

Afinoxifene Effective Therapy for Cyclic Mastalgia

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SAN ANTONIO — Topical afinoxifene proved effective for the treatment of cyclic mastalgia and also showed potential for reduction of mammographic breast density in separate phase II clinical trials presented at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

Afinoxifene is a highly potent tamoxifen metabolite formulated in a topical alcohol-

based gel. Applied to the breast, it avoids first-pass liver metabolism, thus resulting in high levels of the antiestrogen in target breast tissue with low systemic exposure.

The result is an agent designed to have a far quicker onset of benefit than oral tamoxifen, which is prescribed for 5 years for chemoprevention—and afinoxifene also is intended to spare women from the side effects of the parent oral drug, including increased risks of venous thromboembolism, endometrial cancer, and hot flashes.

Dr. Robert E. Mansel reported on 130 premenopausal women with a history of moderate to severe cyclic mastalgia who were randomized to 2 mg or 4 mg/day of afinoxifene or placebo for four menstrual cycles in a double-blind multicenter trial. The primary end point was change in breast pain assessed by patients on a visual analog scale from baseline through the fourth treatment cycle. The 4-mg dose significantly outperformed placebo as evidenced by a mean 32-point reduction from

a baseline of 72 points on the 0-100 scale vs. reductions of 19 points with placebo and 25 points with 2 mg/day of afinoxifene.

The 4-mg dose also outperformed placebo in the secondary end points of blinded physician-assessed breast pain, nodularity, and tenderness, with 67%-70% reductions being recorded relative to placebo in each of these domains, added Dr. Mansel, who is professor and chairman of the department of surgery at the University of Wales, Cardiff.

Rates of hot flashes, night sweats, and nipple discharge were similar in the three groups. Application site skin reactions occurred in 4% of women on 4 mg/day of the topical antiestrogen. Menses duration, cycle length, and estrogen and progesterone

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Rh₀(D) Immune Globulin Intravenous (Human) 1500 IU (300 µg) Rhophylac[®]

Manufactured by:
ZLB Behring AG
Berne, Switzerland
US License No. 1710

Distributed by:
ZLB Behring LLC
Kankakee, IL 60901 USA

ZLB Behring

R_x only

For Intravenous and Intramuscular Injection
Preservative free, ready to use pre-filled syringe

Before prescribing please consult full prescribing information, a brief summary of which follows:

INDICATIONS AND USAGE

Pregnancy and Obstetrical Conditions

Rhophylac[®], Rh₀(D) Immune Globulin Intravenous (Human) is recommended:

- for the suppression of Rh isoimmunization in non-sensitized Rh₀(D)-negative (D-negative) women. The criteria for an Rh-incompatible pregnancy requiring administration of Rhophylac[®] at 28 to 30 weeks of gestation and within 72 hours after delivery are:
 - the mother must be Rh₀(D)-negative,
 - the mother is carrying a child whose father is either Rh₀(D)-positive or Rh₀(D) unknown,
 - the baby is either Rh₀(D)-positive or Rh₀(D) unknown, and the mother must not be previously sensitized to the Rh₀(D) factor.
- for Rhesus prophylaxis in case of obstetric complications, e.g., miscarriage, abortion, threatened abortion, ectopic pregnancy or hydatidiform mole, transplacental hemorrhage resulting from antepartum hemorrhage.
- for Rhesus prophylaxis in case of invasive procedures during pregnancy, e.g., amniocentesis, chorionic biopsy or obstetric manipulative procedures, e.g., external version, or abdominal trauma.

Incompatible Transfusions

Rhophylac[®] is recommended for the suppression of Rh isoimmunization in Rh₀(D)-negative individuals transfused with Rh₀(D)-positive RBCs or blood components containing Rh₀(D)-positive RBCs. Treatment should be initiated within 72 hours of exposure. Treatment should be given (without preceding exchange transfusion) only if the transfused Rh₀(D)-positive blood represents less than 20% of the total circulating red cells. A 1500 IU (300 µg) dose will suppress the immunizing potential of approximately 15 mL of Rh₀(D)-positive RBCs.

CLINICAL STUDIES

The efficacy, safety, tolerability and pharmacokinetics of Rhophylac[®], are supported by the results of two clinical studies in 446 Rh₀(D)-negative pregnant women (1, 2). In both studies, Rh₀(D)-negative women received Rhophylac[®] 1500 IU (300 µg) intravenously or intramuscularly in the 28th week of pregnancy. Mothers who gave birth to a Rh₀(D)-positive child received a further dose of Rhophylac[®] 1500 IU (300 µg) within 72 hours after the birth.

Eight out of 14 pregnant women from the above mentioned pharmacokinetic study gave birth to a Rh₀(D)-positive child and received Rhophylac[®] 1500 IU (300 µg) postpartum as well. The antibody tests performed 6 to 8 months later were negative for all mothers, which suggest that no Rh₀(D) immunization occurred.

In a second study at 22 centers in the United Kingdom and the USA, 432 pregnant women received Rhophylac[®] 1500 IU (300 µg) for antepartum rhesus prophylaxis. Two randomized groups of 216 women each received Rhophylac[®] 1500 IU (300 µg), either as an intravenous or intramuscular injection. Rhophylac[®] 1500 IU (300 µg) was also injected if there was a risk of fetomaternal hemorrhage between routine antepartum rhesus prophylaxis in the 28th week of pregnancy and birth, or if extensive fetomaternal hemorrhage was measured after birth. Of the 432 women who received Rhophylac[®] 1500 IU (300 µg) in the 28th week of pregnancy, 270 women delivered Rh₀(D)-positive children. 248 women were available for the investigation of Rh₀(D) immunization 6 to 11.5 months postpartum. None of those women developed antibodies against the Rh₀(D) antigen as assessed by the absence of anti-D antibodies.

CONTRAINDICATIONS

Rhophylac[®] is contraindicated in persons with hypersensitivity to human globulin.

The concentration of IgA in Rhophylac[®] was found to be below the detection limit of 5 µg/mL. Nevertheless, the product may contain trace amounts of IgA. Although anti-D immunoglobulin has been used to treat selected IgA deficient individuals, the attending physician must weigh the benefit against the potential risk of hypersensitivity reactions. Individuals deficient in IgA have a potential for development of IgA antibodies and anaphylactic reactions after administration of blood components containing IgA.

WARNINGS

Rhophylac[®] is made from human plasma. Products made from human plasma may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the CJD agent. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacturing. The Rhophylac[®] manufacturing process includes a solvent detergent treatment step (using tri-n-butyl phosphate and Triton[®] X-100) that is effective in inactivating enveloped viruses such as HBV, HCV, and HIV (3, 4). Rhophylac[®] is nanofiltered using a Planova[®] 15 nm virus filter that is effective in reducing the level of enveloped as well as non-enveloped viruses (5). These two processes are designed to increase product safety by reducing the risk of transmission of enveloped and non-enveloped

viruses, respectively. Despite these measures, these products could still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to ZLB Behring at 800-504-5434. The physician should discuss the risks and benefits of this product with the patient.

PRECAUTIONS

For postpartum use, Rhophylac[®], Rh₀(D) Immune Globulin Intravenous (Human) is intended for maternal administration. It should not be given to the newborn infant. The product is not intended for use in Rh₀(D)-positive individuals. Patients should be observed for at least 20 minutes after administration.

As with all pharmaceutical agents, allergic responses may occur. If symptoms of allergic or anaphylactic type reactions occur, immediately discontinue administration. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. The treatment required depends on the nature and severity of the side effect. If necessary, the current medical standards for shock treatment should be observed.

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Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

Drug Interactions

Active immunization with live virus vaccines (e.g., measles, mumps, rubella or varicella) should be postponed until 3 months after the last administration of immunoglobulin products, as the efficacy of the live virus vaccine may be impaired. If immunoglobulin needs to be administered within 2-4 weeks of a live virus vaccination, then the efficacy of such a vaccination may be impaired.

The results of blood typing and antibody testing in neonates, including the Coombs or antiglobulin test, may be affected by the administration of anti-D immunoglobulin.

Rhophylac[®] can contain antibodies to other Rh antigens, e.g., anti-C antibodies, which might be detected by sensitive serological test methods following administration of the product.

Pregnancy Category C

This medicinal product is used in pregnancy. Animal reproduction studies have not been conducted with Rhophylac[®]. The available evidence suggests that Rhophylac[®] does not harm the fetus or affect future pregnancies or the reproduction capacity of the maternal recipient.

Rh₀(D) Immune Globulin is not secreted in breast milk. No hazards are expected during breastfeeding.

ADVERSE REACTIONS

When anti-D immunoglobulins are administered by the intramuscular route, local pain and tenderness can be observed at the injection site; this can be prevented by dividing larger doses over several injection sites.

Mild and transient fever, malaise, headache, cutaneous reactions and chills occur occasionally. In rare cases, nausea, vomiting, hypotension, tachycardia, and allergic or anaphylactic type reactions, including dyspnea and shock are reported, even when the patient has shown no hypersensitivity to previous administration.

No data are available on overdosage. Patients with incompatible transfusion who receive an overdose of anti-D immunoglobulin should be monitored clinically and by biological parameters because of the risk of hemolytic reaction. In other Rh₀(D)-negative individuals overdosage should not lead to more frequent or more severe undesirable effects than the normal dose.

HOW SUPPLIED

Rhophylac[®] 1500 IU (300 µg) is available in packages containing one or ten pre-filled 2 mL syringes.

STORAGE

Store at 2°C to 8°C (36°F to 46°F). If stored at this temperature, Rhophylac[®] has a shelf life of 36 months. Do not freeze. Protect from light. The preparation should not be used after the expiration date printed on the label.

REFERENCES

- Bichler J, Schöndorfer G, Pabst G, Andresen I. Pharmacokinetics of anti-D IgG in pregnant RhD-negative women. BJOG 2003; 110:39-45.
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There are at present no approved treatments for mastalgia.

DR. MANSEL

terone levels were unaffected in the three study arms. Mastalgia is experienced by an estimated 8 million premenopausal American women for at least 2 weeks during their menstrual cycles. There are at present no approved treatments, Dr. Mansel noted.

Dr. Jennifer A. Harvey reported on 61 premenopausal women with 50%-80% breast tissue density and 19 with greater than 80% breast density on a screening digital mammogram performed within the prior 42 days who were randomized to 2 mg/day of afinoxifene or placebo in a double-blind study.

Mammographic breast density in the 80% range has been shown to be a biomarker conferring a four- to fivefold increased risk of developing cancer. But unlike many breast cancer risk factors, such as age, family history, and early age at menarche, breast density is modifiable. Radio-dense glandular epithelium and connective tissue also interferes with early diagnosis of breast cancer by hiding mammographic abnormalities, said Dr. Harvey of the University of Virginia Charlottesville.

Results of the trial were mixed: Five of 32 afinoxifene-treated patients and 0 of 29 placebo-treated patients with 50%-80% baseline mammographic breast density showed at least a 10% reduction in density after 4 months, but there was no significant difference between the two study arms at 6 months. None of the 19 patients with greater than 80% baseline breast density showed a 10% improvement at 4 months. In light of the success of 4 mg but not 2 mg/day of afinoxifene in the mastalgia trial, more breast density reduction studies with the higher dosage are planned.

An intriguing finding was that four of five afinoxifene responders were younger than 40 years, suggesting afinoxifene may have potential as a chemopreventive agent in young high-risk women who avoid oral tamoxifen because of side effects.

The trials were sponsored by Ascend Therapeutics. ■