



- Generic (Trade Name):** Levonorgestrel-Releasing Intrauterine System (Mirena®)
- Manufacturer:** Berlex Laboratories Inc.
- Indication:** An intrauterine hormone delivery system for fertility control in women of child-bearing age.
- Current Regulatory Status (in Canada and abroad):** Worldwide, Mirena® is currently available in 47 countries. A Notice of Compliance was granted by the Therapeutic Products Programme to Berlex Canada Inc. on November 24th, 2000 for marketing in Canada. The company launched the device in March 2001.
- Description:** Intrauterine devices (IUDs) are an effective, reversible and continual method of fertility control. All intrauterine devices exert their mechanism of action by causing a "foreign-body" reaction. This inhibits the passage of sperm into the fallopian tubes. Mirena® will be the only progestin-releasing intrauterine device marketed in Canada. The hormone-releasing IUDs have benefits over traditional IUDs; levonorgestrel-releasing devices can thicken the cervical mucous (making it difficult for sperm to pass), prevent proliferation of the endometrium and possibly suppress ovulation. Mirena® is a plastic T-shaped device, 32 mm in length. The stem has a storage system containing 52 mg of levonorgestrel, which releases 20 µg locally on a daily basis. It requires insertion by someone with appropriate training.
- Current Treatment:** Contraceptive devices are numerous, including hormonal and non-hormonal methods. Besides abstinence, fertility may be inhibited by oral contraceptives (estrogen-progestin, or progestin alone), implanted devices (i.e., Norplant®), injectable contraceptives (i.e., Depo-Provera®), barrier methods (i.e. condoms, cervical caps, diaphragms), spermicidal jellies, sponges, intrauterine devices, "natural" methods, and surgery. In Canada, the Nova-T® device is commercially available.
- Cost:** In Canada, the cost of the Mirena® IUD is \$290.00. In comparison, the Nova-T is \$56.20. According to the product literature, Mirena® and Nova-T® can be inserted for a maximum of 60 and 30 months, respectively. The annual cost associated with the use of Mirena® would be \$58.00, contrasting to \$22.48 with the Nova-T®.
- Evidence:** A recent publication in the British Journal of Obstetrics & Gynaecology discusses the levonorgestrel-releasing IUD (LNG-20, Mirena) as compared to other methods of reversible contraceptives. French et al did a systematic review and a meta-analysis of the randomized controlled trials available. Five studies met the criteria for inclusion in the meta-analysis, comparing LNG-20 with IUDs greater than 250 mm³ (CuT 380A, CuT 380 Ag), less than or equal to 250 mm³ (Nova-T, CuT 200, CuT 220), and to Norplant-2®. Overall, users of LNG-20 were significantly less likely to become pregnant or have an ectopic pregnancy when compared to users of intrauterine devices = 250 mm³. A statistically significant difference in observed pregnancy rates was not apparent when comparing LNG-20 to IUDs > 250 mm³. The patients using the non-hormonal IUDs were less likely to discontinue the device due to amenorrhea or



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Evidence (con't): hormone-related adverse effects, but more frequently cited menstrual bleeding and pain as reasons for discontinuance (devices > 250mm³). The difference noted between the users of Norplant[®]-2 and LNG-20 was that those patients using the former were more likely to experience spotting and prolonged bleeding, while those using the latter were significantly more likely to experience oligo-amenorrhea.

Adverse Effects: A low incidence of systemic adverse effects has been reported; these include headache, breast tenderness, nausea, acne, hirsutism and depression. Functional ovarian cysts have been observed, although most are asymptomatic and resolve spontaneously (i.e., over three weeks). Early on in the use of Mirena[®], menstrual irregularities (i.e., prolonged spotting) are common; this normally subsides and a reduction in blood loss is associated with menstruation, and some women become amenorrheic. This amenorrhea does not necessarily suggest a cessation in ovulation, as most users (75%) do continue to ovulate.

Conclusion: Long-acting contraception can be attained via sterilization, injectables, implants and intrauterine devices. Mirena[®] broadens the selection of available IUDs, with the added benefit of the release of levonorgestrel in the uterus. This product may be attractive to some patients, particularly to those who wish to have a long duration of (reversible) action, and to those who suffer with heavy and painful menses. However, the use of IUDs is not very high in Canada; statistics gathered in 1995 suggest that approximately 1.4 percent of women between 15 to 44 years of age using a contraceptive method chose IUDs.

- References:**
1. Anon. Levonorgestrel-releasing intrauterine system has many advantages. *Drugs Ther Perspect* 1997;10(5):11-3.
 2. Anon. Long-acting progestogen-only contraception. *Drug Ther Bulletin* 1996;34(12):93-6.
 3. Boroditsky R, Fisher W, Sand M. The 1995 Canadian Contraceptive Study. *J Soc Obstet Gynaecol Canada* 1996;18:1-31.
 4. Canada Approves Mirena, Intrauterine Hormone Delivery Contraceptive. Accessed at: <http://www.docguide.com/dg.nsf/PrintPrint/C8B72E28B55DD1C2852569BC00557514> (Accessed on March 1, 2001.)
 5. French RS, Cowan FM, Mansour D, et al. Levonorgestrel-releasing (20mcg/day) intrauterine systems (Mirena) compared with other methods of reversible contraceptives. *Br J Obstet Gynecol* 2000;107:1218-25.
 6. Product monograph of Mirena[®] (levonorgestrel-releasing intrauterine system). Berlex Canada Inc. Lachine, PQ. November 2000.
 7. The Canadian Consensus Conference on Contraception. SOGC [Reprint]. Ribosome Communications Inc. Toronto, On. 1998.

The contents of this bulletin are current as of April 2001.

The Emerging Drug List highlights drugs not yet approved in Canada that are anticipated to have a significant impact on the health care system. Minimal information is available about these drugs, and they may in future become the subject of an early assessment.

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