

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

18-680

Trade Name: ParaGard Copper T Model TCU 380A Intrauterine
Contraceptive

Generic Name: intrauterine copper contraceptive

Sponsor: The Population Council

Approval Date: November 15, 1984

Indications: For intrauterine contraception.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-680

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

18-680

APPROVAL LETTER

NOV 15 1984

NDA 18-680

The Population Council
Attention: Harold A. Nash, Ph.D.
1230 York Avenue
New York, New York 10021

Dear Dr. Nash:

Reference is made to your new drug application dated September 4, 1981 and to your resubmission dated January 19, 1983, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Copper T Model TCu 380A (Intrauterine Copper Contraceptive).

We also refer to your communications of April 11, June 21, and August 25, 1983.

The application was filed on August 25, 1983.

We have completed our review of this application and have concluded that this drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

It is understood from the telephone discussion on September 7, 1983 between you and Mr. Helmut Nunn of this Administration that the expiration date for this product will be four years.

The enclosures summarize the conditions relating to the approval of this application.

Sincerely yours,

Sincerely yours,

cc: NDA Orig.

HFN-810

HFL-10

HFN-83

HFN-810/Kertesz, Berliner,

Bennett; Mr. Nunn

HFN-810/LCarter/02/01/84;

rch/3/19; 11/14/84 (3901C)

R/D init. by REastep/2/10/84

Elaine C. Esber, M.D.

Acting Director

Office of Biologics Research and Review

Center for Drugs and Biologics

Enclosures: Records and Reports Requirement (Reg. 310.300)

Conditions of Approval of NDA

Concur: Nunn/2/8, 3/21;

Berliner, Bennett/2/10, 3/21;

Kertesz/2/13, 3/21;

Sobel/2/14, 3/21/84

VGlocklin/3/28/84

APPROVAL

Elaine C. Esber 11/15/84

Elaine C. Esber, M.D.
Acting Director
Office of Biologics Research and Review
Center for Drugs and Biologics

Records and Reports Requirement (Reg. 310.300)
Conditions of Approval of NDA

National Center for Drugs and Biologics

REAPPRAISE NDA

VGlocklin 3/21/84
VGlocklin 3-28-84

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

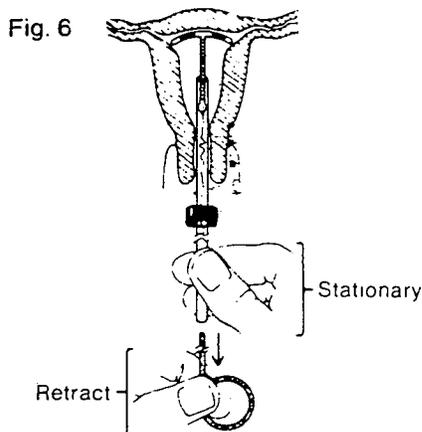
APPLICATION NUMBER:

18-680

LABELING

Step 5

Withdraw the solid rod while holding the insertion tube stationary (Fig. 6)



Step 6

Withdraw the insertion tube from the cervical os until the strings are visible. Be sure sufficient length of string is visible to facilitate checking for the presence of the Copper T (Fig. 7).

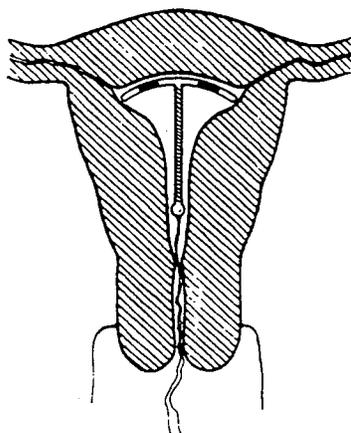


Fig. 7

US Patent 3,533,406
 THE POPULATION COUNCIL
 New York, New York 10017

Manufactured for:
The Population Council
 New York, New York 10017
 by
Finishing Enterprises Inc.
 North Tonawanda, New York 14120

PRESCRIBING INFORMATION

Copper T Model TCU 380A

**Brand of
 Intrauterine Copper Contraceptive**

Description:

The polyethylene body of the Copper T Model 380A intrauterine copper contraceptive is wound with approximately 176 mg of copper wire and carries a copper collar of approximately 66.5 mg of copper on each of its transverse arms. The exposed surface areas of copper is 380 ± 23 mm². The dimensions of the T are 36 mm in the vertical direction and 32 mm in the horizontal direction. The dependent tip of the T is enlarged to a ball having a diameter of 3 mm. The T is equipped with polyethylene threads which are tied through the ball at the tip and are for the purpose of easy removal of the IUD. The T contains barium sulfate to render it radiopaque. It is packaged together with an insertion tube and plunger in a Tyvek - polyethylene pouch and sterilized. The inserter tube is equipped with a movable flange to aid in gauging the depth to which the insertion tube should be inserted through the cervical canal and into the uterine cavity.

Clinical Pharmacology:

Available data indicate that the contraceptive effectiveness of the Copper T is enhanced by a minute quantity of copper being released continuously from the copper coil and sleeves into the uterine cavity. The exact mechanism by which metallic copper enhances the contraceptive effect of an IUD has not been conclusively demonstrated. Various hypotheses have been advanced, the most common being that copper placed in the uterus interferes with enzymatic or other processes that regulate blastocyst implantation.

Animal studies suggest that copper may play a role in reducing sperm transport within the uterine environment.

Indications and Usage:

The Copper T Model TCU 380A is indicated for contraception.

Different event rates have been reported with the use of different intrauterine contraceptives. Inasmuch as these rates are usually derived from separate studies conducted by different investigators in several populations, they cannot be compared with precision. Even in studies with the same device, considerably different rates are likely to be obtained because of differing characteristics of the study population. Furthermore, event rates per unit time tend to decrease as studies are extended because more susceptible subjects discontinue due to expulsions and adverse reactions or pregnancy, leaving the study population richer in less susceptible subjects. In clinical trials conducted in the United States, use-effectiveness of the Copper T Model TCU 380A as calculated by the life table method was determined as follows: (Rates are expressed as events per 100 women through 12, 24, 36 and 48 months of use).

This experience is based on 23,126 woman months of use, including 679 women who completed 12 months of use, 440 women who completed 2 years of use, 284 women who completed 3 years of use, and 153 women who completed 4 years of use.

Cumulative rates were:

	12 MONTHS	24 MONTHS	36 MONTHS	48 MONTHS
Pregnancy	0.9	1.2	1.8	1.9
Expulsion	5.8	8.2	9.2	10.0
Medical removal	14.6	23.9	29.5	33.7
Continuation rate	75.7	56.9	44.5	35.1

Contraindications:

Pregnancy or suspicion of pregnancy; anemia; distortion of uterine cavity; acute pelvic inflammatory disease or a history of repeated pelvic inflammatory disease; postpartum endometritis or infected abortion in the past 3 months; previous ectopic pregnancy; endometrial or cervical malignancy; unexplained genital bleeding until cancer is ruled out; acute cervicitis; known or suspected allergy to copper; diagnosed Wilson's disease, valvular heart disease; leukemia; or use of chronic corticosteroid therapy because of the increased susceptibility to infection with certain microorganisms that may be introduced at the time of an IUD insertion

Warnings:

A. Pregnancy: (1) Septic Abortion: Reports have indicated an increased incidence of septic abortion associated in some instances with septicemia, septic shock and death in patients becoming pregnant with one of several types of IUDs in place. Most of these reports have been associated with the first trimester of pregnancy. In some cases, the initial symptoms have been insidious and not easily recognized. If pregnancy should occur with a Copper T *in situ*, the Copper T should be removed if the string is visible or, if removal proves to be or would be difficult, interruption of the pregnancy should be considered and offered as an option. If the patient elects to maintain the pregnancy and the Copper T remains *in situ*, she should be warned that there may be an increased risk of abortion or premature labor and/or sepsis and she should be followed with close vigilance.

(2) Ectopic Pregnancy:

(a) A pregnancy which occurs with an IUD *in situ* is more likely to be ectopic than a pregnancy occurring without an IUD. Therefore patients who become pregnant while using a TCU 380A should be carefully evaluated for the possibility of an ectopic pregnancy.

(b) Special attention should be directed to patients with delayed menses, slight metrorrhagia and/or unilateral pelvic pain, and to those patients who wish to interrupt a pregnancy occurring in the presence of the IUD, to determine whether ectopic pregnancy has occurred.

(3) Continuation of Pregnancy: If the patient chooses to continue the pregnancy and the TCU 380A remains *in situ*, she must be warned of the increased risk of spontaneous abortion and the increased risk of sepsis, including death. The patient must be closely observed and she must be advised to report immediately all abnormal symptoms, such as flu-like syndrome, fever, abdominal cramping and pain, bleeding or vaginal discharge, because generalized symptoms of septicemia may be insidious.

B. Pelvic Infection: An increased risk of pelvic inflammatory disease associated with the use of IUDs has been reported. This risk appears to be greatest for young women who have a multiplicity of sexual partners. Salpingitis can result in tubal damage and occlusion, thereby threatening future fertility. Therefore, it is recommended that patients be taught to look for symptoms of pelvic inflammatory disease. The decision to use an IUD in a particular case must be made by the physician and patient with the consideration of a possible deleterious effect on future fertility if pelvic infection occurs.

Pelvic infection may occur with a TCU 380A *in situ* and at times result in the development of tubo-ovarian abscesses or general peritonitis. The symptoms of pelvic infection include: new development of menstrual disorders (prolonged or heavy bleeding), abnormal vaginal discharge, abdominal or pelvic pain, dyspareunia, fever. The symptoms are especially significant if they occur following the first two or three cycles after insertion. Appropriate aerobic and anaerobic bacteriologic studies should be done and antibiotic therapy initiated promptly. If the infection does not show marked clinical improvement within 24 to 48 hours, the TCU 380A should be removed and the continuing treatment reassessed on the basis of the results and sensitivity tests. Genital actinomycosis has been associated primarily with long term IUD use. It has been reported with copper bearing IUDs as well. Treatment requires prompt removal of the IUD and appropriate antibiotic therapy.

C. Embedment: Partial penetration or lodging of the TCU 380A in the endometrium or myometrium can result in a difficult removal. This may occur more frequently in smaller uteri.

D. Perforation: Partial or total perforation of the uterine wall or cervix may occur with the use of the TCU 380A, usually during insertions into patients sooner than two months after abortion or delivery or in uterine cavities too small for the TCU 380A. The possibility of perforation must be kept in mind during insertion and at the time of any subsequent examination. If perforation occurs, laparotomy or laparoscopy should be performed as soon as medically feasible and the TCU 380A removed. Abdominal adhesions, intestinal penetration, intestinal obstruction, and local inflammatory reaction with abscess formation and erosion of adjacent viscera may result if the TCU 380A is left in the peritoneal cavity.

E. Medical Diathermy: The use of medical diathermy (short-wave and microwave) in a patient with a metal-containing IUD may cause heat injury to the surrounding tissue. Therefore, medical diathermy to the abdominal and sacral areas should not be used on patients using a TCU 380A.

F. Effects of Copper: Additional amounts of copper available to the body from the TCU 380A may precipitate symptoms in women with undiagnosed Wilson's disease. The incidence of Wilson's disease is 1 in 200,000. The long-term effects of intrauterine copper on the offspring are unknown.

Precautions and Routine Examinations:

A. Patient Counseling:

Prior to the insertion, the physician, nurse, or other trained health professional must provide the patient with the Patient Brochure. The patient should be given the opportunity to read the brochure and discuss fully any questions she may have concerning the TCU 380A as well as other methods of contraception.

B. Patient Evaluation and Clinical Considerations:

(a) A complete medical history should be obtained to determine conditions that might influence the selection of an IUD. A physical examination should include a pelvic examination, "Pap" smear, gonorrhea culture and, if indicated, appropriate tests for other forms of genital disease including actinomycosis, which can usually be detected on the Pap test. The physician should determine that the patient is not pregnant.

(b) The uterus should be carefully sounded prior to the insertion to determine the degree of patency of the endocervical canal and the internal os, and the direction and the depth of the uterine cavity. Exercise care to avoid perforation with the sound. In occasional cases, severe cervical stenosis may be encountered. Do not use excessive force to overcome this resistance.

(c) The uterus usually sounds to a depth of 6 to 8 cm. Insertion of a TCU 380A into a uterine cavity measuring less than 6.5 cm by sounding may increase the incidence of pain, bleeding, partial or complete expulsion, perforation, and possibly pregnancy.

(d) To reduce the possibility of insertion in the presence of an existing undetermined pregnancy, the optimal time for insertion is the latter part of the menstrual flow or one or two days thereafter. The TCU 380A should not be inserted postpartum or postabortion until involution of the uterus is complete. The incidence of perforation and expulsion is greater if involution is not complete.

It is, however, necessary to place the TCU 380A as high as possible within the uterine cavity to help avoid partial or complete expulsion that could result in pregnancy.

Since the Copper T represents a different design in intrauterine contraception, physicians are cautioned that it is imperative for them to become thoroughly familiar with the instructions for use before attempting placement of the Copper T.

(e) IUDs should be used with caution in those patients who have an anemia or a history of menorrhagia or hypermenorrhea. Patients experiencing menorrhagia and/or metrorrhagia following IUD insertion may be at risk for the development of hypochromic microcytic anemia. Also IUDs should be used with caution in patients receiving anticoagulants or having a coagulopathy.

(f) Syncope, bradycardia or other neurovascular episodes may occur during insertion or removal of IUDs, especially in patients with a previous disposition to these conditions.

(g) Patients with valvular or congenital heart disease are more prone to develop subacute bacterial endocarditis than patients who do not have valvular or congenital heart disease. Use of an IUD in these patients may represent a potential source of septic emboli.

(h) Use of an IUD in those patients with acute cervicitis should be postponed until proper treatment has cleared up the infection.

(i) Since the TCU 380A may be partially or completely expelled, patients should be reexamined and evaluated shortly after the first postinsertion menses, but definitely within three months after insertion. Thereafter annual examination with appropriate medical and laboratory evaluation and a Pap smear including examination for actinomycosis organisms should be carried out. The TCU 380A should be replaced every four years.

(j) The patient should be told that some bleeding or cramps may occur during the first few weeks after insertion, but if these symptoms continue or are severe she should report them to her physician. She should be instructed on how to check after each menstrual period to make certain that the thread still protrudes from the cervix and cautioned that there is no contraceptive protection if the TCU 380A has been expelled. She should also be cautioned not to dislodge the TCU 380A by pulling on the thread. If a partial expulsion occurs, removal is indicated and a new TCU 380A may be inserted. The patient should be told to return within four years for removal of the TCU 380A and for replacement if desired.

(k) Rarely, a copper-induced urticarial allergic skin reaction may develop in women using a copper-containing IUD. If symptoms of such an allergic response occur, the patient should be instructed to tell the consulting physician that a copper-containing device is being used.

(l) The TCu 380A should be removed for the following medical reasons: menorrhagia and/or metrorrhagia producing significant anemia; uncontrolled pelvic infection; intractable pain often aggravated by intercourse; dyspareunia; pregnancy, if the thread is visible; endometrial or cervical malignancy; uterine or cervical perforation; or any indication of partial expulsion.

(m) If the retrieval thread cannot be visualized, it may have retracted into the uterus or have been broken off, of the TCu 380A may have been expelled. Localization usually may be made by feeling with a probe; if not, x-ray or sonography can be used. When the physician elects to recover a TCu 380A with the thread not visible, the removal instructions should be considered.

(n) If any patient with a TCu 380A suddenly develops overt clinical hepatitis or abnormal liver function tests, appropriate diagnostic procedures should be initiated.

(o) It has been reported that pregnancy rates in Copper IUD users may be considerably higher among diabetics than among non diabetics: Other reports indicate similar pregnancy rates in the two groups.

C. Requirements for Continuation and Removal:

(1) The Copper T must be replaced before the end of the fourth year of use. There is no evidence of decreasing contraceptive efficacy with time before four years, but the contraceptive effectiveness at longer times has yet to be established; therefore, the patient should be informed of the known duration of contraceptive efficacy and be advised to return in four years for removal and possible reinsertion.

(2) The Copper T should be removed for the following medical reasons: menorrhagia and/or metrorrhagia producing anemia; uncontrolled pelvic infection; genital actinomycosis; intractable pain often aggravated by intercourse; dyspareunia; pregnancy, if the string is visible; on diagnosis of endometrial or cervical malignancy; uterine or cervical perforation; or increase in length of the thread extending from the cervix, or any other indication of partial expulsion.

D. Continuing Care of Patients Using Copper Ts:

(1) Patients should be reexamined and evaluated within 3 months after Copper T insertion.

(2) Routine annual examination with appropriate medical and laboratory evaluation should be carried out.

Adverse Reactions:

Perforations of the uterus and cervix may occur. Perforation into the abdomen may be followed by abdominal adhesions, intestinal penetration, intestinal obstruction, local inflammatory reaction with abscess formation and erosion of adjacent viscera. Pregnancy may occur with the TCu 380A *in situ* or when the TCu 380A has been partially or completely expelled.

The incidence of spontaneous abortion, when conception occurs with intrauterine devices *in situ*, appears to be increased over that in unprotected women. Insertion cramping, usually of no more than a few seconds duration, may occur; however, some women may experience residual cramping for several hours or even days. Intermenstrual spotting or bleeding or prolonged or increased menstrual flow may occur.

Pelvic infection including salpingitis with tubal damage or occlusion may occur. This may result in future infertility. Complete or partial expulsion of the TCu 380A may sometimes occur, particularly in those patients with uteri measuring less than 6.5 cm by sounding. Urticarial allergic skin reaction may occur. The following complaints have also been reported, with IUDs, although their relation to the TCu 380A has not been established: amenorrhea or delayed menses, backaches, cervical erosion, cystic masses in the pelvis, vaginitis, leg pain or soreness, weight loss or gain, nervousness, dyspareunia, cystitis, endometritis, septic abortion, septicemia, leukorrhea, infection of the reproductive organs, with actinomycosis, ectopic pregnancy, difficult removal, uterine embedment, anemia, pain, neurovascular episodes including bradycardia and syncope secondary to insertion, dysmenorrhea, and fragmentation of the IUD.

Dosage and Administration:

The Copper T is placed in the uterine cavity.

The optimal time of insertion is during the latter part of the menstrual period or one of two days thereafter. The cervical canal is relatively patent at this time, and there is little or no chance that the patient may then be pregnant.

Present information indicates that the efficacy is retained for 48 months. Until adequate data indicating a longer effective life become available, the Copper T 380A must be removed and a new one inserted on or before 48 months from the date of insertion.

The physician should become thoroughly familiar with the Instructions for Use before attempting insertion of the Copper T.

How Supplied:

Available in cartons of 20 units. Each Copper T is sterile packaged in a Tyvek[®] — polyethylene pouch, together with an inserter tube and plunger rod.

INSTRUCTIONS FOR USE

Copper T Model TCu 380A

Brand of

Intrauterine Copper Contraceptive

The Copper T Intrauterine Copper Contraceptive represents a different design in intrauterine contraceptives. Physicians are, therefore, cautioned that it is imperative that they become thoroughly familiar with instructions for insertion before attempting placement of the Copper T. The insertion technique is different in several respects from that employed in intrauterine contraceptives currently available, and the physician should pay particular attention to the drawings and commentary accompanying these instructions.

A. Pre-insertion: (1) It is essential that sterile technique be utilized throughout the insertion procedure.

(2) Perform a thorough pelvic examination to determine freedom from overt disease and to determine position and shape of the uterus. Rule out pregnancy and other contraindications.

(3) Gonorrhea cultures should be taken.

(4) The endocervix should be cleansed with an antiseptic solution.

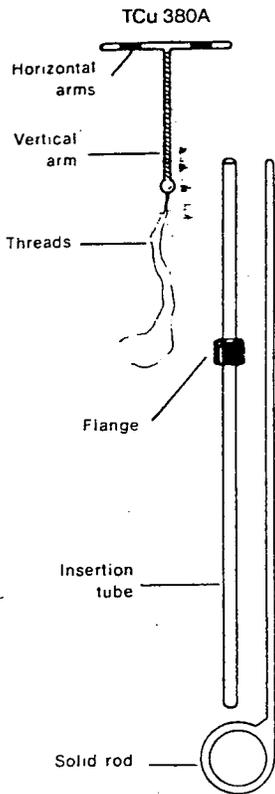
(5) With a speculum in place, gently insert a sterile sound to determine the depth and direction of the uterine canal. Be sure to determine the position of the uterus before insertion. The use of a tenaculum to straighten the uterine canal prior to sounding and insertion is recommended.

(6) The Copper T should preferably be inserted during or shortly after menstruation to insure a non-pregnant state. (*This approach may not be practical in certain clinical situations.*)

Caution:

It is generally believed that most perforations occur at the time of insertion, although the perforation may not be detected until some time later. The position of the uterus should be determined during the pre-insertion examination. Great care must be exercised during the pre-insertion sounding and subsequent insertion. No attempt should be made to force the insertion.

HOW TO INSERT



Step 1

To minimize chance of introducing contamination, do not remove the T from the inserter tube prior to placement in the uterus. Do not bend the arms of the T earlier than 5 minutes before it is to be introduced into the uterus.

In the absence of sterile gloves, this can be accomplished without destroying sterility by folding the arms in the partially opened package. Place the partially opened package on a flat surface and pull the solid rod partially from the package so it will not interfere with assembly. Place thumb and index finger on top of package on ends of the horizontal arms. Push insertion tube against arms of T as indicated by arrow in Fig. 1 to start arms folding.

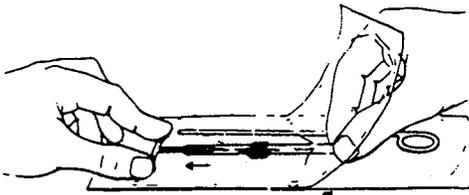


Fig. 1

Complete the bending by bringing thumb and index finger together while using the other hand to maneuver the insertion tube to pick up arms of the T (Fig. 2). *Insert no further than necessary to insure retention of the arms.* Introduce the solid rod into the insertion tube from the bottom alongside the threads until it touches the bottom of the T.

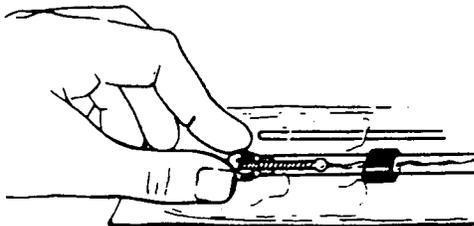


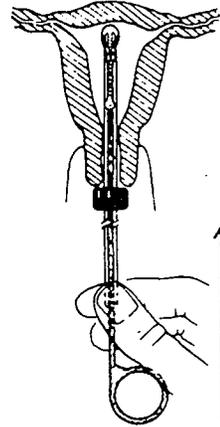
Fig. 2

Step 2

Adjust the movable flange so that it indicates the depth to which the Copper T should be inserted and the direction in which the arms of the T will open. At this point, make certain that the horizontal arms of the T and the long axis of the flange lie in the same horizontal plane. Introduce the loaded inserter through the cervical canal and upwards until the T lies in contact with the fundus. The movable flange should be at the cervix (Fig. 3).

Do not force the insertion

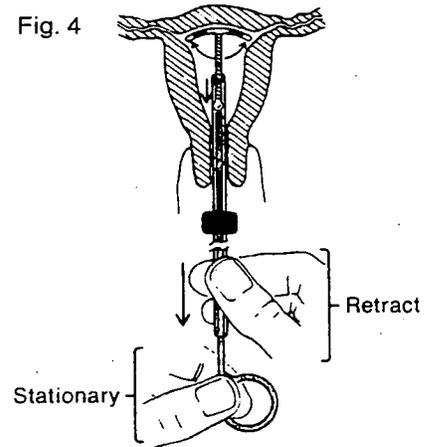
Fig. 3



Step 3

To release the Copper T, withdraw the insertion tube not more than 1/2 inch while the solid rod is not permitted to move. This releases the arms of the T (Fig. 4).

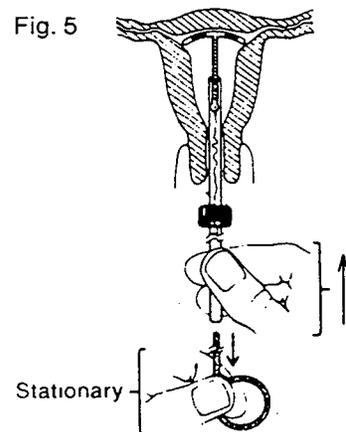
Fig. 4



Step 4

After the arms are released, the inserter tube should be moved upward until the resistance of the fundus is reached. This will assure placement of the T at the highest possible position within the endometrial cavity (Fig. 5).

Fig. 5



PATIENT INFORMATION

Copper T Model TCu 380A Brand of Intrauterine Copper Contraceptive

This brochure provides information on the use of intrauterine contraceptive devices (IUDs) in general, and the Copper T Model TCu 380A in particular. There are other birth control methods that may be suitable. Before deciding which type of birth control method to use, you should read this brochure and have the opportunity to discuss fully with your doctor any questions you may have about the Copper T Model TCu 380A, other IUDs, the Pill, and other methods of contraception.

PREINSERTION INFORMATION

What You Should Know About The IUD

IUDs are small articles of various sizes and shapes that are inserted into the uterus (womb). The purpose of the IUD is to prevent pregnancy.

How the IUD prevents pregnancy is not completely understood. Several theories have been suggested. IUDs seem to interfere in some manner both with fertilization and with the implantation of the fertilized egg in the lining of the uterus when fertilization does occur.

The IUD does not prevent the release of an egg from the ovary. The effectiveness of an IUD is measured by the pregnancy rate of women who use it. Acceptability to the user must also take into account the adverse reactions and side effects that may be associated with its use.

Before insertion your doctor will perform a pelvic examination to determine the size and position of the uterus or the presence of lumps or any other abnormality. The uterus usually is tipped forward a bit, bending at the neck or cervix. However, in some women it is tipped backward or bent sharply forward. Your doctor must know this before inserting anything. In some rare instances a doctor may be unable to insert an IUD due to the very small size, the shape or the position of the uterus.

Using an instrument called a speculum, your doctor exposes the cervix in order to take smears of the secretions to make sure you have a healthy vagina and do not have cancer. The Pap (cancer) test is made from one or more of the smears obtained. Your doctor may also perform other laboratory tests before inserting an IUD, including tests for genital disease.

Your doctor will cleanse the cervix with a surgical antiseptic, then grasp the front lip of the cervix with an instrument called a tenaculum, which may feel like a pin prick or like somebody pinched you. The cervix is gently pulled with the tenaculum to make it easier for the cervical opening to be seen, and to hold the uterus in position for an insertion. This will make the insertion easier.

Your doctor will then insert a sound (a thin, smooth, round-ended probe) through the cervical canal to the top or fundus of the uterus to measure the depth of the uterine cavity. The internal os (opening) sometimes resists, so the doctor may have to exert a little pressure, which may hurt momentarily. Sounding only takes a few seconds after which the instrument is withdrawn. The IUD is then inserted. You could experience a momentary cramping... or you may feel nothing at all.

After removing the insertion instrument, your doctor will cut the thread attached to the end of the IUD stem.

Use Effectiveness

Pregnancy and adverse reaction rates that have been reported with the use of various IUDs differ because these rates are usually derived from separate studies conducted by different investigators in several population groups. Therefore these rates cannot be compared with any precision.

Clinical trials with the Copper T Model 380A covered 21,126 women for 36 months of use including 12 months for 679 women, 24 months for 440 women, 36 months for 284 and 48 months for 153. In the first year of use, the number of unplanned pregnancies was about 1 per 100 women or, 1 woman out of 100 became pregnant while using the Copper T Model 380A. The number of expulsions was about 6 per 100 women; the number of adverse reactions requiring medical removal of the Copper T was about 15 per 100 women.

What You Should Tell Your Doctor

Before you have a Copper T inserted, it is your responsibility to inform your doctor fully of your past medical history. Tell your doctor if you now have, or have had, or suspect that you had, any of the following conditions which might make the Copper T unsuitable as a method of contraception for you:

- Abnormalities of the uterus, or of other reproductive organs
- Allergy to copper
- Anemia
- Bleeding between periods
- Blood-clotting disorders, or if you are taking blood-thinning medicine
- Cancer or other diseases of the uterus, cervix or other reproductive organs
- Chronic cortisone or other steroid therapy
- Diabetes treated with insulin
- Fainting attacks
- Genital actinomycosis (a bacterial disease)
- Heart disease
- Heart murmur
- Heavy menstrual flow
- Infection or inflammation of the uterus or cervix
- Leukemia
- Pelvic infection, for example, pus in the fallopian tubes
- Prior IUD use
- Prior uterine surgery
- Recent abortion or miscarriage
- Recent pregnancy (uterine or ectopic)
- Severe menstrual cramps
- Suspected pregnancy
- Suspicious or abnormal Pap test
- Unexplained vaginal bleeding
- Vaginal discharge or infection
- Venereal disease
- Wilson's disease

Be sure to tell your doctor if you think you are pregnant. An IUD should not be inserted in a pregnant woman.

Adverse Reactions

Some adverse reactions and side effects are very serious and occur rarely, whereas others are less serious, common with IUDs, and transient. As your doctor to tell you what the approximate severity, frequency, and duration are for the various adverse reactions and side effects.

The following adverse reactions and side effects have been reported with IUDs and may occur after the Copper T is inserted:

- Pregnancy with the Copper T in the uterus or when it has been partially or completely expelled
- Spontaneous abortion (miscarriage) if pregnancy occurs with the Copper T in the uterus. This possibility is greater if you have a Copper T than if you do not have an IUD.
- Complete or partial expulsion
- Bleeding or spotting between periods
- Missed or late periods

- Heavy or prolonged periods
- Painful periods
- Anemia
- Pain and cramps at insertion or following insertion
- Difficult removal of the Copper T
 - Embedment in the uterus
- Erosion or infection of the cervix
- Cysts in the pelvis, for example, of the ovaries or fallopian tubes
- Vaginal discharge and infection
- Inflammation of the lining of the uterus
- Inflammation of the lining of the urinary bladder
- Backache
- Leg pain and soreness
- Painful intercourse
- Nervousness
- Septic abortion (infected miscarriage) followed in some cases by blood poisoning (septicemia), which can lead to death. (The small possibility that becoming pregnant may result in a septic abortion is something you may wish to consider before having a Copper T inserted.)
- Blood poisoning (septicemia) which may result from a very severe pelvic infection.
- Pregnancy outside the uterus (ectopic pregnancy, for example, in the fallopian tube or ovary) usually requiring surgery.
- Perforation of the uterus that could result in abdominal adhesions, intestinal penetration, intestinal obstruction, local inflammatory reaction with abscess formation and erosion of adjacent organs. Surgery is required to remove the Copper T in such instances.
- Perforation of the cervix
- Fainting and abnormally slow heart beat at the time of insertion or removal
- Fragmentation of the IUD
 - Pelvic infection including inflammation of the fallopian tubes, which may damage or block them. (This could decrease future chances of getting pregnant or even prevent it and require major surgery.) Bacterial infection of the reproductive organs with *Actinomyces* has been associated primarily with long-term IUD use. It has been reported with the use of the copper-bearing IUDs as well. Treatment requires prompt removal of the IUD and antibiotic therapy.
- Allergic skin reaction due to the copper on the Copper T.

If you decide on the Copper T as your method of birth control, read the following information and instructions carefully. Please keep this brochure so that you may refer to it.

This brochure may be revised from time to time. You may want to check with your doctor at your next visit to see if you have the most recent version. If you have any questions or complaints, consult your doctor.

POSTINSERTION INFORMATION

Description

The Copper T Model TCu 380A, an intrauterine copper contraceptive, is a small plastic object shaped like a letter T, with copper collars on the cross arms and a fine copper wire wrapped around the stem of the T. A monofilament white plastic thread is attached at the end of the stem. The Copper T measures approximately 36 mm high and 32 mm wide. Copper enhances the contraceptive effect of the plastic T, which also serves as a flexible carrier for the copper.

This addition of copper makes the Copper TCu 380A almost as effective as the Pill in preventing pregnancy when the Copper T is properly placed within the uterus. The copper of the Copper T is slowly and continuously released into the uterus, but is largely cast out with the menstrual flow. Because of the presence of copper, the Copper T is considered to be a drug; it therefore underwent the same type of rigid testing as any recently developed drug to establish its relative safety and effectiveness.

Directions for Use

1. Checking your IUD. A white thread with two strands is attached to the Copper T so you can check to see if it is still in place, since the IUD can come out of the uterus without your knowing it. This occurs most often during or right after a menstrual period, especially in the first six months following insertion. Take these steps to make sure your Copper T is in place:

- Wash your hands.
- Squat or seat yourself on the toilet.
- Insert an index or middle finger high in the vagina and locate the cervical opening (mouth of the uterus). The cervix feels firm like the tip of your nose.
- Feel for the thread of the Copper T which should be protruding from the cervix high in your vagina.
- If you can feel the thread, it is likely that the Copper T is in place and working. You should not pull on the thread. This may dislodge the Copper T.

f. During the first month after insertion you should check several times to make sure the thread is protruding from the cervix. Thereafter, it is advisable to check after each menstrual period.

g. If you think the Copper T has come out or has been dislodged, for example, if you cannot feel the thread or you can feel the Copper T itself notify your doctor as soon as you can for an examination. Protect yourself from pregnancy by using another birth control method, such as the condom (rubber). (Except for the Pill these alternative methods of birth control are not as effective as the Copper T when it is properly positioned.)

h. After insertion of your Copper T, you should return to see your doctor as soon as possible after your next menstrual period, but no later than three months after insertion. This will allow the doctor to make sure that the Copper T is in the correct position.

It is not necessary to use another method of contraception with a Copper T if it is in the proper position in the uterus and you have it replaced at the proper time. Don't expect the Copper T to work if you are already pregnant and your doctor doesn't know it.

i. After your first checkup, you should be checked at least once a year by your doctor.

2. Continuation and removal. While you are using the Copper T, you may use tampons or pads and take douches, if this is your usual practice. You may also have sexual relations as usual. With some IUDs, you may use the IUD until you wish to become pregnant. It is necessary that your Copper TCu 380A Model be replaced within four years in order for you to continue being protected against pregnancy. Check with your doctor concerning this. You should return to your doctor if you wish to have your Copper T removed.

Removal of the Copper T is usually a simple procedure that causes little discomfort. When it is time to remove the Copper T, your doctor will exert a firm, steady pull on the retrieval thread with an instrument. Normally the Copper T will come out readily. A new replacement Copper T can be inserted immediately after removal of the old one. **UNDER NO CIRCUMSTANCES SHOULD YOU OR ANYBODY BUT YOUR DOCTOR TRY TO REMOVE THE Copper T.**

Although the Copper T is usually removed easily, exceptions are possible. In some instances the retrieval thread is not visible; or it could break when the doctor pulls on it. If the thread cannot be seen, or if it breaks off, the doctor (after determining that you are not pregnant) may be able to remove the Copper T simply by reaching into the uterus with a slim instrument, or may have to locate the Copper T by x-ray or another technique. If this doesn't succeed, you may have to be hospitalized to have the Copper T removed.

Side Effects

See also the list of adverse reactions and side effects in the section under Preinsertion Information.

Expulsion, cramping, and bleeding are more likely to occur in women with unusually small uterine cavities. The following may occur during or after the Copper T insertion:

- Some bleeding may follow the insertion. Because of this, your doctor may choose to insert your Copper T during or at the end of your menstrual period or one or two days later. Insertion at this time reduces the possibility that you are pregnant at the time of your Copper T insertion.
- Bleeding between menstrual periods, usually in the form of spotting, may occur during the first weeks after insertion. Menstrual periods after the insertion may be heavier and longer. If these conditions continue or are severe, consult your doctor.

3. Pain, usually in the form of uterine cramps or low backache, may occur at the time of insertion and is usually of no more than a few seconds' duration. However, some women may experience cramping for several hours or for as long as several weeks after insertion. Simple pain medication usually relieves the cramping. If you have pelvic pain that is aggravated by intercourse, your Copper T may have to be removed. Consult your doctor.

4. Fainting may occur at the time of insertion or removal of an IUD. This passes quickly and is not usually serious.

5. Expulsion is the partial or complete loss of an IUD from the uterine cavity. The Copper T may be expelled anytime, but expulsion is most frequent during the first six menstrual cycles following insertion. Expulsion increases the risk of unplanned pregnancy.

The Copper T can perform its desired function only when it is entirely within the uterine cavity. Sometimes when the Copper T is not properly placed on insertion, or for other reasons, it may pass into the vagina.

If the Copper T has been partially expelled, it should be removed by your doctor. Expulsion is a major reason why you should feel for the presence of the thread in the vagina. If you are aware that a complete or partial expulsion has occurred, it is recommended that you use a second birth control method such as a contraceptive vaginal foam, cream or jelly, or condoms (rubbers), until another Copper T can be inserted.

Warnings

1. Call your doctor for any of the following reasons:

a. Severe or prolonged bleeding. If the flow is heavier and lasts much longer than your usual menstrual flow, you may need to have the Copper T removed to prevent the development of significant anemia.

b. Pelvic pain and cramps. Pelvic pain and cramps, especially after the first two or three cycles following insertion, could mean an infection has developed requiring treatment.

Pelvic infections have been reported following insertion of a Copper T. These can occur anyway, but it is certainly possible for the Copper T to pick up germs in the vagina and carry them into the uterus on insertion. Even though the Copper T is packaged sterile and aseptic techniques are used, the vagina is not sterile. Most infections can be eliminated by antibiotic therapy, but if not, the Copper T should be removed. If the infection is due to *Actinomyces*, the Copper T must be removed before antibiotic therapy is begun.

An increased risk of pelvic infection associated with the use of IUDs has been reported. While unconfirmed, this risk appears to be greatest for young women who have never had a baby and/or who have many sexual partners. Pelvic infection can be severe and result in abscesses of the ovaries and tubes, or in general peritonitis. Pelvic infection may include inflammation of the fallopian tubes, which can become damaged and blocked. This could decrease future chances of getting pregnant or even prevent it and require major surgery. Therefore, you should report any symptoms of pelvic infection to your doctor immediately. These symptoms include: new development of menstrual disorders (prolonged or heavy bleeding), unusual vaginal discharge, abdominal or pelvic pain, painful intercourse, and fever. The decision to use any IUD in a particular case must be made by the woman and her doctor with the consideration of a possible deleterious effect on future fertility.

c. Exposure to venereal disease (VD). If exposure to VD is suspected, you should be examined and treated promptly. Failure to do so could result in serious pelvic infection due to the VD. The use of an IUD does not prevent or treat VD.

d. Thread disappearance. If you cannot feel the thread coming through the cervix, it is possible that the Copper T has been expelled or dislodged so that perforation has occurred. If any of these has happened, you are no longer protected from becoming pregnant. Use another birth control method, such as contraceptive vaginal foam, cream or jelly, or condoms (rubbers), until you can be checked. (These alternative methods are not as effective as the Copper T.)

e. There are very few people who are allergic to copper; however, if you develop a generalized skin rash you should tell your doctor.

2. Do not undergo medical diathermy (including shortwave or microwave) treatments to your abdomen or lower back areas if you are using a metal-containing IUD such as the Copper T. These treatments may cause heat injury to the surrounding tissues; therefore, inform your doctor that you are using a Copper T.

A microwave oven will not harm you since government regulations require that microwave ovens be shielded and safeguarded to prevent injury to anyone.

Special Warnings About Pregnancy With an IUD in Place

Some women become pregnant while using an IUD. If you miss your menstrual period, or have a scanty flow during your period, or if you suspect that you might be pregnant, see your doctor right away.

The Copper T is placed in the uterus and acts to prevent pregnancy there, but may not prevent an ectopic pregnancy (a fertilized egg which implants in places other than the uterus). A pregnancy that occurs during use of the Copper T is more likely to be ectopic than a pregnancy that occurs to a woman not using a Copper T. Such ectopic pregnancies are rare and occur at a rate of about 1 per 1000 years of use. An ectopic pregnancy usually occurs in one of the fallopian tubes. This is a very serious situation because immediate surgery is usually necessary. Call your doctor if you missed your period, are bleeding irregularly, or have pain in one side of your abdomen.

If your doctor confirms that you are pregnant, the Copper T should be removed if the thread is visible. Removal of an IUD in pregnancy decreases the likelihood of serious complications, but could possibly cause a miscarriage. Let your doctor know how you feel about continuing the pregnancy and learn your doctor's feeling about the possible courses of action.

If removal of your Copper T proves to be difficult, you and your doctor should discuss at that time the question of continuing the pregnancy in view of the serious complications that may occur. In reaching a decision as to whether or not to have an abortion, it should be remembered that the risks associated with terminating a pregnancy increase with the length of time you are pregnant.

There seems to be a greater chance that spontaneous abortion (miscarriage) will occur if the Copper T is left in the uterus than there is if a Copper T had never been inserted.

The effects on the offspring of leaving the Copper T in the uterus during pregnancy are unknown.

When a pregnancy continues with a Copper T left in the uterus, there is an increased risk that serious complications may result, such as sepsis (severe infection) and septic abortion (infected miscarriage), which may lead to death. Most of the cases of serious complications happen in the middle third of pregnancy and occur spontaneously. Report all unusual symptoms to your doctor immediately if you choose to continue a pregnancy with a Copper T in your uterus. Be especially alert to flu-like symptoms, fever, abdominal cramping and pain, bleeding and vaginal discharge.

US Patent 3,533,406
THE POPULATION COUNCIL
New York, New York 10017

Manufactured for:
The Population Council
New York, New York 10017
by
Finishing Enterprises Inc.
North Tonawanda, New York 14120

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

18-680

SUMMARY REVIEW

Summary of Basis of Approval

NDA 18-680

Applicant:
The Population Council
New York, New York 10021

Drug Generic Name:
Intrauterine Copper Contraceptive

Drug Trade Name:
Copper T Model TCu 380A

I. Indications for Use:

Contraception.

II. Dosage form, route of administration, and recommended dosage:

Intrauterine device having the shape of the letter T which is made of _____ polyethylene. Coiled around the vertical limb is 176 mg of _____ copper wire providing approximately _____ copper surface area. Swaged onto each horizontal arm is a 66.5 mg copper sleeve. The two sleeves provide an additional _____ copper surface area.

b(4)

III. Manufacturing and Controls:

A. Manufacturing and Controls

1. Synthesis: No synthetic procedures are involved in the manufacture of the device other than the preparation of _____.
2. Tests and Specifications: Acceptance specifications for all raw materials and the methods used to check compliance with those specifications have been evaluated and are satisfactory. The IUD is packaged in a sealed _____ pouch along with an insertion tube and rod. The finished product is checked for identity, physical properties and sterility to assure compliance with the specifications prescribed in the NDA.
3. Manufacturing: All procedures are described in reasonable detail and follow good manufacturing practice. All equipment employed is suitable for the production of this device.

b(4)

B. Stability

The four year expiration date is supported by the submitted stability data.

C. Methods Validation

Validation of the submitted test methods by our laboratories has been waived by virtue of the nature of the device. The methods consist of relatively simple physical measurements and basic chemical tests. Sterility tests are conducted according to the USP.

D. Labeling

The labels, cartons and package insert are satisfactory with respect to the technical requirements and contain the mandatory information for an intrauterine device. The trade name is not in conflict with the name of any other IUD.

E. Establishment Inspection

Our Manufacturing Review Branch has evaluated the operations of all involved contract manufacturers as they relate to compliance with Current Good Manufacturing Practice Regulations and has found no reason to withhold approval of the application.

F. Environmental Impact Analysis Report

There are no known risks to the environment and a further analysis with regard to an Environmental Impact Statement is not necessary.

G. Bioavailability

This is an intrauterine device for contraception and therefore does not fall under the requirements of the bioavailability regulations.

IV. Pharmacology:

A. Pharmacologic Profile

The Copper T Model TCu 380A intrauterine device consists of a polyethylene T with copper sleeves on the horizontal arms and a copper coil on the vertical stem. The total amount of copper in the device is ca. with an exposed surface area of ca.

No preclinical investigations were conducted in animals with the Copper T Model TCU 380A. Such tests were not requested because preclinical studies with regard to the pharmacological and toxicological properties of the copper component and assessment of safety and contraceptive efficacy were handled by reference to preclinical tests with the Copper T IUD Model TCU 200 submitted by the same applicant in the original and supplements to NDA 17-455.

B. Toxicity Tests

As above, referenced to NDA 17-455. Among the most important are:

1. 7 Years Test in Rhesus Monkeys with Copper TCU 200 and Its Models Adapted to the Monkey Uterine Size.

Endometriosis, considered to be the after-effect of uterotomies performed for the surgical insertion of the device also occurred in uteri carrying a device without copper wire. One sham-operated monkey without any device had a non-invasive endometrial adenocarcinoma.

2. Toxicity Tests in Rats and Rabbits

These tests did not show any neoplastic lesions in uterine tissue induced by copper in the device.

3. Teratogenicity Tests in Rats, Rabbits, and Hamsters

Fetuses surviving in the presence of the copper bearing device developed normally without any indication of teratogenic complications.

Under certain conditions in these tests, copper exerts an embryocidal function. It is most effective when it is in place at the time of implantation and, also, at the early post-implantation stages of gestation when resorption of implants is induced in these species.

A modified teratogenicity test in rats indicated that the embryocidal effect of copper increased with duration of exposure when judged by the criterion of the incidence rate of occurring resorptions. There were also indications that the embryo-lethal effect once initiated in an embryo leads to its resorption even when the copper device is removed. This phenomenon might be species specific for the rat with its mechanism for rapid resorption of implants.

Rabbit teratogenicity tests with copper devices showed elevated copper levels in the livers of fetuses and placentae and uterine tissues of the dams. Fetal livers did not show histological changes indicative of a toxic reaction.

V. Medical:

- A. The Copper T Model TCU 380A intrauterine copper contraceptive device consists of a polyethylene support of T shape wound with _____ copper wire. In addition, there is a single copper sleeve on each transverse arm of the T, which is designed to _____

_____ of the copper device now being manufactured. This location places copper _____

b(4)

_____ The sleeves are also designed to _____

_____ The actual life is frequently much shorter due to local corrosion at two or more points and loss of sections of the winding and, eventually, the entire winding.

Other copper intrauterine devices marketed in the United States are the Copper T Model TCU 200, the Tatum T and the Copper 7. The Model TCU 380A is similar to Model TCU 200 (NDA 17-455) except that the _____

b(4)

To test the effect of design changes from the standard Copper T Model TCU 200 (NDA 17-455), the TCU 380A and the TCU 200 were studied in double blind trials through two years of use. Additional data on the TCU 380A were also collected in non-blinded studies.

B. TCu 380A vs. TCU 200 U.S. "Double Blind" Study:

A study was conducted to compare the TCU 380A and the TCU 200. Although it was not possible to disguise the IUD model from the physician making the insertion, the protocol required that the clinic record contain no entry stating which Copper T device had been assigned to the acceptor. This reduced the likelihood that the identity of the device would be known to clinic personnel on return visits. Information on the identity of the device was sent to The Population Council. The strings of the Copper T's were made of the same color and material so that until removal neither subject nor physician could determine which device had been inserted.

Allocation of devices to the women followed a protocol designed by Tietze. All devices inserted on a given day within the clinic were to be the same, the choice being governed by chance. This clustered randomization, although simple to carry out, caused variations from the expected 50% assignment for each device.

The data were analyzed excluding investigators with a lost-to-follow-up in excess of 30% in the initial year. The effects of these omissions are a reduction in the number of total insertions from 2704 to 1679 for the TCU 380A and 3325 to 1851 for the TCU 200 device. These reductions do not have a substantial influence on the number of women completing 24 months. In the overall study, 542 women completed two years of use whereas the total select group includes 434 TCU 380A users. Correspondingly, there were 562 and 460 insertions of the TCU 200.

Seven investigators met the follow-up criteria set for inclusion in the analysis. Enrollment was primarily during the years 1972 and 1973 with the majority of women accepting in 1973. The cut-off date for analysis was December 31, 1975, and the last data update was October 1976.

The median age of participants was 22.7 and 22.6 for the TCU 380A and TCU 200 acceptors, respectively. About 72% of the women using either device were under age 25 at acceptance. Half of the women were nulliparous prior to entry into the study and about 40% had never been pregnant. Approximately 23% of the insertions were performed between 1 and 3 months after pregnancy (late postpartum or late postabortion), and 31% were interval insertions.

The double blind study covers two years of use. The analysis employs the Tietze method of computation of months of use. Given the dates of enrollment, cut-off, and analysis, there is little difference between the Tietze and Potter estimates through two years of experience.

RESULTS

General: The two devices, the TCU 380A and TCU 200, had similar continuation rates at one year and virtually identical continuation rates at the end of two years. Termination rates for expulsion, medical removals other than bleeding or pain, planning pregnancy and other personal reasons differed only slightly between devices. The TCU 380A showed a statistically significant increase in effectiveness in comparison with the TCU 200, but the TCU 200 had significantly lower termination rates attributable to bleeding and pain.

Pregnancy rates: In the first year of use, the TCU 380A had a net pregnancy rate of 1.0 per 100. In the second year of use of the TCU 380A in which 905 women were observed at the beginning and 434 were observed to have completed the year, no additional pregnancies were reported. Women using the standard TCU 200 device experienced three times as many pregnancies in the first year of use or a net rate of 3.1 per 100. At the end of two years the net cumulative pregnancy rate for users of the TCU 200 was 5.6 per 100.

Pregnancy rates at two years among both parous and nulliparous users of the TCU 380A device were significantly lower than the rates observed among women using the TCU 200. For the nulliparous women, the pregnancy rate with the TCU 380A device (1.2 per 100) was about one-fifth the rate occurring with the TCU 200 device. For parous women the two year pregnancy rate appeared to be an even smaller fraction of the rate observed among users of the TCU 200 (0.8 per 100 vs. 5.4 per 100).

Gross rates show the same pattern as the net rates for the two parity groups. In the first as well as in the second year, every age comparison was favorable to the TCU 380A device. In every classification - by year of acceptance or timing of insertion, as well as for the age and parity groupings - the TCU 380A exhibited a lower pregnancy rate than did the TCU 200 in both the first and second year of the double blind study.

Expulsion: At the end of 12 months of use the net expulsion rates were identical, 7.1 per 100. There was a somewhat greater expulsion rate among TCU 380A users in the second year than among users of the TCU 200, but this produced only a small and not statistically significant difference in the cumulative rates. Among nulliparous women there was no difference at all in net expulsion rates for the two devices at the end of two years.

Interval insertions and late post abortion (29 to 90 days following termination of pregnancy) insertions were associated with the lowest rate of expulsion for both models. "Others," i.e., early postpartum and early post abortion insertions (within four weeks of pregnancy termination), had the highest expulsion rates.

Bleeding and pain: In the comparative study, removals for bleeding and pain were significantly more frequent among users of the TCU 380A device than among users of the TCU 200 device. At the end of two years net removal rates for this reason were 23.7 per 100 women for users of the TCU 380A and 18.9 for users of the TCU 200 device. The differential was largely confined to nulliparous women where the two-year cumulative rates were 24.6 per 100 women for TCU 380A users and 17.6 for TCU 200 users ($p < 0.01$). The corresponding rates for parous women were 22.8 vs. 20.1, $p > 0.05$. The sample size for both parous and nulliparous women was sufficiently large to detect differences of 4 or more points per 100.

When analysis of removal rates for bleeding and pain are confined to the TCU 380A, there were no significant differences as a function of parity. The relative differences in the rates for the TCU 380A and TCU 200 discussed in the previous paragraph arise because of differences in opposite directions in the rates for the two devices between nulliparous and parous users. There were no consistent correlations of removal rates for bleeding and pain as a function of age. These findings differ from those of Tietze and Lewit on non-medicated IUDs (Studies in Family Planning 1, No. 55, July 1970) in which they found a clear negative correlation between removal rates for bleeding/pain and age, and a negative correlation for removals for bleeding/pain and parity for each of the non-medicated devices.

The termination rates for all investigators does not differ from those of clinical investigators with meaningful follow-up.

Conclusion Regarding TCU 380A vs. TCU 200 "Double Blind" Study:

This study is considered the pivotal study in this new drug application. The pregnancy rate with the TCU 380A is lower than that of the TCU 200 which is currently being marketed in this country. The lower pregnancy rate with the TCU 380A is a benefit which offsets the slightly higher removal rate for bleeding and pain. The TCU 380A appears to be safe and effective for general use as a contraceptive device in this country.

TCu 380A - TCu 200
All Investigators

Double Blind, Random Assignment Study
Net Cumulative First Segment Termination and
Continuation Rates per 100 Acceptors
By Year and Device

	<u>Year 1</u>		<u>Year 2</u>	
	<u>380A</u>	<u>200</u>	<u>380A</u>	<u>200</u>
Pregnancy	1.1	3.2	1.2	5.6
Expulsion	6.8	7.0	8.9	8.4
Removal				
Bleeding/Pain	14.2	13.0	23.1	20.2
Other Medical	2.5	2.9	4.1	4.3
Planning Pregnancy	2.7	2.8	6.9	8.2
Other Personal	2.2	3.0	4.8	5.8
Continuation Rate	70.5	68.2	51.0	47.6
Woman Months Use	19,926	22,714	30,133	33,656
Insertions	2,704	3,325	-----	-----
% Lost to Follow-Up	33.1	38.2	41.0	45.6
No. Completing 12 months	1,173	1,276	542	562

C. TCu 380A Composite U.S. Study:

This includes all subjects in the "in program" studies who used the TCu 380A device in the United States, whether or not they were part of the double blind study. (Acceptors of the Copper T Model TCu 380A with no prior IUD use since their last pregnancy or those never pregnant women with no IUD experience are considered "in program." "Out of program" refers to those acceptors with prior IUD use since their last pregnancy and nulligravida women with IUD use.)

Excluded from the analysis of "in program" studies were 113 cases from investigator number 66. They were excluded because of high lost-to-follow-up rate (83 of 113, 73.5%), because the type of Copper T inserted was occasionally misidentified, and because several of the TCu 380A insertions at this site were inappropriately assigned to another study by the investigator (comparative trials of the TCu 200 and TCu 300).

Several analyses were conducted on the experience of the composite group.

- (i.) An analysis of the total composite study population.
- (ii.) An analysis of the part of the population enrolled in clinics with not more than 30% of subjects lost-to-follow-up at the end of the first year, 40% at the end of the second year or 50% at the end of the third year.
- (iii.) An analysis of the cohort of subjects enrolled in 1972.
- (iv.) An analysis of that part of the 1972 cohort enrolled in clinics with not more than 30% of subjects lost-to-follow-up at the end of the first year, 40% at the end of the second year or 50% at the end of the third year.

1. All Investigations

The overall study comprised 5344 insertions of the TCu 380A representing 17 clinical investigators. The majority of the acceptors were nulliparous (58.1%), 44.5% had never been pregnant at the time of insertion and two-thirds of the women were under age 25. At the end of 42 months of use 39 pregnancies were recorded, for a net pregnancy rate of 1.3 per 100 women. (There were four additional

pregnancies in the "in program" studies which were not included in the current analysis. However, one of the original 39 pregnancies was diagnosed later as a false positive. In addition, there have been five pregnancies in the "out of program" studies.) The pregnancy rate is about one-fifth the rate obtained in the United States and Canadian composite studies of the TCu 200. The three-year cumulative net expulsion rate was lower for the TCu 380A than the TCu 200. Removals for bleeding and pain occurred at higher rates in the TCu 380A investigations as compared to the TCu 200 (three-year rate, 26.5 vs. 18.0). The continuation rate for the TCu 380A was 36.4 at the end of 42 months covering 6053 woman-years of use with 116 women completing 42 months of experience. However, almost 40% of the subjects were lost-to-follow-up at the end of three years.

2. Investigations with "adequate follow-up"

To increase the reliability of the analysis, those investigators with more than 30% lost-to-follow-up at the end of the first year, 40% at the end of the second year or 50% at the end of the third year of use were excluded. The effects of these omissions are a reduction in the number of insertions from 5349 to 3536 and the number of clinical investigators from 10 to 7. The characteristics of the acceptors in the latter group are similar to those of the total investigations. In the group with meaningful follow-up 63.7% were nulliparous, 49.2% were nulligravida and 68.2% were under age 25 at the time of acceptance.

The three-year net cumulative pregnancy rate was 1.1. This was only one-tenth of a point lower than that observed in the entire study group. In fact, all of the remaining termination rates were similar for both investigations.

Three-year cumulative gross pregnancy rates reached 1.7 per 100 by the Potter estimate and 1.6 by the Tietze estimate. In the third year the annual gross pregnancy rate of 0.6-0.7 per 100 was approximately what it had been in the first year, 0.8 per 100. The highest pregnancy rates were among women under 20, with the cumulative rates showing a negative correlation with increasing age. The three-year cumulative pregnancy rate for women who had an interval insertion was 1.1 per 100; for nulliparous women the three-year rate was 1.7 and for never-pregnant women it was 1.9.

Cumulative three-year gross rates for removal for bleeding and pain were 35.2 per 100 by the Potter method and 32.6 per 100 by the Tietze method. The 1972 cohort of acceptors experienced removals at a gross rate of 11.5 per 100 in the first year, but the 1973 and 1974 cohorts had higher rates, reaching a value of 17.6 per 100 for the 1974 acceptors. The difference in the cohorts is statistically significant ($p < .05$).

Continuation rates were 73.0 at the end of the first year, 53.7 at the end of two years and 41.1 at the end of three years. The 1972 cohort had the highest continuation rate and the 1974 cohort the lowest rate.

TCu 380A

All Investigators
 Net Cumulative First Segment Termination Rates
 (Rate, Percent or Number)

	<u>Y E A R</u>			
	<u>1</u>	<u>2</u>	<u>3</u>	<u>3.5</u>
Pregnancy	0.7	0.9	1.2	1.3
Expulsion	5.5	7.2	8.1	8.3
Medical Removal				
Bleeding Pain	13.5	22.1	26.5	28.5
Other Medical	2.6	4.3	5.2	5.8
Personal Removal				
Planning Pregnancy	2.8	7.3	10.6	12.0
Other Personal	2.0	4.8	6.9	7.7
Terminations	27.1	46.7	58.5	63.6
Continuation	72.9	53.3	41.5	36.4
Woman Years of Use	3389.5	5265	5948	6053
Cumulative Percent Lost to Follow-Up	32.0	38.2	39.8	39.9
Insertions	5344			

TCu 380ANet Cumulative First Segment
Termination Rates with Standard ErrorU.S. Studies with Adequate Follow-Up
(Rate, Percent or Number)

	Y E A R					
	1		2		3	
	<u>Rate</u>	<u>S.E.</u>	<u>Rate</u>	<u>S.E.</u>	<u>Rate</u>	<u>S.E.</u>
Pregnancy	0.7	0.1	0.8	0.2	1.1	0.2
Expulsion	5.5	0.4	7.5	0.5	8.5	0.5
Medical Removal						
Bleeding Pain	13.1	0.6	21.8	0.7	26.7	0.9
Other Medical	3.0	0.3	4.6	0.4	5.4	0.4
Personal Removal						
Planning Pregnancy	2.7	0.3	6.7	0.5	9.9	0.6
Other Personal	2.1	0.3	5.0	0.4	7.3	0.5
Terminations	27.0	0.8	46.3	1.0	58.9	1.2
Continuation	73.0	0.8	53.7	1.0	41.1	1.2
Woman Years of Use	2602		4161		4750	
Number Continuing at End of Year						
Tietze	2026		1056		296	
Potter	1995		934		233	
Cumulative Percent Lost to Follow Up	18.3		24.3		26.2	
Insertions	3536					

1972 Insertions

In 1972, 1202 women in the United States accepted the TCU 380A representing 10 clinical investigators. The majority of the women in this cohort were nulligravid (58.7%) and about three-fourths were nulliparous. Seventy-six percent of the women were less than 25 years of age at the time of acceptance.

Through the end of four years of observation, the acceptors had accrued 25,509 woman-months of use. In that period a total of 18 accidental pregnancies were recorded, for a net cumulative pregnancy rate of 1.9 per 100. The net expulsion rate at four years was 9.7. Removals for bleeding or pain constituted the single major category of termination. The net termination rate at the end of the fourth year was 24.8. The cumulative continuation rate through four years of use was 35.7.

1972 Insertions with "adequate follow-up"

Seven investigators having a total of 1051 acceptors in 1972 had "adequate follow-up" information. Lost-to-follow-up for the clinics was 13.1% for the first year and cumulated to 28.1% at the end of the fourth year of acceptance. The characteristics of the acceptors followed a pattern similar to the group of 1202 insertions given above. Eighty-one percent of the acceptors were nulliparous, 62.5% nulligravida and 80% under 25 years of age.

As in the preceding analysis, the pregnancy rate for the TCU 380A users was low, with the cumulative rate at four years being 1.9. Four-year cumulative expulsion rates were 10.0 and removals for bleeding and pain were 25.3. The four year continuation rate was 35.1 with 1,972 woman-years of use. The gross cumulative pregnancy rate at four years was 2.8 per 100 acceptors. The two-year gross cumulative pregnancy rate declined as the age of the acceptor increased, although the differences are not statistically significant. Two-year gross pregnancy rates were similar for nulliparous and parous-1+ women.

3. Conclusion Regarding Composite Study of TCU 380A:

The composite study of the TCU 380A confirms the findings of the pivotal "double blind" study that the TCU 380A is a safe and effective intrauterine contraceptive device.

TCu 380A - 1972 Acceptors
 Gross (Single Decrement) Rates Per 100 Acceptors
 U.S. Studies with Adequate Follow-Up

	Annual Rates			
	<u>Year 1</u>	<u>Year 2</u>	<u>Year 3</u>	<u>Year 4</u>
Pregnancy	1.0	0.4	1.1	0.4
Expulsion	6.4	3.4	2.0	2.1
Removal-Bleeding/Pain	11.9	10.1	8.6	6.4
Other Medical	3.9	3.5	2.1	4.0

	Cumulative Rates			
	<u>Year 1</u>	<u>Year 2</u>	<u>Year 3</u>	<u>Year 4</u>
Pregnancy	1.0	1.4	2.4	2.8
Expulsion	6.4	9.6	11.4	13.2
Removal-Bleeding/Pain	11.9	20.8	27.6	32.2
Other Medical	3.9	7.3	9.2	12.8

D. Supportive Studies

1. Comparative I.U.D. Studies at the University of Southern California - Dr. Daniel Mishell:

Although his studies are included in the U.S. composite study, Dr. Mishell and coworkers have made an independent comparison of the Copper T Models TCu 380A, TCu 220C and TCu 300. The pregnancy rate was lowest for the TCu 380A at one, two, and three years of use but the differences in rates among the devices were not statistically significant. At three years cumulative net probabilities calculated by the long-rank method for pregnancy were 1.0, 3.4 and 4.3% for the TCu 380A, TCu 220C and TCu 300, respectively. Continuation rates after three years were highest for the TCu 220C (43.0) and lowest for the TCu 300 (41.1) and TCu 380A (37.8). A continuation rate of 41.1 was observed for the TCu 380A in the U.S. composite study.

In an earlier report, Dr. Mishell and coworkers compared, in a randomized clinic population of nulliparous women, the effectiveness of the Copper T Models TCu 380A (785 insertions), TCu 200 (472 insertions) and TCu 300 (347 insertions). That study was also part of the U.S. composite investigations of the TCu 380A. Approximately three-fourths of the acceptors in this independent report were under 24 years of age. At one year, the net cumulative pregnancy rate was lowest for the TCu 380A (0.2) and highest for the TCu 200 (1.6). Expulsion rates ranged from 3.8 (TCu 380A) to 6.1 (TCu 300); removals for bleeding and pain were similar for all devices (range, 9.1 for the TCu 380A to 10.7 for the TCu 200). One year continuation rates were highest for the TCu 380A (81.9) followed by the TCu 300 (80.7) and the TCu 200 (74.2).

2. Comparative I.U.D. Studies in Portland, Oregon; Planned Parenthood Clinic of Portland and Private Practice - Dr. William O. Thomas, Jr.:

Although his studies were part of the U.S. randomized "double blind" studies, Dr. Thomas made an independent comparison of the Copper T Models TCu 200 and TCu 380A. Of a total of 579 insertions, 109 (19%) were private and 470 (81%) were clinic patients. Cumulative two-year pregnancy rates were lower for the TCu 380A (0.6) than for the TCu 200 (1.9) whereas the rates of other events were similar for the two devices. These rates were below those observed in the entire U.S. "double blind" studies where two-year rates of 1.0 and 5.6 for the TCu 380A and TCu 200 were obtained. At two years, removals for bleeding/pain

were similar for the TCU 380A (24.5) and TCU 200 (23.9). The removal rate for bleeding/pain for the TCU 380A device was similar to the overall U.S. study but the TCU 200 rate was 5.0 points higher. Continuation rates reported by Dr. Thomas were similar to the overall U.S. study, 49.8 and 51.0 at two years for the TCU 200 and TCU 380A, respectively.

3. Comparative I.U.D. Studies at the Medical University of South Carolina - Dr. H. Oliver Williamson:

The studies at the Medical University of South Carolina reported by Dr. Williamson and coworkers are part of the U.S. "double blind" studies. This preliminary report focused on the TCU 200 with lesser numbers of subjects on the TCU 300 and the TCU 380A. There were 479 insertions covering 2847 woman-months of use associated with the TCU 380A. Two hundred and thirty-eight women had completed six months and 32 had completed one year at the time of the report. Net cumulative event rates at six months for the TCU 380A: pregnancy - 0.3; expulsion - 4.3; removals for bleeding and/or pain - 6.8; and continuation rate - 85.6.

4. Comparative I.U.D. Mexican Study:

Dr. Martinez and coworkers reported on the clinical effectiveness of the Copper T Models TCU 380A (92 insertions) and TCU 300 (320 insertions), and the Copper 7 (41 insertions) in Mexico. The acceptors differed in many parameters. Mean age was lowest for the Copper 7 group (22 years) and highest for the Copper T users (27 to 28 years). Four to seven percent of the Copper T users were nulliparous compared to 85% of the Copper 7 subjects. Months of use varied from 275 months for the Copper 7; 1565 months for the TCU 300 and 2,033 months for the TCU 380A. There were one observed pregnancy and one expulsion in the study occurring with the TCU 300 and the TCU 380A, respectively. Removals for bleeding and pain expressed as a percent of the total insertions were lowest for the TCU 380A (9.9%) and Copper 7 (9.7%), and somewhat higher for the TCU 300 (14.7%). Continuation rates were highest for the TCU 300 (80.4%), and lowest for the Copper 7 (70.7%) and TCU 380A (68.1%).

5. Comparative I.U.D. Indian Study:

In an annual report of 1977, the Indian Council of Medical Research reported that randomized clinical trials with the Copper T Models TCU 200, TCU 220C, and TCU 380A and the

Copper Y were conducted in India. The specific event rates or number of insertions were not stated. However, at one year of use, expulsions were apparently lowest with the TCU 200 and highest with the Copper Y. The TCU 380A had significantly more expulsions than the TCU 200. Removals for bleeding were lowest with the TCU 200 and Copper Y and highest with the TCU 220C. The TCU 380A rate presumably lies in between. No additional data were obtained on this study.

E. Clinical Evidence Related to Special Aspects of Effectiveness and Safety

1. Relevance of time of insertion

Data are available to compare event rates for late postpartum insertion (21 to 90 days postpartum), late postabortion (21 to 90 days postabortion), interval (greater than 90 days postpartum or postabortion) and never pregnant. No significant differences were found in two-year pregnancy rates for the TCU 380A as a function of time of insertion although the TCU 200 gave higher rates when inserted late postabortion or late postpartum. Expulsion rates were moderately higher for the late postpartum and never pregnant insertion of the TCU 380A than for interval insertion. Time of insertion made little difference to removal rates for bleeding and pain, although the lowest rate among TCU 380A users was observed in late postabortion insertions.

2. Age

Age at acceptance had appreciable effects on most aspects of performance. Pregnancy rates and expulsion rates among TCU 380A users at two years were highest in the below 20 age group. Removals for bleeding and pain were similar for those women less than 20 years and those 20 to 24 years of age at acceptance, but slightly higher than those TCU 380A users 25 years and older.

3. Parity

No remarkable differences were observed in pregnancy or expulsion rates for nulliparous or parous-1 or -2 acceptors. Pregnancy and expulsion rates were significantly lower for the parous-3+ group. Removal rate for bleeding and pain were similar for nulliparous and parous acceptors of the TCU 380A.

4. Pelvic Inflammatory Disease

Termination rates for pelvic inflammatory disease during the first two years were 1.06 per 100 women-years for the TCU 380A. With the diagnosis of endometritis added, closures of the first segment were at a rate of 1.28 per 100 woman-years. By either calculation termination rates are essentially the same as the rates reported by Tietze and Lewit (Studies in Family Planning 1, No. 55, July 1970) for inert or non-medicated devices. However, episodes of PID treated with the IUD in situ are not reflected in these results and thus the true incidence of PID cannot be determined for either study.

5. Outcome of pregnancies

Twenty-one of 47 accidental pregnancies associated with the TCU 380A device were terminated by elective abortion; there were 6 spontaneous abortions, 3 ectopic pregnancies, 8 live births, 1 still birth and 8 were still pregnant at last observation. Thirty-seven of the 47 pregnancies occurred with a TCU 380A device in situ; the location of the device was undetermined in eight cases and in two cases the device had perforated the uterus.

Ectopic pregnancy rates per 1000 women-years for the TCU 380A were 0.40 for investigators with "adequate follow-up" and 0.49 for all women studied.

6. Reversibility

Lifetable pregnancy rates show that 78.4% of 293 subjects who had their Copper T 380A device removed for a planned pregnancy conceived by the end of the calendar year. The one year rates were similar for nulliparous (76.1) and parous (80.3) women.

7. Allergy

Seven instances of copper allergy have been reported in subjects using a copper IUD. One of five associated with a Copper T occurred in a TCU 380A user. There were two published cases where the type of copper device was not stated.

8. Perforation

Perforation of the uterus has occurred in 17 Copper T users, all models, for an overall rate of 0.66 per 1000 acceptors. Three of these occurred in Copper T 380A users giving a rate of 0.56.

The incidence of cervical perforations was similar for all Copper T models. Ten of 45 cervical perforations occurred among TCU 380A users for a rate of one per 534 insertions.

F. Clinical Laboratory Studies Related to Safety

1. Cytology

Initial and repeat Papanicolaou smears data were available on 1767 acceptors of the TCU 380A. Percentages of women in class III (dysplasia) and higher ranked smears both at insertion (1.3%) and at the last test (1.5%) were similar and well within expected ranges for a normal population.

In the group with "adequate follow-up", five terminations for abnormal cytology and one case of carcinoma of the cervix occurred during the first two years among 3536 TCU 380A acceptors. Pearl rates per 100 woman-years were 0.12 and 0.02, correspondingly.

2. Biochemical changes

Studies of biochemical changes in the endometrium, cervical and uterine fluids of copper IUD users have yielded a variety of deviations from "normal." These have been primarily associated with the Copper T Model TCU 200. Included among changes in the endometrium during the proliferative phase of the menstrual cycle are decreased zinc levels, decreased manganese levels, decreased potassium levels, increased protein concentration, decreased alkaline phosphatase activity, increased acid phosphatase activity, decreased α -amylase activity, and increased n-acetyl-glucosaminidase activity. In the secretory phase, there are increased magnesium levels, increased calcium levels, decreased zinc levels, decreased alkaline phosphatase activity, increased n-acetyl-glycosaminidase activity, increased acid phosphatase activity, and a significant decrease in total RNA, mRNA, rRNA and protein content. The tRNA content significantly increased in both states of the menstrual cycle. A decrease in most parameters was related to glucose metabolism, i.e., oxygen uptake, glucose incorporation into glycogen and conversion of glucose to lactate, during both phases of the cycle.

Morphological studies showed no evidence of the copper having hormone-like influences on the endometrium. Intrauterine copper did not interfere with the binding of progesterone to its receptors. Uterine washings showed decreased alkaline phosphatase activity in the

proliferative phase and increased B-glucuronidase activity. Decreased zinc, iron and manganese levels were reported in the cervical mucus during the secretory phase. None of the above changes appear to be of major magnitude.

3. Copper levels in tissues and fluids

Copper levels in the endometrium, myometrium, cervical mucus, menstrual fluids, uterine secretions and serum have been determined for Copper T users and have been described in detail. The data are primarily based on the Copper T Model TCu 200 which has a daily copper loss about two-thirds of that observed for the Copper T Model TCu 380A during the first two years of use. Hagenfeldt observed a significant increase in the copper concentration in endometrial biopsies taken during the proliferative stage of a cycle after two to three cycles of Copper T use (Models TCu 120 or TCu 135 - copper release about 29 ug/day over one year of use). During the sixth to the twelfth cycle of Copper T use, the copper concentration was similar to preinsertion levels, whereas in the secretory endometrium copper levels remained elevated after one year of Copper T use. Moo Young et al. found that the copper content of endometrial biopsies taken from Copper T Model TCu 200 users (4 to 28 months of use) was significantly greater than in controls. Although copper levels were about 35% higher during the secretory phase and 10% higher in the proliferative stage than in the menstrual phase, these differences were not statistically significant. Moo Young et al. also observed that the myometrial copper levels from Copper T users (one to six months of use) did not differ significantly from controls.

Hagenfeldt observed an increase in copper content of cervical mucus, which was most accentuated in the proliferative phase and during the first six cycles with the Copper T in situ. Singh reported that the copper content of cervical mucus in TCu 200 users (six to seven months of use) ranged from two to six times higher during the menstrual cycle as compared to normal human levels.

Moo Young et al. found that the menstrual fluids (day two of the cycle) of women using the TCu 200 (3 to 24 months of use) showed a two-fold increase in their copper content as compared to controls.

The mean serum copper level in women using the TCu 200 device (115.78 ± 1.78 ug%, n=129) was almost identical to that observed in normal women (114.18 ± 2.32 , n=45) who neither used IUDs nor were taking oral contraceptives (Moo Young et al.). The Copper T users were between ages 19 and 33 years and were using the TCu 200 for periods of between 42 and 750 days. Serum copper levels among different TCu 380A users (10 to 12 women per group) after one, two or three years of use were within normal limits and showed no trend with increased duration of use. In a recent study, reported by Prema et al. of India (Fertil Steril 34:32, 1980), the mean serum copper levels in TCu 200 users ranging from 6 to 48 months of use did not differ from normal controls.

4. Blood Loss

Quantitative studies on menstrual blood loss have primarily centered on the Copper T Model TCu 200. It was found in several of these investigations that the amount of menstrual bleeding was significantly lower in Copper T users than in Lippes Loop users. Second, it was found that the menstrual blood loss is highest during the first few postinsertion cycles and gradually declines toward preinsertion levels. A recent study of Shaw et al. [Contraception 21 (4):343, 1980] found that the volume of menstrual bleeding increased by an average of 99 and 42% for Lippes Loop and Copper T 200 users over one year, respectively. However, at the twelfth postinsertion cycle, the menstrual blood loss for Copper T users (small group) was not significantly higher than the preinsertion levels.

The majority of the increased menstrual blood losses associated with IUD use are not reflected in circulating hemoglobin levels. In the studies by both the International Committee for Contraception Research and Shaw et al., it was found that the mean hemoglobin level among Copper T 200 users after one year was essentially the same as before insertion. A study conducted in India found no difference in hemoglobin levels among copper IUD users after one to three years of use compared to controls. Gallegos et al. of Mexico observed a significant decrease in hemoglobin levels in TCu 380A users after six cycles as compared to preinsertion levels. This was coincident with a significant increase in the menstrual blood loss.

In a study of Swedish women, Liedholm et al. observed no significant difference in the hemoglobin concentration, serum iron concentration or total iron binding capacity at six or twelve months after insertion of the TCU 200 as compared to preinsertion levels.

5. Clinical Pharmacology

Serum chemistry profiles of organ function showed very few abnormalities for fifteen subjects using the TCU 380A through three years. The most frequent deviation from normal occurred in a low glucose or potassium level. These findings are not thought to be of physiological significance. Because the Copper T Model TCU 220C loses copper at a rate somewhat greater than any of the other models of the Copper T, studies of the pharmacological effects of copper devices in women have focused on that device. Complete serum chemistry analyses were obtained on 39 subjects with 48 or more ordinal months of use including 14 with 60 or more months of use. The observed frequency of abnormal values appears to be well within the expected incidence in any normal population. Repeat observations on the same subjects at three and four or four and five years of use showed no trend with increased IUD use. Serum indicators of organ function were also determined on 53 subjects with five or more years of Copper T Model TCU 200 use including 19 with at least six years of continuous use.

6. Copper levels in offspring

Evidence on the copper levels in offspring conceived and developed in the presence of a copper IUD come from a case reported in the literature. Alderman reported that the levels of serum copper and ceruloplasmin concentrations from a premature neonate (delivered at 30 weeks gestation, weighing 1.19 kg) which developed in the presence of a Copper 7 IUD were greater than those expected for a fetus of equivalent gestational age. Alderman stated that conclusions may not be drawn from single cases, but felt that his "results support the suggestion that the fetus is largely, but not completely, isolated from the intrauterine copper-containing environment."

The remaining data were obtained from fetal tissues which have been recovered from patients who conceived with a Copper T in utero and who had an elective abortion. In one fetus of 20 weeks gestation, all tissue copper concentrations fell near the median for the control fetuses except in the brain. The other fetus of 14 weeks pregnancy presents a different and unexplainable picture. Copper concentrations in the brain, liver and placenta were similar to the control group whereas the levels in the adrenals, heart, kidney, lung, thymus, pancreas and spleen were above the controls. The fetus was younger than any of the controls but it is not known that this would be a cause of high values in several tissues. In addition, Gosden et al. found that the copper levels in the brain, kidney, liver, limb and lung of a 17 week fetus, conceived with a Copper 7 device in situ (20 months of use) were similar to a control fetus of 15 weeks.

7. Wire fragmentation

One hundred and sixty-two of 1093 (19.1%) examined TCu 380A devices (13 to 67 months of use) had fragmented copper coils. About 10% of the devices examined during the second year of use (13 to 24 months of use) had fragmented coils, 15% in the third year (25 to 36 months) and 17% during the fourth year of use (37 to 48 months). In the longest term devices averaging 51 ordinal months of use, 24 of 107 (22.4%) had fragmented and/or missing copper coils.

Sixty-four percent of all devices with fragmented coils had breaks affecting one to five coils. Assuming the entire five coils were missing, this represents only a 6.4% loss of the total original copper. The percentage of breaks in six or more coils was most severe for devices with four plus years of use. About three percent of all devices with 13 to 48 months in utero had breaks in six or more coils compared to 12% in the four plus years of use group.

VI. Approved Package Insert:

A copy of the approved package insert is attached.

APPEARS THIS WAY
ON ORIGINAL

cc: Orig. NDA (white bond)

HFN-810

HFN-105 (white bond)

HFN-810/LCarter/2.3.84/rde/2.7.84/3385C

HFN-810/LRipper/11/15/84 (7627C)

rch/3/20; 11/21,23/84/lwr/1/31/85

Concurrence: RBennett, VBerliner/2/10; SSobel/3/14; DKertesz/3/15/84
Sobel, Nunn, Kertesz, Berliner, RBennett/3/21/84

ASobel
2/5/85

20 Sterile Units

Manufactured 1986

Lot No.

Use Before:

Copper T Model TCu380A

BRAND OF INTRAUTERINE COPPER CONTRACEPTIVE

Each unit wound with approximately 176 mg of copper wire. In addition a single copper sleeve is swaged on each of the two transverse arms. Each sleeve contains approximately 66.5 mg of copper. The total surface area of copper on the device is $380 \pm 23 \text{ mm}^2$.

To be inserted in the uterus only by or under the supervision of a physician. See detailed instructions for use.

Administration: It is recommended that the unit be replaced by 4 years from the date of insertion.

CAUTION: Federal (U.S.) law prohibits dispensing without prescription.

Manufactured for The Population Council, New York, N. Y. 10017

U.S. Patent 3,533,406

Manufactured by Finishing Enterprises Inc., North Tonawanda, N. Y. 14120

Sterile

Unless package opened or damaged

Copper T
Model TCu380A
BRAND OF INTRAUTERINE COPPER CONTRACEPTIVE

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Manufactured 1986.

Use before: Jan. 1990

Manufactured for The Population Council, New York, N.Y.
By Finishing Enterprises Inc., North Tonawanda, N.Y. 14120

U.S. Patent

PRESCRIBING INFORMATION

Copper T Model TCu 380A

Brand of

Intrauterine Copper Contraceptive

Description:

The polyethylene body of the Copper T Model 380A intrauterine copper contraceptive is wound with approximately 176 mg of copper wire and carries a copper collar of approximately 66.5 mg of copper on each of its transverse arms. The exposed surface areas of copper is $380 \pm 23 \text{ mm}^2$. The dimensions of the T are 36 mm in the vertical direction and 32 mm in the horizontal direction. The dependent tip of the T is enlarged to a ball having a diameter of 3 mm. The T is equipped with polyethylene threads which are tied through the ball at the tip and are for the purpose of easy removal of the IUD. The T contains barium sulfate to render it radiopaque. It is packaged together with an insertion tube and plunger in a Tyvek®—polyethylene pouch and sterilized. The inserter tube is equipped with a movable flange to aid in gauging the depth to which the insertion tube should be inserted through the cervical canal and into the uterine cavity.

Clinical Pharmacology:

Available data indicate that the contraceptive effectiveness of the Copper T is enhanced by a minute quantity of copper being released continuously from the copper coil and sleeves into the uterine cavity. The exact mechanism by which metallic copper enhances the contraceptive effect of an IUD has not been conclusively demonstrated. Various hypotheses have been advanced, the most common being that copper placed in the uterus interferes with enzymatic or other processes that regulate blastocyst implantation.

Animal studies suggest that copper may play a role in reducing sperm transport within the uterine environment.

Indications and Usage:

The Copper T Model TCu 380A is indicated for contraception.

Different event rates have been reported with the use of different intrauterine contraceptives. Inasmuch as these rates are usually derived from separate studies conducted by different investigators in several populations, they cannot be compared with precision. Even in studies with the same device, considerably different rates are likely to be obtained because of differing characteristics of the study population. Furthermore, event rates per unit time tend to decrease as studies are extended because more susceptible subjects discontinue due to expulsions and adverse reactions or pregnancy, leaving the study population richer in less susceptible subjects. In clinical trials conducted in the United States, use-effectiveness of the Copper T Model TCu 380A as calculated by the life table method was determined as follows: (Rates are expressed as events per 100 women through 12, 24, 36 and 48 months of use).

This experience is based on 23,126 woman months of use, including 679 women who completed 12 months of use, 440 women who completed 2 years of use, 284 women who completed 3 years of use, and 153 women who completed 4 years of use.

Cumulative rates were:

	12 MOS.	24 MOS.	36 MOS.	48 MOS.
Pregnancy	0.9	1.2	1.8	1.9
Expulsion	5.8	8.2	9.2	10.0
Medical removal	14.6	23.9	29.5	33.7
Continuation rate	75.7	56.9	44.5	35.1

Contraindications:

Pregnancy or suspicion of pregnancy; anemia; distortion of uterine cavity; acute pelvic inflammatory disease or a history of repeated pelvic inflammatory disease; postpartum endometritis or infected abortion in the past 3 months; previous ectopic pregnancy; endometrial or cervical malignancy; unexplained genital bleeding until cancer is ruled out; acute cervicitis; known or suspected allergy to copper; diagnosed Wilson's disease, valvular heart disease; leukemia; or use of chronic corticosteroid therapy because of the increased susceptibility to infection with certain microorganisms that may be introduced at the time of an IUD insertion.

Warnings:

A. Pregnancy: (1) Septic Abortion: Reports have indicated an increased incidence of septic abortion associated in some instances with septicemia, septic shock and death in patients becoming pregnant with one of several types of IUDs in place. Most of these reports have been associated with the mid trimester of pregnancy. In some cases, the initial symptoms have been insidious and not easily recognized. If pregnancy should occur with a Copper T *in situ*, the Copper T should be removed if the string is visible or, if removal proves to be or would be difficult, interruption of the pregnancy should be considered and offered as an option. If the patient elects to maintain the pregnancy and the Copper T remains *in situ*, she should be warned that there may be an increased risk of abortion or premature labor and/or sepsis and she should be followed with close vigilance.

(2) Ectopic Pregnancy:

(a) A pregnancy which occurs with an IUD *in situ* is more likely to be ectopic than a pregnancy occurring without an IUD. Therefore patients who become pregnant while using a Copper TCu 380A should be carefully evaluated for the possibility of an ectopic pregnancy.

(b) Special attention should be directed to patients with delayed menses, slight metrorrhagia and/or unilateral pelvic pain, and to those patients who wish to interrupt a pregnancy occurring in the presence of the IUD, to determine whether ectopic pregnancy has occurred.

(3) **Continuation of Pregnancy:** If the patient chooses to continue the pregnancy and the Copper T remains *in situ*, she must be warned of the increased risk of spontaneous abortion and the increased risk of sepsis, including death. The patient must be closely observed and she must be advised to report immediately all abnormal symptoms, such as flu-like syndrome, fever, abdominal cramping and pain, bleeding or vaginal discharge, because generalized symptoms of septicemia may be insidious.

B. Pelvic Infection: An increased risk of pelvic inflammatory disease associated with the use of IUDs has been reported. This risk appears to be greatest for

and occlusion, thereby threatening future fertility. Therefore, it is that patients be taught to look for symptoms of pelvic disease. The decision to use an IUD in a particular case must be physician and patient with the consideration of a possible effect on future fertility if pelvic infection occurs.

infection may occur with a TCU 380A *in situ* and at times result in the formation of tubo-ovarian abscesses or general peritonitis. The symptoms of infection include: new development of menstrual disorders (prolonged or irregular), abnormal vaginal discharge, abdominal or pelvic pain, fever. The symptoms are especially significant if they occur during the first two or three cycles after insertion. Appropriate aerobic and anaerobic microbiologic studies should be done and antibiotic therapy initiated if infection does not show marked clinical improvement within 24 hours. The TCU 380A should be removed and the continuing treatment determined on the basis of the results and sensitivity tests. Genital infection has been associated primarily with long term IUD use. It has been reported that copper bearing IUDs as well. Treatment requires prompt removal and appropriate antibiotic therapy.

(k) Partial penetration or lodging of the TCU 380A in the myometrium can result in a difficult removal. This may occur especially in smaller uteri.

(l) Partial or total perforation of the uterine wall or cervix may occur with the TCU 380A, usually during insertions into patients sooner than after abortion or delivery or in uterine cavities too small for the TCU 380A. Ability of perforation must be kept in mind during insertion and at the time of subsequent examination. If perforation occurs, laparotomy or hysterectomy should be performed as soon as medically feasible and the TCU 380A removed. Abdominal adhesions, intestinal penetration, intestinal obstruction, and local inflammatory reaction with abscess formation and perforation of adjacent viscera may result if the TCU 380A is left in the peritoneal cavity.

Diathermy: The use of medical diathermy (short-wave and radio frequency) on a patient with a metal-containing IUD may cause heat injury to the tissue. Therefore, medical diathermy to the abdominal and sacral areas should not be used on patients using a TCU 380A.

Copper: Additional amounts of copper available to the body from the IUD may precipitate symptoms in women with undiagnosed Wilson's disease. The incidence of Wilson's disease is 1 in 200,000. The long-term effects of copper on the offspring are unknown.

Routine Examinations:

Insertion:

Before insertion, the physician, nurse, or other trained health professional should examine the patient with the Patient Brochure. The patient should be given time to read the brochure and discuss fully any questions she may have regarding the TCU 380A as well as other methods of contraception.

Preinsertion and Clinical Considerations:

A complete medical history should be obtained to determine conditions that might contraindicate the selection of an IUD. A physical examination should include a pelvic examination, "Pap" smear, gonorrhea culture and, if indicated, tests for other forms of genital disease including actinomycosis. Actinomycosis is usually not detected on the Pap test. The physician should determine if the patient is not pregnant.

The physician should carefully sound the uterine cavity prior to the insertion to determine the patency of the endocervical canal and the internal os, and the depth of the uterine cavity. Exercise care to avoid perforation of the uterine wall. In occasional cases, severe cervical stenosis may be present and the physician should not use excessive force to overcome this resistance. The physician should usually sound to a depth of 6 to 8 cm. Insertion of a TCU 380A into a uterine cavity measuring less than 6.5 cm by sounding may increase the risk of pain, bleeding, partial or complete expulsion, perforation, and pregnancy.

The possibility of insertion in the presence of an existing pregnancy, the optimal time for insertion is the latter part of the menstrual cycle or one or two days thereafter. The TCU 380A should not be inserted during menstruation or postabortion until involution of the uterus is complete.

The risk of perforation and expulsion is greater if involution is not complete.

When necessary, necessary to place the TCU 380A as high as possible within the uterine cavity to help avoid partial or complete expulsion that could result in pregnancy.

Copper T represents a different design in intrauterine devices. Physicians are cautioned that it is imperative for them to become familiar with the instructions for use before attempting placement of the device.

Caution should be used with caution in those patients who have an anemia or menorrhagia or hypermenorrhagia. Patients experiencing menorrhagia or menorrhagia following IUD insertion may be at risk for the development of microcytic anemia. Also IUDs should be used with caution in patients with a history of bleeding disorders or having a coagulopathy.

Bradycardia or other neurovascular episodes may occur during the use of IUDs, especially in patients with a previous disposition to syncope.

Patients with valvular or congenital heart disease are more prone to develop bacterial endocarditis than patients who do not have valvular or congenital heart disease. Use of an IUD in these patients may represent a risk for septic emboli.

IUD in those patients with acute cervicitis should be postponed until the infection has been cleared up.

When the TCU 380A may be partially or completely expelled, patients should be examined and evaluated shortly after the first postinsertion menses, but not later than three months after insertion. Thereafter annual examination and medical and laboratory evaluation and a Pap smear including tests for actinomycosis organisms should be carried out. The TCU 380A should be replaced every four years.

Patients should be told that some bleeding or cramps may occur during the first three months after insertion, but if these symptoms continue or are severe they should report them to her physician. She should be instructed on how to

check after each menstrual period to make certain that the thread still protrudes from the cervix and cautioned that there is no contraceptive protection if the TCU 380A has been expelled. She should also be cautioned not to dislodge the TCU 380A by pulling on the thread. If a partial expulsion occurs, removal is indicated and a new TCU 380A may be inserted. The patient should be told to return within four years for removal of the TCU 380A and for replacement if desired.

(k) Rarely, a copper-induced urticarial allergic skin reaction may develop in women using a copper-containing IUD. If symptoms of such an allergic response occur, the patient should be instructed to tell the consulting physician that a copper-containing device is being used.

(l) The TCU 380A should be removed for the following medical reasons: menorrhagia and/or metrorrhagia producing significant anemia; uncontrolled pelvic infection; intractable pain often aggravated by intercourse, dyspareunia; pregnancy, if the thread is visible; endometrial or cervical malignancy; uterine or cervical perforation; or any indication of partial expulsion.

(m) If the retrieval thread cannot be visualized, it may have retracted into the uterus or have been broken off, or the TCU 380A may have been expelled. Localization usually may be made by feeling with a probe; if not, x-ray or sonography can be used. When the physician elects to recover a TCU 380A with the thread not visible, the removal instructions should be considered.

(n) If any patient with a TCU 380A suddenly develops overt clinical hepatitis or abnormal liver function tests, appropriate diagnostic procedures should be initiated.

(o) It has been reported that pregnancy rates in Copper IUD users may be considerably higher among diabetics than among non diabetics. Other reports indicate similar pregnancy rates in the two groups.

C. Requirements for Continuation and Removal:

(1) The Copper T must be replaced before the end of the fourth year of use. There is no evidence of decreasing contraceptive efficacy with time before four years, but the contraceptive effectiveness at longer times has yet to be established; therefore, the patient should be informed of the known duration of contraceptive efficacy and be advised to return in four years for removal and possible reinsertion.

(2) The Copper T should be removed for the following medical reasons: menorrhagia and/or metrorrhagia producing anemia; uncontrolled pelvic infection; genital actinomycosis; intractable pain often aggravated by intercourse; dyspareunia; pregnancy, if the string is visible; on diagnosis of endometrial or cervical malignancy; uterine or cervical perforation; or increase in length of the thread extending from the cervix, or any other indication of partial expulsion.

D. Continuing Care of Patients Using Copper Ts:

(1) Patients should be reexamined and evaluated within 3 months after Copper T insertion.

(2) Routine annual examination with appropriate medical and laboratory evaluation should be carried out.

Adverse Reactions:

Perforations of the uterus and cervix may occur. Perforation into the abdominal cavity may be followed by abdominal adhesions, intestinal penetration, intestinal obstruction, local inflammatory reaction with abscess formation and erosion of adjacent viscera. Pregnancy may occur with the TCU 380A *in situ* or when the TCU 380A has been partially or completely expelled.

The incidence of spontaneous abortion, when conception occurs with intrauterine devices *in situ*, appears to be increased over that in unprotected women. Insertion cramping, usually of no more than a few seconds duration, may occur; however, some women may experience residual cramping for several hours or even days. Intermenstrual spotting or bleeding or prolonged or increased menstrual flow may occur.

Pelvic infection including salpingitis with tubal damage or occlusion may occur. They may result in future infertility. Complete or partial expulsion of the TCU 380A may sometimes occur, particularly in those patients with uteri measuring less than 6.5 cm by sounding. Urticarial allergic skin reaction may occur. The following complaints have also been reported, with IUDs, although their relation to the TCU 380A has not been established: amenorrhea or delayed menses, backaches, cervical erosion, cystic masses in the pelvis, vaginitis, leg pain or soreness, weight loss or gain, nervousness, dyspareunia, cystitis, endometritis, septic abortion, septicemia, leukorrhea, infection of reproductive organs with actinomycosis, ectopic pregnancy, difficult removal, uterine embedment, anemia, pain, neurovascular episodes including bradycardia and syncope secondary to insertion, dysmenorrhea, and fragmentation of the IUD.

Dosage and Administration:

The Copper T is placed in the uterine cavity.

The optimal time of insertion is during the latter part of the menstrual period or one or two days thereafter. The cervical canal is relatively patent at this time and there is little or no chance that the patient may then be pregnant.

Present information indicates that the efficacy is retained for 48 months. Until adequate data indicating a longer effective life become available, the Copper T 380A must be removed and a new one inserted on or before 48 months from the date of insertion.

The physician should become thoroughly familiar with the Instructions for Use before attempting insertion of the Copper T.

How Supplied:

Available in cartons of 20 units. Each Copper T is sterile packaged in a Tyvek®—polyethylene pouch, together with an inserter tube and plunger rod.

the bending by bringing thumb and index finger together while r hand to maneuver the insertion tube to pick up arms of the T (Fig. *rather than necessary to insure retention of the arms.* Introduce the the insertion tube from the bottom alongside the threads until it ottom of the T.

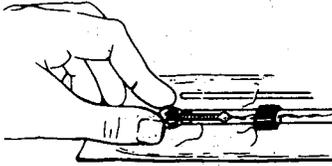


Fig. 2

movable flange so that it indicates the depth to which the Copper erted and the direction in which the arms of the T will open. At this rtain that the horizontal arms of T and the long axis of the flange e horizontal plane. Introduce the loaded inserter through the and upwards until the T lies in contact with the fundus. The a should be at the cervix. (Fig. 3).

Do not force the insertion

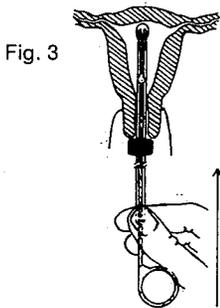


Fig. 3

the Copper T, withdraw the insertion tube not more than 1/2 inch rod is not permitted to move. This releases the arms of the T (Fig.

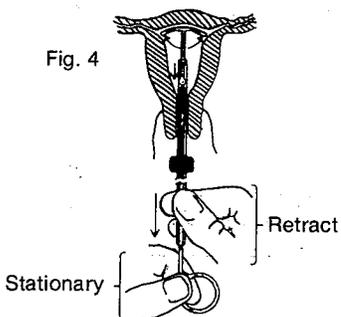


Fig. 4

Step 4

After the arms are released, the inserter tube should be moved upward until the resistance of the fundus is reached. This will assure placement of the T at the highest possible position within the endometrial cavity (Fig. 5).

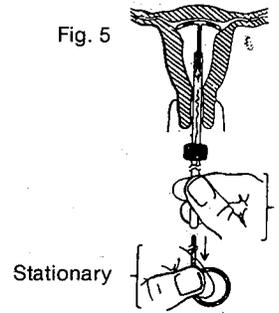


Fig. 5

Step 5

Withdraw the solid rod while holding the insertion tube stationary (Fig. 6).

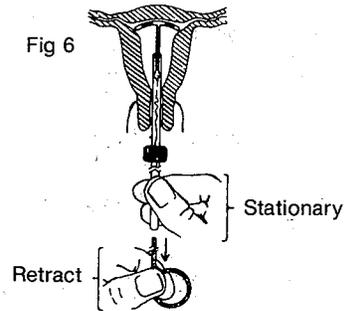


Fig. 6

Step 6

Withdraw the insertion tube from the cervical os until the strings are visible. Be sure sufficient length of string is visible to facilitate checking for the presence of the Copper T (Fig. 7).

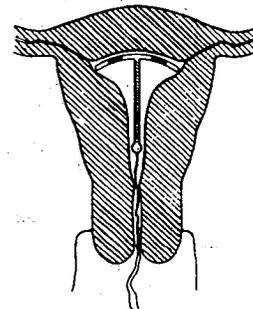


Fig. 7

US Patent 3,533,406
THE POPULATION COUNCIL
New York, New York 10017

Manufactured for:
The Population Council
New York, New York 10017
by
Finishing Enterprises Inc.
N. Tonawanda, New York 14120

PATIENT INFORMATION

Copper T Model TCu 380A Brand of Intrauterine Copper Contraceptive

This brochure provides information on the use of intrauterine contraceptive devices (IUDs) in general, and the Copper T Model TCu 380A in particular. There are other birth control methods that may be suitable. Before deciding which type of birth control method to use, you should read this brochure and have the opportunity to discuss fully with your doctor any questions you may have about the Copper T Model TCu 380A, other IUDs, the Pill, and other methods of contraception.

PREINSERTION INFORMATION

What You Should Know About The IUD

IUDs are small articles of various sizes and shapes that are inserted into the uterus (womb). The purpose of the IUD is to prevent pregnancy.

How the IUD prevents pregnancy is not completely understood. Several theories have been suggested. IUDs seem to interfere in some manner both with fertilization and with the implantation of the fertilized egg in the lining of the uterus when fertilization does occur.

The IUD does not prevent the release of an egg from the ovary. The effectiveness of an IUD is measured by the pregnancy rate of women who use it. Acceptability to the user must also take into account the adverse reactions and side effects that may be associated with its use.

Before insertion your doctor will perform a pelvic examination to determine the size and position of the uterus or the presence of lumps or any other abnormality. The uterus usually is tipped forward a bit, bending at the neck or cervix. However, in some women it is tipped backward or bent sharply forward. Your doctor must know this before inserting anything. In some rare instances a doctor may be unable to insert an IUD due to the very small size, the shape or the position of the uterus.

Using an instrument called a speculum, your doctor exposes the cervix in order to take smears of the secretions to make sure you have a healthy vagina and do not have cancer. The Pap (cancer) test is made from one or more of the smears obtained. Your doctor may also perform other laboratory tests before inserting an IUD, including tests for genital disease.

Your doctor will cleanse the cervix with a surgical antiseptic, then grasp the front lip of the cervix with an instrument called a tenaculum, which may feel like a pin prick or like somebody pinched you. The cervix is gently pulled with the tenaculum to make it easier for the cervical opening to be seen, and to hold the uterus in position for an insertion. This will make the insertion easier.

Your doctor will then insert a sound (a thin, smooth, round-ended probe) through the cervical canal to the top or fundus of the uterus to measure the depth of the uterine cavity. The internal os (opening) sometimes resists, so the doctor may have to exert a little pressure, which may hurt momentarily. Sounding only takes a few seconds after which the instrument is withdrawn. The IUD is then inserted. You could experience a momentary cramping... or you may feel nothing at all.

After removing the insertion instrument, your doctor will cut the thread attached to the end of the IUD stem.

Use Effectiveness

Pregnancy and adverse reaction rates that have been reported with the use of various IUDs differ because these rates are usually derived from separate studies conducted by different investigators in several population groups. Therefore these rates cannot be compared with any precision.

Clinical trials with the Copper T Model 380A covered 21,126 woman months of use including 12 months for 679 women, 24 months for 440, 36 months for 284 and 48 months for 153. In the first year of use, the number of unplanned pregnancies was about 1 per 100 women or 1 woman out of 100 became pregnant while using the Copper T Model 380A. The number of expulsions was about 6 per 100 women; the number of adverse reactions requiring medical removal of the Copper T was about 15 per 100 women.

What You Should Tell Your Doctor

Before you have a Copper T inserted, it is your responsibility to inform your doctor fully of your past medical history. Tell your doctor if you now have, or have had, or suspect that you had, any of the following conditions which might make the Copper T unsuitable as a method of contraception for you:

- Abnormalities of the uterus, or of other reproductive organs
- Allergy to copper
- Anemia
- Bleeding between periods
- Blood-clotting disorders, or if you are taking blood-thinning medicine.
- Cancer or other diseases of the uterus, cervix or other reproductive organs
- Chronic cortisone or other steroid therapy
- Diabetes treated with insulin
- Fainting attacks
- Genital actinomycosis (a bacterial disease)
- Heart disease
- Heart murmur
- Heavy menstrual flow
- Infection or inflammation of the uterus or cervix
- Leukemia
- Pelvic infection, for example, pus in the fallopian tubes
- Prior IUD use
- Prior uterine surgery
- Recent abortion or miscarriage
- Recent pregnancy (uterine or ectopic)
- Severe menstrual cramps
- Suspected pregnancy
- Suspicious or abnormal Pap test
- Unexplained vaginal bleeding
- Vaginal discharge or infection
- Venereal disease
- Wilson's disease

Be sure to tell your doctor if you think you are pregnant. An IUD should not be inserted in a pregnant woman.

Adverse Reactions

Some adverse reactions and side effects are very serious and occur rarely, whereas others are less serious, common with IUDs, and transient. Ask your doctor to tell you what the approximate severity, frequency, and duration are for the various adverse reactions and side effects.

The following adverse reactions and side effects have been reported with IUDs and may occur after the Copper T is inserted:

- Pregnancy with the Copper T in the uterus or when it has been partially or completely expelled
- Spontaneous abortion (miscarriage) if pregnancy occurs with the Copper T in the uterus. This possibility is greater if you have a Copper T than if you do not have an IUD.
- Complete or partial expulsion
- Bleeding or spotting between periods
- Missed or late periods

- Heavy or prolonged periods
- Painful periods
- Anemia
- Pain and cramps at insertion or following insertion
- Difficult removal of the Copper T
- Embedment in the uterus
- Erosion or infection of the cervix
- Cysts in the pelvis, for example, in the ovaries or fallopian tubes
- Vaginal discharge and infection
- Inflammation of the lining of the uterus
- Inflammation of the lining of the urinary bladder
- Backache
- Leg pain and soreness
- Painful intercourse
- Nervousness
- Septic abortion (infected miscarriage) followed in some cases by blood poisoning (septicemia), which can lead to death. (The small possibility that becoming pregnant may result in a septic abortion is something you may wish to consider before having a Copper T inserted.)
- Blood poisoning (septicemia) which may result from a very severe pelvic infection.
- Pregnancy outside the uterus (ectopic pregnancy, for example, in the fallopian tube or ovary) usually requiring surgery.
- Perforation of the uterus that could result in abdominal adhesions, intestinal penetration, intestinal obstruction, local inflammatory reaction with abscess formation and erosion of adjacent organs. Surgery is required to remove the Copper T in such instances.
- Perforation of the cervix
- Fainting and abnormally slow heart beat at the time of insertion or removal
- Fragmentation of the IUD
- Pelvic infection including inflammation of the fallopian tubes, which may damage or block them. (This could decrease future chances of getting pregnant or even prevent it and require major surgery.) Bacterial infection of the reproductive organs with *Actinomyces* has been associated primarily with long-term IUD use. It has been reported with the use of the copper-bearing IUDs as well. Treatment requires prompt removal of the IUD and antibiotic therapy.
- Allergic skin reaction due to the copper on the Copper T.

If you decide on the Copper T as your method of birth control, read the following information and instructions carefully. Please keep this brochure so that you may refer to it.

This brochure may be revised from time to time. You may want to check with your doctor at your next visit to see if you have the most recent version. If you have any questions or complaints, consult your doctor.

POSTINSERTION INFORMATION

Description

The Copper T Model TCU 380A, an intrauterine copper contraceptive, is a small plastic object shaped like a letter T, with copper collars on the cross arms and a fine copper wire wrapped around the stem of the T. A monofilament white plastic thread is attached at the end of the stem. The Copper T measures approximately 36 mm high and 32 mm wide. Copper enhances the contraceptive effect of the plastic T, which also serves as a flexible carrier for the copper.

This addition of copper makes the Copper TCU 380A almost as effective as the Pill in preventing pregnancy when the Copper T is properly placed within the uterus. The copper of the Copper T is slowly and continuously released into the uterus, but is largely cast out with the menstrual flow. Because of the presence of copper, the Copper T is considered to be a drug; it therefore underwent the same type of rigid testing as any recently

Directions for Use

1. Checking your IUD. A white thread with two strands is attached to the Copper T so you can check to see if it is still in place, since the IUD can come out of the uterus without your knowing it. This occurs most often during or right after a menstrual period, especially in the first six months following insertion. Take these steps to make sure your Copper T is in place:

- a. Wash your hands.
- b. Squat or seat yourself on the toilet.
- c. Insert an index or middle finger high in the vagina and locate the cervical opening (mouth of the uterus). The cervix feels firm like the tip of your nose.
- d. Feel for the thread of the Copper T which should be protruding from the cervix high in your vagina.
- e. If you can feel the thread, it is likely that the Copper T is in place and working. You should not pull on the thread. This may dislodge the Copper T.
- f. During the first month after insertion you should check several times to make sure the thread is protruding from the cervix. Thereafter, it is advisable to check after each menstrual period.
- g. If you think the Copper T has come out or has been dislodged, for example, if you cannot feel the thread or you can feel the Copper T itself, notify your doctor as soon as you can for an examination. Protect yourself from pregnancy by using another birth control method, such as the condom (rubber). (Except for the Pill these alternative methods of birth control are not as effective as the Copper T when it is properly positioned.)
- h. After insertion of your Copper T, you should return to see your doctor as soon as possible after your next menstrual period, but no later than three months after insertion. This will allow the doctor to make sure that the Copper T is in the correct position.

It is not necessary to use another method of contraception with a Copper T if it is in the proper position in the uterus and you have it replaced at the proper time. Don't expect the Copper T to work if you are already pregnant and your doctor doesn't know it.

- i. After your first checkup, you should be checked at least once a year by your doctor.

2. Continuation and removal. While you are using the Copper T, you may use tampons or pads and take douches, if this is your usual practice. You may also have sexual relations as usual. With some IUDs, you may use the IUD until you wish to become pregnant. It is necessary that your Copper TCu 380A Model be replaced within four years in order for you to continue being protected against pregnancy. Check with your doctor concerning this. You should return to your doctor if you wish to have your Copper T removed.

Removal of the Copper T is usually a simple procedure that causes little discomfort. When it is time to remove the Copper T, your doctor will exert a firm, steady pull on the retrieval thread with an instrument. Normally the Copper T will come out readily. A new replacement Copper T can be inserted immediately after removal of the old one. **UNDER NO CIRCUMSTANCES SHOULD YOU OR ANYBODY BUT YOUR DOCTOR TRY TO REMOVE THE Copper T.**

Although the Copper T is usually removed easily, exceptions are possible. In some instances the retrieval thread is not visible; or it could break when the doctor pulls on it. If the thread cannot be seen, or if it breaks off, the doctor (after determining that you are not pregnant) may be able to remove the Copper T simply by reaching into the uterus with a slim instrument, or may have to locate the Copper T by x-ray or another technique. If this doesn't succeed, you may have to be hospitalized to have the Copper T removed.

Side Effects

See also the list of adverse reactions and side effects in the section under Preinsertion Information.

Expulsion, cramping, and bleeding are more likely to occur in women with unusually small uterine cavities. The following may occur during or after the Copper T insertion:

1. Some bleeding may follow the insertion. Because of this, your doctor may choose to insert your Copper T during or at the end of your menstrual period or one or two days later. Insertion at this time reduces the possibility that you are pregnant at the time of your Copper T insertion.
2. Bleeding between menstrual periods, usually in the form of spotting, may occur during the first weeks after insertion. Menstrual periods after the insertion may be heavier and longer. If these conditions continue or are severe, consult your doctor.

3. Pain, usually in the form of uterine cramps or low backache, may occur at the time of insertion and is usually of no more than a few seconds' duration. However, some women may experience cramping for several hours or for as long as several weeks after insertion. Simple pain medication usually relieves the cramping. If you have pelvic pain that is aggravated by intercourse, your Copper T may have to be removed. Consult your doctor.

4. Fainting may occur at the time of insertion or removal of an IUD. This passes quickly and is not usually serious.

5. Expulsion is the partial or complete loss of an IUD from the uterine cavity. The Copper T may be expelled anytime, but expulsion is most frequent during the first six menstrual cycles following insertion. Expulsion increases the risk of unplanned pregnancy.

The Copper T can perform its desired function only when it is entirely within the uterine cavity. Sometimes when the Copper T is not properly placed on insertion, or for other reasons, it may pass into the vagina.

If the Copper T has been partially expelled, it should be removed by your doctor. Expulsion is a major reason why you should feel for the presence of the thread in the vagina. If you are aware that a complete or partial expulsion has occurred, it is recommended that you use a second birth control method such as a contraceptive vaginal foam, cream or jelly, or condoms (rubbers), until another Copper T can be inserted.

Warnings

1. Call your doctor for any of the following reasons:

a. Severe or prolonged bleeding. If the flow is heavier and lasts much longer than your usual menstrual flow, you may need to have the Copper T removed to prevent the development of significant anemia.

b. Pelvic pain and cramps. Pelvic pain and cramps, especially after the first two or three cycles following insertion, could mean an infection has developed requiring treatment.

Pelvic infections have been reported following insertion of a Copper T. These can occur anyway, but it is certainly possible for the Copper T to pick up germs in the vagina and carry them into the uterus on insertion. Even though the Copper T is packaged sterile and aseptic techniques are used, the vagina is not sterile. Most infections can be eliminated by antibiotic therapy, but if not, the Copper T should be removed. If the infection is due to *Actinomyces*, the Copper T must be removed before antibiotic therapy is begun.

An increased risk of pelvic infection associated with the use of IUDs has been reported. While unconfirmed, this risk appears to be greatest for young women who have never had a baby and/or who have many sexual partners. Pelvic infection can be severe and result in abscesses of the ovaries and tubes, or in general peritonitis. Pelvic infection may include inflammation of the fallopian tubes, which can become damaged and blocked. This could decrease future chances of getting pregnant or even prevent it and require major surgery. Therefore, you should report any symptoms of pelvic infection to your doctor immediately. These symptoms include: new development of menstrual disorders (prolonged or heavy bleeding), unusual vaginal discharge, abdominal or pelvic pain, painful intercourse, and fever. The decision to use any IUD in a particular case must be made by the woman and her doctor with the consideration of a possible deleterious effect on future fertility.

c. Exposure to venereal disease (VD). If exposure to VD is suspected, you should be examined and treated promptly. Failure to do so could result in serious pelvic infection due to the VD. The use of an IUD does not prevent or treat VD.

d. Thread disappearance. If you cannot feel the thread coming through the cervix, it is possible that the Copper T has been expelled or dislodged so that perforation has occurred. If any of these has happened, you are no longer protected from becoming pregnant. Use another birth control method, such as contraceptive vaginal foam, cream or jelly, or condoms (rubbers), until you can be checked. (These alternative methods are not as effective as the Copper T.)

e. There are very few people who are allergic to copper; however, if you develop a generalized skin rash you should tell your doctor.

2. Do not undergo medical diathermy (including shortwave or microwave) treatments to your abdomen or lower back areas if you are using a metal-containing IUD such as the Copper T. These treatments may cause heat injury to the surrounding tissues; therefore, inform your doctor that you are using a Copper T.

A microwave oven will not harm you since government regulations require that microwave ovens be shielded and safeguarded to prevent injury to anyone.

Special Warnings About Pregnancy With an IUD in Place

Some women become pregnant while using an IUD. If you miss your menstrual period, or have a scanty flow during your period, or if you suspect that you might be pregnant, see your doctor right away.

The Copper T is placed in the uterus and acts to prevent pregnancy there, but may not prevent an ectopic pregnancy (a fertilized egg which implants in places other than the uterus). A pregnancy that occurs during use of the Copper T is more likely to be ectopic than a pregnancy that occurs to a woman not using a Copper T. Such ectopic pregnancies are rare and occur at a rate of about 1 per 1000 years of use. An ectopic pregnancy usually occurs in one of the fallopian tubes. This is a very serious situation because immediate surgery is usually necessary. Call your doctor if you missed your period, are bleeding irregularly, or have pain in one side of your abdomen.

If your doctor confirms that you are pregnant, the Copper T should be removed if the thread is visible. Removal of an IUD in pregnancy decreases the likelihood of serious complications, but could possibly cause a miscarriage. Let your doctor know how you feel about continuing the pregnancy and learn your doctor's feeling about the possible courses of action.

If removal of your Copper T proves to be difficult, you and your doctor should discuss at that time the question of continuing the pregnancy in view of the serious complications that may occur. In reaching a decision as to whether or not to have an abortion, it should be remembered that the risks associated with terminating a pregnancy increase with the length of time you are pregnant.

There seems to be a greater chance that spontaneous abortion (miscarriage) will occur if the Copper T is left in the uterus than there is if a Copper T had never been inserted.

The effects on the offspring of leaving the Copper T in the uterus during pregnancy are unknown.

When a pregnancy continues with a Copper T left in the uterus, there is an increased risk that serious complications may result, such as sepsis (severe infection) and septic abortion (infected miscarriage), which may lead to death. Most of the cases of serious complications happen in the middle third of pregnancy and occur spontaneously. Report all unusual symptoms to your doctor immediately if you choose to continue a pregnancy with a Copper T in your uterus. Be especially alert to flu-like symptoms, fever, abdominal cramping and pain, bleeding and vaginal discharge.

US Patent 3,533,406
THE POPULATION COUNCIL
New York, New York 10017

Manufactured for:
The Population Council
New York, New York 10017
by
Finishing Enterprises Inc.
North Tonawanda, New York 14120

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
18-680

MEDICAL REVIEW(S)

NDA 18-680
Copper T Model TCu 380A

September 27, 1983
The Population Council

Medical Officer's Review of Final Printed Labeling

Submission dated June 21, 1983 contains final printed labeling.

Comment: The submitted labeling is satisfactory.

Recommendation: Approval of the application is recommended.

Ridgely C. Bennett
Ridgely C. Bennett, M.D.

*agree with
recommended
approval*

Moore 10/1/84

cc.
Orig. NDA
HFN-130
HFN-220
HFN-130/RCBennett/9/27/83/CG/9/27/83
Wang No. 2328C

MR

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

18-680

CHEMISTRY REVIEW(S)

DRAFT

Summary Basis of Approval - Chemistry

NDA 18-680

Applicant: The Population Council
New York, NY 10021

DRUG GENERIC NAME: Intrauterine copper contraceptive.
DRUG TRADE NAME: Copper T Model T Cu380A

I. Indications for Use: Will be furnished by M.D.

II. Dosage forms: Intrauterine device having the shape of the letter T which is made of _____ polyethylene. Coiled around the vertical limb is 176 mg of _____ copper wire providing approximately _____ copper surface area. Swaged onto each horizontal arm is a 66.5 mg copper sleeve. The two sleeves provide an additional _____ copper surface area. b(4)

III. Manufacturing and Controls:

A. Manufacturing and Controls:

1. Synthesis: No synthetic procedures are involved in the manufacture of the device other than the preparation of the _____

2. Tests and Specifications: Acceptance specifications for all raw materials and the methods used to check compliance with those specifications have been evaluated and are satisfactory. The IUD is packaged in a sealed _____ pouch along with an insertion tube and rod. The finished product is checked for identity, physical properties and sterility to assure compliance with the specifications prescribed in the NDA. b(4)

3. Manufacturing: All procedures are described in reasonable detail and they follow good manufacturing practice. All equipment employed is suitable for the production of this device.

B. Stability:

The four year expiration date is supported by the submitted stability data.

C. Methods Validation:

Validation of the submitted test methods by our laboratories has been waived by virtue of the nature of the device. The methods consist of relatively simple physical measurements and basic chemical tests. Sterility tests are conducted according to the USP.

D. Labeling:

The labels, cartons and package insert are satisfactory with respect to the technical requirements and contain the mandatory information for an intrauterine device. The trade name is not in conflict with the name of any other IUD.

E. Establishment Inspection:

Our Manufacturing Review Branch has evaluated the operations of all involved contract manufacturers as they relate to compliance with Current Good Manufacturing Practice Regulations and they found no reason to withhold approval of the application.

F. Environmental Impact Analysis Report:

There are no known risks to the environment and a further analysis with regard to an Environmental Impact Statement is not necessary.

cc: Orig. IND ✓
HFN-130
HFN-102/Kumkumian
HFN-130/HBNunn/9/29/83/mk1/10/3/83
R/D init. by DJKertesz/9/30/83
Wang No. 2367C

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

18-680

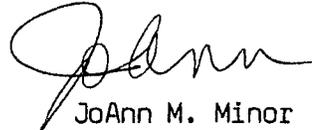
ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

October 26, 1984

MEMORANDUM FOR THE FILE

SUBJECT: Submission Patent Information for NDA 18-680 in
Accordance with Drug Price Competition and Patent Term
Restoration Act

I telephoned Dr. Harold Nash. He will supply us with all pertinent patent
information on Copper T Model, TCu 380A.


JoAnn M. Minor

cc: ✓ Dr. Bilstad/HFN-800
Leah Ripper/HFN-810
NDA 18-680

JMMinor:pec:11/1/84:0395S

JoAnn

The Population Council

Center for
Biomedical Research

1230 York Avenue
New York, New York 10021
Cable: Popbiomed, New York
Telephone (212) 570-8731
Telex: 238274 POBI UR

October 29, 1984

Commissioner
Food and Drug Administration
Division of Metabolism and Endocrine
Drug Products, HFN-810
Center for Drugs and Biologics
Food and Drug Administration
Rockville, Maryland 20857

Subject: Patent, re NDA 18-680

Gentlemen:

The following product which is the subject of a pending NDA is included within the claims of a US Patent assigned to the Population Council.

Trade name: Copper T Model TCu380A
Active ingredient: copper
Strength: 176[±]11 mg copper: surface area of copper - 380[±]23 mm²
Dosage form & route: T shaped intrauterine device with copper wire wound on the vertical arm and with copper collars on each of the horizontal arms. The device is placed in the uterus for purposes of contraception.
NDA no.: 18-680
Applicant: The Population Council
1230 York Avenue
New York, New York 10021
NDA approval date: Pending
Applicable Patent: US Patent 3,533,406 entitled "Intrauterine Contraceptive Device." This patent claims an intrauterine contraceptive device of T-shape and the method of contraception using such a device.

Manufacture of the Copper T Model TCu380A is being carried out using

b(4)

Expiration Date: US Patent 3,533,406 - October 13, 1987.
US Patent 3,711,035 - January 16, 1990.

Sincerely yours,
Harold Nash
Harold A. Nash, Ph.D.
Associate Division Director

Copper T Model TCU 380A
The Population Council

February 4, 1986

MEMORANDUM OF TELEPHONE CONVERSATION

Dr. Nash called to ask whether we had any comments on his December 13, 1985, letter regarding a _____
_____. After speaking with Dr. Ridgely Bennett, I told him that we did not have any comments at the present time other than that the proposed study should be randomized. He replied that although not so specified in his letter they do indeed plan to randomize the study. He asked whether there would be any problems with the study being done completely overseas as long as it is well-controlled, monitored, etc. I replied that we accept NDA's based only on foreign data. The protocol is to be submitted to the IND.

b(4)

LWR
Lee Ripper

cc: Orig NDA 18-680
HPN-810
LWR/2-4-86/1121R

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER

18-680

DATE APPROVAL LETTER ISSUED

NOV 15 1984

TO:

~~XXXXXXXXXXXXXXXXXXXX~~
Press Release Form (FD-300)
HFN-500

FROM:

Bureau of Medicine

Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION

ORIGINAL NDA

SUPPLEMENT TO NDA

CATEGORY

HUMAN

VETERINARY

TRADE NAME (or other designated name) AND ESTABLISHED OR NONPROPRIETARY NAME (if any) OF DRUG

Copper T Model TCu 380A (Intrauterine Copper Contraceptive)

DOSAGE FORM

The Copper T is placed in the uterine cavity.

HOW DISPENSED

RX

OTC

ACTIVE INGREDIENT(S) (as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)

The polyethylene body of the Copper T Model 380A intrauterine copper contraceptive is wound with approximately 176 mg of copper wire and carries a copper collar of approximately 66.5 mg of copper on each of its transverse arms.

NAME OF APPLICANT (Include City and State)

The Population Council
1230 York Avenue
New York, New York 10021

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

Intrauterine contraceptive

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY

NAME

Linda Carter

Linda Carter

DATE

3/21/84

FORM APPROVED BY

NAME

Roan J...

DATE

3/21/84