia); hypoestrogenic adverse effects (hot flashes, vaginal dryness)
    - considered when:
        - low-dose hormonal contraception ineffective or contraindicated
        - GnRH agonist therapy not used because:
            - marked unrecovered bone loss with GnRH agonist therapy
            - BMD not being evaluated
            - risk factors for osteoporosis
    - generally dosed 600 mg to 800 mg daily in two to four divided doses for three to six months
- See Tables 1-4 for alternatives to danazol for treatment of endometriosis

Table 1: Analgesics[4-7]

Agent	Place in Therapy	Dose for Endometriosis / Comments
Non-Steroidal Anti-Inflammatory Drugs	1st line for mild – moderate pelvic pain and dysmenorrhea Monotherapy or adjunct	See individual agents in Dysmenorrhea minor ailment guideline

Table 2: Hormonal Contraceptives[4-7]

Agent	Place in Therapy	Dose for Endometriosis	Comments	
Combined Hormonal Contraceptives				
Combined Oral Contraceptives	1st line Useful for pain, reducing menorrhagia and suppressing ovulation	See Hormonal Contraceptives minor ailment guideline Cyclical or continuous	See Hormonal Contraceptives minor ailment guideline Continuous use associated with irregular bleeding[8]	
Contraceptive Vaginal Ring				May be more effective than the patch for pain associated with rectovaginal endometriotic lesions[8]
Transdermal Contraceptive				More dysmenorrhea than COCs[9]
Progestin Only – women who cannot or choose to not use estrogen				
Depo-Medroxy-progesterone	Pain reduction Amenorrhea Consider when low-dose COC ineffective or contraindicated	150 mg intramuscularly every 6-12 weeks	Ovulation delayed upon discontinuation May be associated with irregular bleeding, weight gain, mood changes	
Oral Progestin	Pain Consider when low-dose COC ineffective or contraindicated.	Medroxyprogesterone 20-40 mg orally once daily Norethindrone 5-15 mg orally daily Dienogest 2mg orally once daily	May be associated with irregular bleeding, weight gain, mood changes	
Levonorgestrel Intrauterine System	May improve staging of endometriosis[10] Symptom control[10]	Effectiveness of low dose (less than 20 mcg/day) unknown Insert every 5 years	Irregular bleeding common in first 3 months; 35% amenorrheic at 1 year Provides effective symptom control for at least 3 years[11]	

Table 3: Gonadotropin-Releasing Hormone (GnRH) Analogues[4-6]

Agent	Place in Therapy	Dose for Endometriosis	Comments
GnRH Agonists + Add-Back Hormone Treatment	Pain (as effective as COCs, progestins) Consider when low-dose COC ineffective or contraindicated, recurrent symptoms or severe symptoms	**GnRH Agonists** Buserelin acetate 200 mcg TID into each nostril x 6 months Goserelin acetate 3.6 mg SC once monthly x 6 months Goserelin acetate long acting 10.8 mg SC every 12 weeks x 2 doses Leuprolide acetate 3.75 mg IM once monthly x 6 months or 11.25 mg IM every 3 months x 2 doses Nafarelin acetate 200 mcg into 1 nostril once daily in the morning and 200 mcg into other nostril once daily in the evening x 6 months Triptorelin pamoate 3.75 mg IM every 28 days x 6 months	Bone mineral density ↓ 1-3% after 3-6 months' use Symptoms commonly return 9-12 months following treatment completion Hypoestrogenic effects: hot flashes, insomnia, mood changes, vaginal atrophy All agents are equally effectvie; choose based on patient preference, cost, availability
		Add-Back: GnRH agonist as above + Estradiol-17-β 1 mg orally once daily (or equivalent) and progestin (e.g. medroxyprogesterone 2.5-5 mg orally once daily or norethindrone 5 mg orally once daily) Estrogen/progestin (combined oral contraceptive) Norethindrone 5 mg orally once daily	Relieves hypoestrogenic adverse effects and preserves bone mineral density without negatively impacting effectiveness for pain
GnRH Antagonist	Dysmenorrhea and non-menstrual pain Dyspareunia (higher dose) GnRH agonist indicated but patient prefers oral route	Elagolix 150 mg orally once daily up to 12 months (no evidence of benefit /safety beyond 12 months' exposure[12]) or 200 mg orally twice daily up to 6 months (limit to 6 months because of loss of bone mineral density[12]) Use lowest effective dose	Hypoestrogenic effects: hot flashes, insomnia, mood changes, vaginal atrophy, reduced bone mineral density
COC = combined oral contraceptive; IM=intramuscular; SC= subcutaneous; TID = three times daily			

Table 4: Aromatase Inhibitors[4-6]

Agent	Place in Therapy	Dose for Endometriosis	Comments
Aromatase inhibitors	Reserved for those with severe refractory symptoms Symptoms despite GnRH analogue treatment	Anastrozole 1 mg PO once daily Letrozole 2.5 mg PO once daily	Often used in combination with progestins. ↓ bone mineral density with prolonged use Ovarian follicular cyst development

Benign Breast Pain (Mastalgia)[13-15]

- **First line treatments (conservative)**
  - Reassurance of benign nature
    - when appropriate; has been found to reduce pain[16]
  - Physical
    - support garments → well-fitting and supportive bras; sports bras during activity
      - a non-randomized comparative trial reported 85% benefit among the sports bra arm and 58% among the danazol arm[17]
    - compresses → warm or cold
  - Acetaminophen
  - NSAIDs → oral or topical
  - Hormonal therapy manipulation
    - consider reducing doses/discontinuing hormone therapy in menopausal women
    - consider reducing estrogen content of combined hormonal contraceptives (COCs); however, in some studies COCs improved mastalgia
    - switch from cyclical to continuous COC regimen

- **Second line treatments → those with <u>severe, refractory mastalgia</u>**
  - Danazol - while it is the only agent with an official indication for mastalgia, it is second line because of its adverse effects profile
  - Tamoxifen (also in shortage situation until end of 2019)
    - relieves breast pain at doses of 10 mg or 20 mg once daily; fewer adverse effects with 10 mg
    - adverse effects: menopause-like symptoms, ↑risk of blood clots, strokes, uterine cancer and cataracts

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