PDR®

45

EDITION

1991

PHYSICIANS' DESK REFERENCE®

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TABLE I

LIPPES LOOP Size	Number Woman/Months	Woman/Months of Use 1st Year After Insertion	Woman/Months of Use 2nd Year After Insertion
A	13,453	8,751	4,702
B	12,463	9,660	2,803
C	50,775	31,032	19,743
D	121,566	72,046	49,520

Tables II–V below give the pregnancy, expulsion, medical removal and continuation rates for each individual size LOOP:

TABLE II
LOOP A
(Annual Rates Per 100 Users)

	12 Months	24 Months (cumulative)
Pregnancy	5.3	9.7
Expulsion	23.9	27.7
Medical Removal	12.2	20.0
Continuation Rate	75.2	63.6

TABLE III
LOOP B
(Annual Rates Per 100 Users)

	12 Months	24 Months (cumulative)
Pregnancy	3.4	6.3
Expulsion	18.9	24.9
Medical Removal	15.1	23.8
Continuation Rate	74.6	59.2

TABLE IV
LOOP C
(Annual Rates Per 100 Users)

	12 Months	24 Months (cumulative)
Pregnancy	3.0	4.8
Expulsion	19.1	24.6
Medical Removal	14.3	22.1
Continuation Rate	76.5	62.8

TABLE V
LOOP D
(Annual Rates Per 100 Users)

	12 Months	24 Months (cumulative)
Pregnancy	2.7	4.2
Expulsion	12.7	16.0
Medical Removal	15.2	23.3
Continuation Rate	77.4	65.6

the bulbous tip and the inserter flange are in a horizontal plane.

Do this not more than one minute before insertion.

2. How to insert LIPPES LOOP Intrauterine Double-S.

Insert the loaded inserter gently through the endocervical canal, with the flange in a horizontal plane. DO NOT FORCE THE INSERTION. If resistance is encountered, do not proceed; perforation of the uterus may occur. If the flange makes contact with the cervix WITHOUT the inserter touching the fundal wall, withdraw ¼ inch before pressing the push rod to release the device in utero. Should the inserter touch the fundal wall BEFORE the flange makes contact, withdraw ½ inch prior to pressing the push rod to release the device in utero. With the inserter now in place, proceed, and WITHOUT UNDUE PRESSURE, push the rod slowly as far as it will go. LIPPES LOOP Intrauterine Double-S should now be in place. Withdraw the inserter tube and push rod from the cervical os until the tail is visible. Cut the tail leaving it as long as possible.

Time of Insertion

LIPPES LOOP Intrauterine Double-S should be inserted preferably the last one or two days of a normal menstrual period or the two days following the last day.

The expulsion and perforation rate may be increased when insertions are made before normal uterine involution occurs (usually four to six weeks postpartum or postabortion).

To Remove

To remove LIPPES LOOP Intrauterine Double-S, pull gently on the exposed tail. On those rare occasions that the tail is not available, the device should be carefully removed.

CLINICAL STUDIES

Different event rates have been recorded with the use of different IUD's. Inasmuch as these rates are usually derived from separate studies conducted by different investigators in several population groups, they cannot be compared with precision. Furthermore, event rates tend to be lower as clinical experience is expanded, possibly due to retention in the

Council with the LIPPES LOOP, use effectiveness was determined as follows for women, as tabulated by the life table method. (Rates are expressed as events per 100 women through 12 and 24 months of use). This experience is based on 198,257 woman/months of use, including 121,489 woman/months of use in first year after insertion, and 76,768 woman/months of use in second year after insertion. LIPPES LOOP Intrauterine Double-S devices are manufactured in four different sizes, and the figures given above represent the totals for the four sizes. The following table presents these figures individually for each size LOOP:

[See table above.]

LUTREPULSE® for Injection

(gonadorelin acetate)
Synthetic Gonadotropin-Releasing Hormone (GnRH)
For Pulsatile Intravenous Injection

DESCRIPTION

LUTREPULSE (gonadorelin acetate) for Injection is used for the induction of ovulation in women with primary hypothalamic amenorrhea. Gonadorelin acetate is a synthetic decapeptide that is identical in amino acid sequence to endogenous gonadotropin-releasing hormone (GnRH) synthesized in the human hypothalamus and in various neurons terminating in the hypothalamus. The molecular formula of gonadorelin acetate is:

$$C_{55}H_{75}N_{17}O_{13} \cdot xC_2H_4O_2 \cdot yH_2O$$

Its molecular weight is 1182.3 + x60 + y18, where x and y represent a non-stoichiometric ratio of acetate and water associated with the peptide, and x ranges from 1–2 and y ranges from 2–3. The amino acid sequence of GnRH is:

5-oxoPro-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2

LUTREPULSE for injection is a sterile, lyophilized powder intended for intravenous pulsatile injection after reconstitution. It is white and very soluble in water. Vials are available containing 0.8 mg or 3.2 mg gonadorelin acetate (expressed as the diacetate) and 10.0 mg mannitol as a carrier. After reconstituting with 8 mL of diluent (sterile 0.9% Sodium Chloride Solution and hydrochloric acid to adjust the pH) for LUTREPULSE for Injection, the concentration of gonadorelin acetate is 5 µg per 50 µl in each vial containing 0.8 mg lyophilized hormone, and 20 µg per 50 µl in each vial containing 3.2 mg lyophilized hormone. LUTREPULSE (gonadorelin acetate) for Injection is intended for use with the LUTREPULSE for Injection KITS. The volumes and concentrations are specific for use with the LUTREPULSE PUMP for appropriate dosing.

CLINICAL PHARMACOLOGY

Under physiologic conditions, gonadotropin-releasing hormone (GnRH) is released by the hypothalamus in a pulsatile fashion. The primary effect of GnRH is the synthesis and release of luteinizing hormone (LH) in the anterior pituitary gland. GnRH also stimulates the synthesis and release of follicle stimulating hormone (FSH), but this effect is less pronounced. LH and FSH subsequently stimulate the gonads to produce steroids which are instrumental in regulating reproductive hormonal status. Unlike human menopausal gonadotropin (hMG) which supplies pituitary hormones, pulsatile administration of LUTREPULSE for Injection replaces defective hypothalamic secretion of GnRH. The pulsatile administration of LUTREPULSE for Injection approximates the natural hormonal secretory pattern, causing pulsatile release of pituitary gonadotropins. Accordingly, LUTREPULSE for Injection is useful in treating conditions of infertility caused by defective GnRH stimulation from the hypothalamus (See **INDICATIONS AND USAGE**). The following information summarizes clinical efficacy of gonadorelin acetate administered by pulsatile intravenous injection to patients with primary hypothalamic amenorrhea.

44 patients with primary hypothalamic amenorrhea (HA)
93% (41/44) patients ovulatory with gonadorelin acetate therapy
62% (24/39)* patients pregnant
100% (7/7) of those failing past attempts at ovulation induction by other methods were ovulatory on gonadorelin acetate.

*Five patients did not desire pregnancy.

Following intravenous injection of GnRH into normal subjects and/or hypogonadotropic patients, plasma GnRH concentrations ... of distribution (10–15 L) were calculated. The pharmacokinetics of GnRH in normal subjects and in hypogonadotropic patients were similar. GnRH was rapidly metabolized to various biologically inactive peptide fragments which are readily excreted in urine. Renal failure, but not hepatic disease, prolonged the half-life and reduced the clearance of GnRH.

INDICATIONS AND USAGE

LUTREPULSE (gonadorelin acetate) for Injection is indicated in the treatment of primary hypothalamic amenorrhea.

DIFFERENTIAL DIAGNOSIS: Proper diagnosis is critical for successful treatment with LUTREPULSE for Injection. It must be established that hypothalamic amenorrhea or hypogamadism is, in fact, due to a deficiency in quantity or pulsing of endogenous GnRH. The diagnosis of hypothalamic amenorrhea or hypogonadism is based on the exclusion of other causes of the dysfunction, since there is currently no practical technique to directly assess hypothalamic function. Prior to initiation of therapy with LUTREPULSE (gonadorelin acetate) for injection, the physician should rule out disorders of general health, reproductive organs, anterior pituitary, and central nervous system, other than abnormalities of GnRH secretion.

CONTRAINDICATIONS

LUTREPULSE for Injection is contraindicated in women with any condition that could be exacerbated by pregnancy. For example, pituitary prolactinoma should be considered one such condition. Additionally, any history of sensitivity to gonadorelin acetate, gonadorelin hydrochloride or any component of LUTREPULSE for Injection is a contraindication. Patients who have ovarian cysts or causes of anovulation other than those of hypothalamic origin should not receive LUTREPULSE for Injection.

LUTREPULSE for Injection is intended to initiate events including the production of reproductive hormones (e.g. estrogens and progestins). Therefore, any condition that may be worsened by reproductive hormones, such as hormonally-dependent tumor, is a contraindication to the use of LUTREPULSE for Injection.

WARNINGS

Therapy with LUTREPULSE (gonadorelin acetate) for Injection should be conducted by physicians familiar with pulsatile GnRH delivery and the clinical ramifications of ovulation induction While there have been few cases of hyperstimulation(< 1%) this possibility must be considered. If hyperstimulation should occur, therapy should be discontinued and spontaneous resolution can be expected. The preservation of the endogenous feedback mechanisms makes severe hyperstimulation (with ascites and pleural effusion) rare. However, the physician shoud be aware of the possibility and be alert for any evidence of ascites, pleural effusion, hemoconcentration, rupture of a cyst, fluid or electrolyte imbalance, or sepsis.

Multiple pregnancy is a possibility that can be minimized by careful attention to the recommended doses and ultrasonographic monitoring of the ovarian response to therapy. Following a baseline pelvic ultrasound, follow-up studies should be conducted at a minimum on day 7 and day 14 of therapy.

As with any intravenous medication, scrupulous attention to asepsis is important. The infusion area must be monitored as with all indwelling parenteral approaches. The cannula and IV site should be changed at 48-hour intervals.

PRECAUTIONS

GENERAL: Ovarian hyperstimulation has been reported. This may be related to pulse dosage or concomitant use of other ovulation stimulators. Hyperstimulation may be a greater risk in patients where spontaneous variations in endogenous GnRH secretion occur. Multiple follicle development, multiple pregnancy, and spontaneous termination of pregnancy have been reported. Multiple pregnancy can be minimized by appropriate monitoring of follicle formation; nonetheless, the patient and her partner should be advised of the frequency (12%) and potential risks of multiple pregnancy before starting treatment.

Ovarian hyperstimulation, a syndrome of sudden ovarian enlargement, ascites with or without pain, and/or pleural effusion, is rare with pulsatile GnRH therapy. Among 268 patients participating in clinical trials, one case of moderate hyperstimulation has been reported, but this cycle included the concomitant use of clomiphene citrate.

LUTREPULSE (gonadorelin acetate) for Injection should be administered only with the LUTREPULSE PUMP. The patient should be provided with detailed oral and written instructions regarding infusion pump usage and potential sepsis in order to minimize the frequency of infusion pump malfunction and inflammation, infection, mild phlebitis, or hematoma at the catheter site.

LABORATORY TESTS: Following a diagnosis of primary

Ortho Pharm.—Cont.

(gonadorelin acetate) for Injection therapy may be monitored by the following:
1) Ovarian ultrasound—baseline, therapy day 7, therapy day 14.
2) Mid-luteal phase serum progesterone.
3) Clinical observation of infusion site at each visit as needed.
4) Physical examination including pelvic at regularly scheduled visits.

DRUG INTERACTIONS: None are known. LUTREPULSE for Injection should not be used concomitantly with other ovulation stimulators.

DRUG/LABORATORY TEST INTERACTIONS: None are known.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Since GnRH is a natural substance normally present in humans, long-term studies in animals have not been performed to evaluate carcinogenic potential. Mutagenicity testing was not done.

PREGNANCY: Pregnancy Category B

Reproduction studies (teratology and embryo-toxicity) performed in rats and rabbits have not revealed any evidence of harm to the fetus due to gonadorelin acetate There was no evidence of teratogenicity when gonadorelin acetate was administered intravenously up to 120 μg/kg/day (> 70 times the recommended human dose of 5 μg per pulse) in rats and rabbits.

Studies in pregnant women have shown that gonadorelin acetate does not increase the risk of abnormalities when administered during the first trimester of pregnancy. It appears that the possibility of fetal harm is remote, if the drug is used during pregnancy. In clinical studies, 47 pregnant patients have used gonadorelin acetate during the first trimester of pregnancy (51 pregnancies) and the drug had no apparent adverse effect on the course of pregnancy. Available follow-up reports on infants born to these women reveal no adverse effects or complications that were attributable to gonadorelin acetate. Nevertheless, because the studies in humans cannot rule out the possibility of harm, gonadorelin acetate should be used during pregnancy only for maintenance of the corpus luteum in ovulation induction cycles.

NURSING MOTHERS: It is not known whether this drug is excreted in human milk. There is no indication for use of LUTREPULSE (gonadorelin acetate) for Injection in a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children under the age of 18 have not been established.

ADVERSE REACTIONS

Adverse reactions have been reported in approximately 10% of treatment regimens. Ten of 268 patients interrupted therapy because of an adverse reaction but subsequently resumed treatment. One other subject did not resume treatment.

In clinical studies involving 268 women, one case of moderate ovarian hyperstimulation has been reported. This cycle included concomitant use of clomiphene citrate. This low incidence of hyperstimulation appears to be due to the preservation of normal feedback mechanisms of the pituitary-ovarian axis.

Despite the preservation of feedback mechanisms, some incidents of multiple follicle development, multiple pregnancy, and spontaneous termination of pregnancy have been reported. Multiple pregnancy can be minimized by appropriate monitoring of follicle formation; nonetheless, the patient and her partner should be advised of the frequency and potential hazards of multiple pregnancy before starting treatment. In clinical studies involving 142 pregnancies, delivery information was available on 89 pregnancies. Eleven of these LUTREPULSE (gonadorelin acetate) for Injection-induced pregnancies (12%) were multiple (10 sets of twins, 1 set of triplets).

The following adverse reactions are related to use of the infusion pump: inflammation, infection, mild phlebitis, or hematoma at the catheter site. Additionally, infusion set malfunction and interruption of infusion may occur; this has no known adverse effect other than interruption of therapy.

Anaphylaxis (bronchospasm, tachycardia, flushing, urticaria, induration at injection site) has been reported with the related polypeptide hormone gonadorelin hydrochloride (FACTREL®).

® registered trademark of Wyeth-Ayerst Laboratories.

OVERDOSAGE

Continuous, non-pulsatile exposure to gonadorelin acetate could temporarily reduce pituitary responsiveness. If the pump should malfunction and deliver the entire contents of the 3.2 mg system, no harmful effects would be expected. Bolus doses as high as 3000 μg of gonadorelin hydrochloride Administration of 640 μg/kg in monkeys as a single intravenous bolus resulted in no compound-related effects in clinical observations or gross morphologic evaluations.

DOSAGE AND ADMINISTRATION

DOSAGE: Dosages between 1 and 20 μg have been successfully used in clinical studies. The recommended dose in primary hypothalamic amenorrhea is 5 μg every 90 minutes. This is delivered by LUTREPULSE PUMP using the 0.8 mg solution at 50 μl per pulse (see physician pump manual). Sixty-eight percent of the 5 μg every 90 minute regimens induced ovulation in patients with primary hypothalamic amenorrhea.

The LUTREPULSE PUMP is capable of delivering 2.5, 5, 10, or 20 μg of gonadorelin acetate every 90 minutes. Some women may require a reduction in the recommended dose of 5 μg should laboratory testing and patient monitoring indicate an inappropriate response. While most primary hypothalamic amenorrhea patients will ovulate during the first cycle of 5 μg therapy, some may be refractory to this dose. The recommended treatment interval is 21 days. It may be necessary to raise the dose cautiously, and in stepwise fashion if there is no response after three treatment intervals. All dose changes should be carefully monitored for inappropriate response.

The following table can be used to calculate the dose per pulse when individualizing treatment:

Vial	Diluent	Volume/pulse	Dose/pulse
0.8 mg	8 mL	25 μL	2.5 μg
0.8 mg	8 mL	50 μL	5 μg
3.2 mg	8 mL	25 μL	10 μg
3.2 mg	8 mL	50 μL	20 μg

The response to LUTREPULSE (gonadorelin acetate) for Injection usually occurs within two to three weeks after therapy initiation. When ovulation occurs with the LUTREPULSE PUMP in place, therapy should be continued for another two weeks to maintain the corpus luteum. A comparison of LUTREPULSE for Injection to hCG or hCG + LUTREPULSE for Injection for corpus luteum maintenance revealed the following information:

hCG
Delivered = $\frac{43}{63} = 68\%$
Aborted = $\frac{20}{63} = 32\%$

LUTREPULSE for Injection
Delivered = $\frac{19}{26} = 73\%$
Aborted = $\frac{7}{26} = 27\%$

hCG + LUTREPULSE for Injection
Delivered = $\frac{19}{25} = 76\%$
Aborted = $\frac{6}{25} = 24\%$

LUTREPULSE (gonadorelin acetate) for Injection alone was able to maintain the corpus luteum during pregnancy.

ADMINISTRATION: LUTREPULSE for Injection is to be reconstituted aseptically with 8 mL of diluent for LUTREPULSE for Injection. *The drug product should be reconstituted immediately prior to use and transferred to the plastic reservoir.* First withdraw 8 mL of the saline diluent and then inject it onto the lyophile (drug product) cake. The product is shaken for a few seconds to produce a solution which should be clear, colorless, and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulate matter or discoloration are present, the solution should not be used. A presterilized reservoir (bag) with the infusion catheter set supplied with the LUTREPULSE for Injection is filled with the reconstituted solution, and administered intravenously using the LUTREPULSE PUMP. The pump should be set to deliver 25 or 50 μL of solution, based upon the dose selected, over a pulse period of one minute and at a pulse frequency of 90 minutes. The 8 mL of solution will supply 90 minute pulsatile doses for approximately 7 consecutive days.

HOW SUPPLIED

LUTREPULSE (gonadorelin acetate) for Injection is supplied in a LUTREPULSE for Injection 0.8 mg (NDC 0062-7212-11) or 3.2 mg (NDC 0062-7211-11) KIT. Each kit contains one 10 mL vial of 0.8 mg or 3.2 mg LUTREPULSE for Injection as a lyophilized, sterile powder which should be stored at controlled room temperature (15–30°C, 59–86°F). The following components are included in each kit:
10 mL diluent for LUTREPULSE for Injection
Sterile catheter tubing
Sterile reservoir catheter with double-female luer adaptor
Elastic belt
9 V battery
Physician package insert, physician pump manual, and patient instructions

The LUTREPULSE PUMP kit contains the following components:
LUTREPULSE Pump
9 V batteries (two supplied)
3 V lithium battery
Physician pump manual
Physician package insert
Warranty card

Manufactured for
ORTHO PHARMACEUTICAL CORPORATION
RARITAN, NEW JERSEY 08869
by FERRING ARZNEIMITTEL GmbH, Kiel, W. Germany
 Revised May 1990 632-10-600-3

MASSE' ® Breast Cream

(See PDR For Nonprescription Drugs.)

MONISTAT® 7 Vaginal Cream ℞

(miconazole nitrate 2%)

DESCRIPTION

MONISTAT 7 Vaginal Cream (miconazole nitrate 2%) is a water-miscible, white cream containing as the active ingredient, 2% miconazole nitrate, 1-[2,4-dichloro-β-[(2,4-dichlorobenzyl)oxy]phenethyl] imidazole nitrate.

ACTIONS

MONISTAT 7 Vaginal Cream exhibits fungicidal activity *in vitro* against species of the genus *Candida*. The pharmacologic mode of action is unknown.

INDICATIONS

MONISTAT 7 Vaginal Cream is indicated for the local treatment of vulvovaginal candidiasis (moniliasis). As MONISTAT 7 Vaginal Cream is effective only for candidal vulvovaginitis, the diagnosis should be confirmed by KOH smears and/or cultures. Other pathogens commonly associated with vulvovaginitis (*Trichomonas* and *Haemophilus vaginalis* [*Gardnerella*]) should be ruled out by appropriate laboratory methods.

MONISTAT 7 is effective in both pregnant and non-pregnant women, as well as in women taking oral contraceptives. (See PRECAUTIONS.)

CONTRAINDICATIONS

Patients known to be hypersensitive to this drug.

PRECAUTIONS

General: Discontinue drug if sensitization or irritation is reported during use. Laboratory Tests: If there is a lack of response to MONISTAT 7, appropriate microbiological studies should be repeated to confirm the diagnosis and rule out other pathogens.

Pregnancy: Since MONISTAT is absorbed in small amounts from the human vagina, it should be used in the first trimester of pregnancy only when the physician considers it essential to the welfare of the patient.

Clinical studies, during which MONISTAT was used for 14 days, included 209 pregnant patients. Follow-up reports now available in 117 of these patients reveal no adverse effects or complications attributable to MONISTAT therapy in infants born to these women.

ADVERSE REACTIONS

During clinical studies with MONISTAT for a 14-day regimen, 39 of the 528 patients (7.4%) treated with MONISTAT reported complaints during therapy that were possibly drug-related. Most complaints were reported during the first week of therapy. Vulvovaginal burning, itching or irritation occurred in 6.6%, while other complaints such as vaginal burning, pelvic cramps, hives, skin rash and headache occurred rarely (each less than 0.2% patient incidence). The therapy-related dropout rate was 0.9%.

CLINICAL

Statistical analysis of randomized clinical trials, conducted to determine the shortest effective course of therapy with MONISTAT, demonstrates that a regimen of seven or more days has a cure rate equivalent to the 14-day regimen.

The graphic representation of this conclusion plots Days of Therapy versus Cure Rates. The solid line represents the mean therapeutic cure rate and the shaded area represents the 95% confidence interval. [See next page.]

DOSAGE AND ADMINISTRATION

One applicatorful is administered intravaginally once daily at bedtime for seven days. Course of therapy may be repeated after other pathogens have been ruled out by appropriate smears and cultures.

HOW SUPPLIED

COLOSCREEN
Fecal Occult Blood Test

DESCRIPTION
ColoScreen is the standard guaiac slide test for the detection of occult blood in the stool. The patient smears a small fecal sample on the slide and then returns the slide to the physician's office or lab for testing. ColoScreen is identical in specificity and sensitivity to Hemoccult® (a registered trademark of SmithKline Diagnostics, Inc.). As with other guaiac slide tests, certain fruits and vegetables, red meats and vitamin C should be restricted from the diet.

ORDER INFORMATION
ColoScreen Kits contain all materials necessary for complete testing, including developer and instructions. (Lab packs are also available in cartons of 1000 tests.)

ColoScreen III Office Pack **Cat. No. 5071**
100 Patient Kits (300 Tests). Each patient kit consists of one ColoScreen triple slide with monitors and applicators in a mail-back envelope printed with instructions for the patient.

ColoScreen Lab Pack **Cat. No. 5072**
100 Single Slides with Monitors (100 Tests)

ColoScreen III Lab Pack **Cat. No. 5082**
34 Triple Slides with Monitors (102 Tests)

ColoScreen Tape **Cat. No. 5079**
2 Rolls (100 Tests/Roll) with perforated Segments and Monitors

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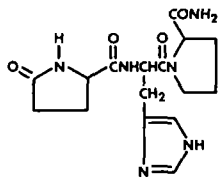
Hoechst-Roussel Pharmaceuticals Inc.
SOMERVILLE, NJ 08876-1258

RELEFACT® TRH
(protirelin)
Injection IV

℞

DESCRIPTION
Chemically, Relefact® TRH (protirelin) is identified as 5-oxo-L-prolyl-L-histidyl-L-proline amide. It is a synthetic tripeptide which is believed to be structurally identical with the naturally-occurring thyrotropin-releasing hormone produced by the hypothalamus.
The structural formula is:

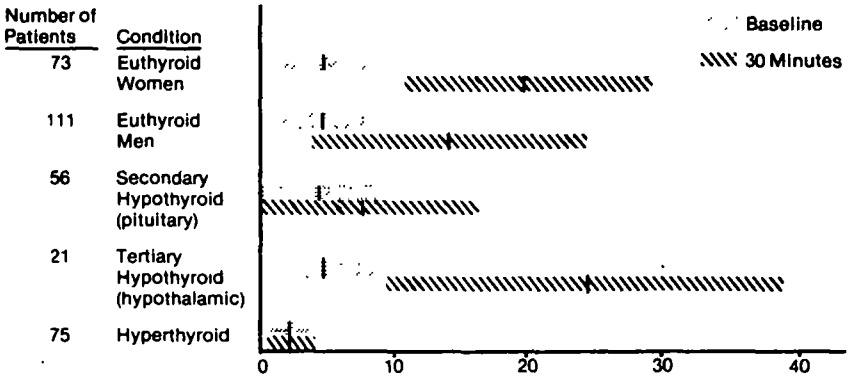


Relefact TRH is supplied as 1 mL ampuls. Each ampul contains 500 mcg protirelin in a sterile non-pyrogenic isotonic saline solution having a pH of approximately 6 5. In addition, each ampul contains sodium chloride, 9.0 mg, Water for Injection, and hydrochloric acid as needed to adjust pH. Relefact TRH is intended for intravenous administration.

CLINICAL PHARMACOLOGY
Pharmacologically, Relefact TRH increases the release of the thyroid stimulating hormone (TSH) from the anterior pituitary. Prolactin release is also increased. It has recently been observed that approximately 65% of acromegalic patients tested respond with a rise in circulating growth hormone levels; the clinical significance is as yet not clear. Following intravenous administration, the mean plasma half-life of protirelin in normal subjects is approximately five minutes. TSH levels rise rapidly and reach a peak at 20 to 30 minutes. The decline in TSH levels takes place more slowly, approaching baseline levels after approximately three hours.

INDICATIONS AND USAGE
Relefact® TRH (protirelin) is indicated as an adjunctive agent in the diagnostic assessment of thyroid function. As an adjunct to other diagnostic procedures, testing with Relefact TRH may yield useful information in patients with pituitary or hypothalamic dysfunction.
Relefact TRH is indicated as an adjunct to evaluate the effectiveness of thyrotropin suppression with a particular dose of T4 in patients with nodular or diffuse goitre. A normal TSH baseline value and a minimal difference between the 30 minute and baseline response to Relefact TRH injection would indicate adequate suppression of the pituitary secretion of TSH.

Figure 1
Mean ± One Standard Deviation of TSH Levels (μU/mL)
Observed at Baseline and 30 Minutes After Relefact® TRH (protirelin)



thirty minutes following Relefact TRH injection, would indicate adequate replacement therapy.

WARNINGS
Transient changes in blood pressure, either increases or decreases, frequently occur immediately following administration of Relefact TRH (protirelin). Blood pressure should therefore be measured before Relefact TRH is administered and at frequent intervals during the first 15 minutes after its administration.

Increases in systolic pressure (usually less than 30 mm Hg) and/or increases in diastolic pressure (usually less than 20 mm Hg) have been observed more frequently than decreases in pressure. These changes have not ordinarily persisted for more than 15 minutes nor have they required therapy. More severe degrees of hypertension or hypotension with or without syncope have been reported in a few patients. To minimize the incidence and/or severity of hypotension, the patient should be supine before, during, and after Relefact TRH administration. If a clinically important change in blood pressure occurs, monitoring of blood pressure should be continued until it returns to baseline levels.

Relefact® TRH (protirelin) should not be administered to patients in whom marked, rapid changes in blood pressure would be dangerous unless the potential benefit clearly outweighs the potential risk.

PRECAUTIONS
Thyroid hormones reduce the TSH response to Relefact TRH. Accordingly, patients in whom Relefact TRH is to be used diagnostically should be taken off liothyronine (T3) approximately seven days prior to testing and should be taken off thyroid medications containing levothyroxine (T4), e.g., desiccated thyroid, thyroglobulin, or liatrix, at least 14 days before testing. Hormone therapy is NOT to be discontinued when the test is used to evaluate the effectiveness of thyroid suppression with a particular dose of T4 in patients with nodular or diffuse goitre, or for adjustment of thyroid hormone dosage given to patients with primary hypothyroidism.
Chronic administration of levodopa has been reported to inhibit the TSH response to Relefact TRH.
It is not advisable to withdraw maintenance doses of adrenocortical drugs used in the therapy of known hypopituitarism. Several published reports have shown that prolonged treatment with glucocorticoids at physiologic doses has no significant effect on the TSH response to thyrotropin releasing hormone, but that the administration of pharmacologic doses of steroids reduces the TSH response.
Therapeutic doses of acetylsalicylic acid (2 to 3.6 g/day) have been reported to inhibit the TSH response to protirelin. The ingestion of acetylsalicylic acid caused the peak level of TSH to decrease approximately 30% as compared to values obtained without acetylsalicylic acid administration. In both cases, the TSH peak occurred 30 minutes post-administration of protirelin.

Pregnancy: Reproduction studies have been performed in rats and rabbits. At doses 1½ and 6 times the human dose, there was an increase in the number of resorption sites in the pregnant rabbit. There are no studies in pregnant women which bear on the safety of Relefact® TRH (protirelin) for the human fetus. Relefact TRH should be used in pregnant women only when clearly needed.

ADVERSE REACTIONS
Side effects have been reported in about 50% of the patients to

Cardiovascular reactions:
Marked changes in blood pressure, including both hypertension and hypotension with or without syncope, have been reported in a small number of patients.
Endocrine reaction: Breast enlargement and leakage in lactating women for up to two or three days.
Other reactions:
Headaches, sometimes severe, and transient amaurosis in patients with pituitary tumors.
Rarely, convulsions may occur in patients with predisposing conditions, e.g. epilepsy, brain damage.
Nausea; urge to urinate; flushed sensation; lightheadedness; bad taste; abdominal discomfort; and dry mouth. Less frequently reported were: anxiety; sweating; tightness in the throat; pressure in the chest; tingling sensation; and drowsiness.
Pituitary apoplexy requiring acute neurosurgical intervention has been reported infrequently for patients with pituitary macroadenomas following the acute administration of protirelin (TRH) injection in the setting of combined anterior pituitary function testing in conjunction with LHRH and insulin

DOSAGE AND ADMINISTRATION
Relefact TRH is intended for intravenous administration with the patient in the supine position. The drug is administered as a bolus over a period of 15 to 30 seconds, with the patient remaining supine until all scheduled postinjection blood samples have been taken. Blood pressure should be measured before Relefact TRH is administered and at frequent intervals during the first 15 minutes thereafter (see **Warnings**).
Dosage: Adults: 500 mcg. Doses between 200 and 500 mcg have been used. 500 mcg is considered the optimum dose to give the maximum response in the greatest number of patients. Doses greater than 500 mcg are unlikely to elicit a greater TSH response.
Children age 6 to 16 years: 7 mcg/kg body weight up to a dose of 500 mcg.
Infants and children up to 6 years: Experience is limited in this age group; doses of 7 mcg/kg have been administered.
One blood sample for TSH assay should be drawn immediately prior to the injection of Relefact® TRH (protirelin), and a second sample should be obtained 30 minutes after injection.
The TSH response to Relefact TRH is reduced by repetitive administration of the drug. Accordingly, if the Relefact TRH test is repeated, an interval of seven days before testing is recommended.
Elevated serum lipids may interfere with the TSH assay. Thus, fasting (except in patients with hypopituitarism) or a low-fat meal is recommended prior to the test.

INTERPRETATION OF TEST RESULTS
Interpretation of the TSH response to Relefact TRH requires an understanding of thyroid-pituitary-hypothalamic physiology and knowledge of the clinical status of the individual patient.
Because the TSH test results may vary with the laboratory, the physician should be familiar with the TSH assay method used and the normal range for the laboratory performing the assay.
TSH response 30 minutes after Relefact TRH administration in normal subjects and in patients with hyperthyroidism and hypothyroidism are presented in Figure 1. The diagnoses were established prior to the administration of Relefact

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