SAFETY ATTACHMENT: APRIL 2004

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1. SELECTED DEFINITIONS

GLOSSARY

**Adverse Reaction / Adverse Drug Reaction**

In the preapproval clinical experience with a new medicinal product or its new usages in particular, as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product, related to any dose, should be considered adverse drug reactions. Regarding marketed medicinal products: a response that is noxious and unintended and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy of disease or for modification of physiologic function.

**Adverse Event**

An adverse event is defined as any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a human being in a temporal relationship to the use of a Wyeth product regardless of causal relationship. This includes the following:

- any clinically important worsening of a preexisting condition;
- an adverse event occurring from overdose (ie, a dose higher than that prescribed by a health care professional for clinical reasons) of a Wyeth product, whether accidental or intentional;
- an adverse event occurring from abuse (ie, use for nonclinical reasons) of a Wyeth product;
- an adverse event associated with the discontinuation of the use of a Wyeth product.

Clinically important laboratory abnormalities (including, for example, abnormal x-ray films, electrocardiograms) that occur or worsen during the clinical study also are adverse events.
**GLOSSARY**

**Product (Drug, Biological Product) Related**
An adverse event will be considered “product related” (ie, drug related, vaccine related, etc) for studies if either the investigator, or the medical monitor assesses the adverse event(s) as possibly, probably, or definitely related.
- An adverse event will be considered “not product related” for studies if the investigator and the medical monitor(s) assess the adverse event(s) as probably not related or definitely not related, or “relationship remote.”
- Whenever the investigator’s assessment is unknown or unclear, the adverse event(s) will be treated as product related.

**Definitely Related**
The event can be fully explained by administration of the investigational product.

**Probably Related**
The event is more likely to be explained by administration of the investigational product rather than the patient/subject’s clinical state or other agents/therapies.

**Possibly Related**
The event may be explained by administration of the investigational product, or by the patient/subject's clinical state or other agents/therapies.

**Probably Not Related**
The event is more likely to be explained by the patient/subject’s clinical state or other agents/therapies rather than the investigational product.

**Definitely Not Related**
The event can be fully explained by the patient/subject's clinical state or other agents/therapies.

**Protocol Related**
Adverse events from clinical trials that are not product related may nevertheless be considered by the investigator or medical monitor to be protocol related.
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Serious Adverse Event

A serious adverse event is defined as an adverse event occurring at any dose that
• results in death;
• is life threatening (see below);
• requires inpatient hospitalization or prolongation of an existing hospitalization;
• results in a persistent or significant disability or incapacity (see below);
• results in cancer;
  • results in a congenital anomaly or birth defect.

Additionally, important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious adverse events when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, and the development of drug dependency or abuse.

A serious adverse event obtained from tests in laboratory animals is any experience suggesting a significant risk for human subjects, including any findings of mutagenicity, teratogenicity, or carcinogenicity.

Life Threatening

Life threatening refers to immediate risk of death as the event occurred. A life-threatening experience does not include an experience that, had it occurred in a more severe form, might have caused death but as it actually occurred did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.
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Disability
Disability is defined as a substantial disruption in a person’s ability to conduct normal life functions.

Unexpected Adverse Event
An unexpected adverse event is one that is not listed in the current product labeling. The current product labeling is either the package insert (for marketed products) or the current investigator’s brochure (for investigational products). An unexpected adverse event includes any event that may be symptomatically and pathophysiologically related to an event listed in the labeling but that differs from the labeled event because of greater severity or specificity. For example, hepatic necrosis would be unexpected (by virtue of greater severity) if the product labeling referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents.

- An adverse event is considered unexpected for local reporting purposes if it does not appear in the labeling for the country to which the adverse event is being reported.
- An adverse event is considered unexpected for core labeling purposes when it does not appear in the company’s core data sheet, if it exists.

2. DEVELOPMENT CORE SAFETY INFORMATION

2.1 Contraindications, Special Warnings, and Special Precautions for Use
Contraindications, special warnings, and special precautions for use have not yet been determined for moxidectin. See section 5 (Other Considerations) for safety information relating to other macrocyclic lactone drugs.

2.2 Interactions With Other Therapeutic Substances and Other Forms of Interaction
Compounds that bind to gamma aminobutyric acid (GABA)-containing neurons and receptors may decrease the activity of moxidectin at the GABA binding sites of the
peripheral nervous systems in nematodes and arthropods and decrease the efficacy of moxidectin. Package inserts for marketed ivermectin products in animals caution against the concomitant administration of ivermectin with Valium and other members of the benzodiazepine class. Because radiolabeled ligand studies suggest that moxidectin has activity at the GABA-A receptor in a manner similar to ivermectin, there is the potential for interaction of moxidectin with benzodiazepines.

The potential for moxidectin to inhibit the activity of cytochrome P450 (CYP) CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 was evaluated in human liver microsomes at moxidectin concentrations ranging from 0.1 to 100 µM. Moxidectin was a weak inhibitor of CYP1A2 and CYP2C9, with extrapolated IC$_{50}$ values of 459 µM and 145 µM, respectively. There was no inhibition of the other CYP enzymes examined. In humans, the mean C$_{max}$ after an 18-mg oral dose was 141 ng/mL (0.2 µM). Therefore, it is unlikely that clinical drug-drug interactions involving these CYP enzymes would occur.

2.3 Pregnancy and Lactation
There is no information on the effect of moxidectin on pregnancy and lactation in humans. Women of childbearing age should be given moxidectin only if they are practicing the birth control method specified in the study protocol. If a patient should become pregnant while receiving this drug, the patient should be apprised of the potential risks to the fetus based on what has been observed with other drugs in this class. Because of the unknown risk to nursing infants, treatment of mothers who intend to breastfeed should only be undertaken when the risk of delayed treatment to the mother outweighs the possible risk to the nursing infant. See section 5 (Other Considerations) for safety information relating to pregnancy and lactation in animal studies.

2.4 Adverse Drug Reactions (Undesirable Effects) Reported From Clinical Trials
To date, a total of 95 subjects have received oral moxidectin, 37 subjects in a phase 1 safety and tolerability study (protocol 3110A1-100-EU) and 58 subjects in a phase 1 bioavailability study of orally administered moxidectin liquid and tablets (protocol 3110A1-101-EU). Based on this limited exposure, no adverse events can be identified as expected adverse drug
reactions. A summary of the adverse events for these studies may be found in section 5 of the Investigator's Brochure.

2.5 Overdose
There is no experience with moxidectin overdosage in humans. In general, the adverse events of an overdose with moxidectin are expected to be related to the pharmacologic effect of the drug, including central nervous system and neuromuscular effects. General supportive measures should be followed in all cases of overdoses of moxidectin. See section 5 (Other Considerations) for overdose information relating to other macrocyclic lactone drugs.

2.6 Drug Abuse and Dependence
Given the pharmacologic effects of this agent, the use of moxidectin is not anticipated to result in drug abuse or dependence.

3. SERIOUS DRUG-RELATED ADVERSE EVENTS FROM CLINICAL TRIALS
No drug-related serious adverse events were reported for the 37 healthy adult male subjects enrolled in the first-in-man (FIM) study (protocol 3110A1-100-EU) or for the 58 healthy adult male subjects enrolled in the moxidectin liquid and tablet bioavailability study (protocol 3110A1-101-EU).

4. SERIOUS NONDRUG-RELATED ADVERSE EVENTS FROM CLINICAL TRIALS
No nondrug-related serious adverse events were reported in the first-in-man (FIM) study (protocol 3110A1-100-EU) or in the moxidectin liquid and tablet bioavailability study (protocol 3110A1-101-EU).
5. OTHER CONSIDERATIONS

5.1 Summary of Adverse Events Observed in Phase 1 Clinical Studies

5.1.1 Single-Ascending Dose, Safety, Tolerability, and Pharmacokinetic Study

In the first clinical moxidectin study (3110A1-100-EU), only 1 adverse event higher than grade 2 (moderate toxicity) was reported (enteritis resulting from food poisoning [grade 3; severe toxicity] in the 36-mg fasting group), which was considered unrelated to study drug. The most common adverse events (reported by $\geq 10\%$ of subjects) were headache (35%) and infection (29%). The majority (7 of 9) of moxidectin-treated subjects reporting infection had colds or upper respiratory tract infections. Of the remaining 2 subjects, 1 had a right big toe infection and 1 had a tooth abscess. Four (4) subjects withdrew from the study (1 before receiving study drug and 3 after dose administration: 1 each in the 3-mg fasting, 9-mg fed, and 36-mg fasting groups). The withdrawal of these subjects from the study was unrelated to adverse events. Adverse events affecting the central nervous system (nausea, vomiting, and somnolence) were found to occur more frequently in the later cohorts (the 18-mg and 36-mg groups) than in the earlier cohorts (the 3-mg and 9-mg groups). These adverse events were believed to be indicative of the mechanism of action of moxidectin, and similar events have been seen in humans treated with ivermectin.

No clinically significant adverse events were seen in the 3-mg and 9-mg treatment groups, so treatment at these levels is considered to be safe.

5.1.2 Relative Bioavailability of a Tablet and Liquid Formulation of Moxidectin in Healthy Subjects

A total of 36 of 58 (62.1%) subjects had treatment-emergent adverse events (TEAEs) during this study (protocol 3110A1-101-EU), with the same number and percentage of subjects (18; 62.1% in each group) reporting TEAEs in both the moxidectin liquid and tablet groups. The most commonly reported TEAEs (reported by $\geq 5\%$ of subjects) were flu syndrome (reported by 17.2% and 20.7% of subjects in the liquid and tablet groups, respectively), headache (reported by 17.2% and 13.8% of subjects in the liquid and tablet groups, respectively), infection (reported by 13.8% and 6.9% of subjects in the liquid and tablet
groups, respectively), diarrhea (reported by 10.3% of subjects in the liquid group), myalgia (reported by 6.9% of subjects in the tablet group), and dizziness (reported by 6.9% of subjects in the tablet group).

A total of 19 of 58 subjects (32.8%) reported TEAEs within the first week after administration of study drug (on or before day 7). During this period, TEAEs were reported by 10 of 29 subjects (34.5%) in the group receiving moxidectin liquid and by 9 of 29 subjects (31.0%) in the group receiving moxidectin tablets. The most commonly reported TEAEs (reported by \( \geq 5\% \) of subjects) during this period were asthenia (reported by 10.3% of subjects in the tablet group), headache (reported by 13.8% and 6.9% of subjects in the liquid and tablet groups, respectively), infection (reported by 6.9% of subjects in the liquid group), diarrhea (reported by 6.9% of subjects in the liquid group), myalgia (reported by 6.9% of subjects in the tablet group), and dizziness (reported by 6.9% of subjects in the tablet group).

A total of 22 of 58 subjects (37.9%) reported TEAEs during the outpatient period of the study (after study day 7 and up to study day 180); 10 of 29 subjects (34.5%) were in the liquid group and 12 of 29 (41.4%) were in the tablet group. The most commonly reported events (reported by \( \geq 5\% \) of subjects) were flu syndrome (reported by 17.2% and 20.7% of subjects in the liquid and tablet groups, respectively), headache (reported by 6.9% of subjects in the tablet group), and infection (reported by 6.9% of subjects in the tablet group).

All TEAEs that were reported during the study were mild to moderate in intensity, and none were considered to be related to treatment. During the course of this study there were no serious adverse events and no subjects discontinued the study as the result of an adverse event.

No clinically relevant abnormalities were observed in vital sign measurements, electrocardiograms, or laboratory tests during the study.
5.2 Mazzotti Reaction

Historical data have shown that microfilaricidal drugs, such as diethylcarbamazine citrate (DEC-C), might cause cutaneous and/or systemic reactions of varying severity (the Mazzotti reaction) and ophthalmologic reactions in patients with onchocerciasis. Observed signs and symptoms may include itching; rash; headache; arthralgia; myalgia; lymph node pain, swelling, and tenderness; fever; chills; tachycardia; postural hypertension; and polyarthritis. These reactions are probably due to allergic and inflammatory responses of the host to the death of microfilariae. These tend to be seen within the first month after treatment because that is the time of the greatest microfilaricidal effect.

The treatment of severe Mazzotti reactions has not been subjected to controlled clinical trials. Oral hydration, recumbency, intravenous normal saline, and/or parenteral corticosteroids have been used to treat postural hypotension. Antihistamines and/or aspirin have been used for most mild to moderate cases.

5.3 Relevant Safety Information From Animal Studies

5.3.1 Pregnancy and Lactation

In animal studies with repeated exposure to maternally toxic doses, there was decreased fetal and/or pup survival and there were significant increases in the number of fetuses born with malformations and/or variations. However, based on the available data, the yearly oral intake of even 32 mg of moxidectin (or 16 mg every 6 months) by women is unlikely to pose a risk to the developing human fetus (the highest dose to be evaluated in patients is a single yearly 8-mg dose).

Moxidectin is lipophilic and has been shown to be excreted into the milk of lactating cows. It is conceivable that moxidectin-treated nursing mothers may excrete moxidectin in their breast milk.

5.3.2 Clinical Experience With Oral Moxidectin in the Dog

ProHeart Tablets (moxidectin) are available in the United States and abroad for use as a monthly heartworm preventive in dogs (monthly oral dose of 3 µg/kg).
Overall, adverse reactions were rare when the drug was administered orally at the labeled dose. Adverse reactions reported in clinical studies following the use of ProHeart Tablets included lethargy, vomiting, ataxia, anorexia, diarrhea, nervousness, weakness, increased thirst and itching. Postmarketing surveillance of field use from 1998 through 2002 in the United States reveals the following reporting pattern and frequency:

Total adverse drug reaction reports (6 reports) = .0005% of doses sold in the US market

- Lethargy/vomiting/diarrhea (4 reports) = .0003%
- Seizure after administration (1 report) = .0001%
- Toenail bruising (1 report) = .0001%

All of these potential side effects in dogs appear to be rare when the product is administered orally at the labeled dose.

5.3.3 Clinical Experience With Subcutaneous Moxidectin in the Dog

Allergic reactions (1.4 reports per 10,000 doses) have been reported in dogs receiving subcutaneous (SC) ProHeart 6, a sustained-release injectable moxidectin administered twice yearly for the prevention of heartworm. Similar reactions have not been reported in dogs receiving oral monthly ProHeart Tablets. The relevance of the allergic reactions observed in dogs after SC administration of ProHeart 6 to the proposed clinical trials in which subjects will receive an oral formulation is unknown.

5.4 Safety Information About Other Macrocyclic Lactone Drugs

5.4.1 Pregnancy and Lactation

Ivermectin has been shown to be teratogenic in mice, rats, and rabbits when given in repeated doses of 0.2, 8.1, and 4.5 times the maximum recommended human dose, respectively (on a mg/m²/day basis). Teratogenicity was characterized in the 3 species by cleft palate; clubbed forepaws were additionally observed in rabbits. These developmental effects were found only at or near doses that were maternotoxic to the pregnant female.
Therefore, ivermectin does not appear to be selectively fetotoxic to the developing fetus. There are, however, no adequate and well-controlled studies with pregnant women. Ivermectin should not be used during pregnancy since safety in pregnancy has not been established.

Ivermectin is excreted in human milk in low concentrations. Treatment of mothers who intend to breastfeed should only be undertaken when the risk of delayed treatment to the mother outweighs the possible risk to the newborn.

5.4.2 Overdosage
In accidental intoxication with or significant exposure to unknown quantities of veterinary formulations of ivermectin in humans, either by ingestion, inhalation, injection, or exposure to body surfaces, the following adverse effects have been reported most frequently: rash, edema, headache, dizziness, asthenia, nausea, vomiting, and diarrhea. Other reported adverse effects include seizure, ataxia, dyspnea, abdominal pain, paresthesia, and urticaria. The manufacturer recommends that in cases of accidental ivermectin poisoning, supportive therapy, if indicated, should include parenteral fluids and electrolytes, respiratory support (oxygen and mechanical ventilation if necessary), and pressor agents if clinically significant hypotension is present. Induction of emesis and/or gastric lavage as soon as possible, followed by purgatives and other routine antipoison measures, may be indicated if needed to prevent absorption of ingested material.

5.5 Safety Information Relative to the Excipients
Moxidectin tablets in capsules (TIC) for clinical studies will be supplied as 2-mg tablets encapsulated in hydroxypropyl methylcellulose (HPMC) capsules. The capsules will be filled with a mixture of inert ingredients including lactose, microcrystalline cellulose, sodium starch glycolate and magnesium stearate. No unusual or novel excipients will be used in the tablets or capsules and as such no undesirable adverse effects relative to the excipients are expected.
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One (1) moxidectin TIC is required for a 2-mg dose; 2 TICs are required for a 4-mg dose; 4 TICs are required for an 8-mg dose. Matching placebo in HPMC capsules filled with the same inert ingredients as the moxidectin capsules will also be provided for clinical trials.