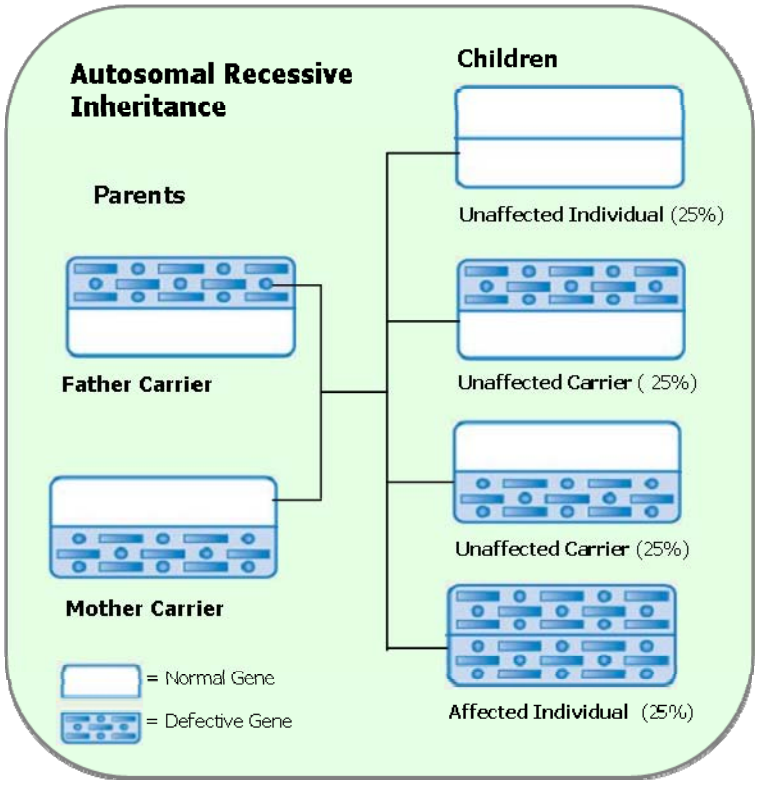
POMPE Connections

Having Children When You Have Pompe Disease

Pompe disease is a genetic disease. Genetic diseases are caused by abnormalities in gene(s) or chromosomes. Genetic diseases are passed from parents to their children through genes. Genes are basic units of heredity and consist of small segments of DNA that contain instructions for processes and structures in the human body, as well as features that make a person unique. Some genes control traits and features such as gender, height, and eye color. Other genes control bodily processes, such as making the enzymes that help the body function.



Pompe disease is caused by a genetic mutation that blocks the production of an enzyme (a type of protein) called *acid alpha-glucosidase.* This can lead to muscle damage throughout the body. You can only get Pompe disease when you inherit, 1 copy of the defective gene from each parent, as shown in this diagram. This is called *autosomal recessive inheritance. For this reason, men and women with a family history of Pompe disease may be concerned about having children. Partners of people with Pompe disease may want to know if they are carriers of the defective gene. Women who have Pompe disease may also worry about the health risks of becoming pregnant. If you are thinking about having children, it is important to be aware of both the chances of passing on the disease, and the problems that could arise before, during, and after pregnancy. If you already have children, you may want to know their risk for having the disease or passing it on. This handout talks about some of the issues you will want to think about. It also describes the tests that can help predict whether your baby will be affected by Pompe disease.*

Q: What is human genetics and what does it have to do with Pompe disease?

A: Human genetic makeup is encoded into complex chemical structure called DNA (short for deoxyribonucleic acid). DNA molecules form the basis of structures called chromosomes. Every person has 46 chromosomes, grouped into 23 pairs, which are

Supported by an Unrestricted grant from genzyme
August 2005 **Code 010**
Rev Aug 2011

found inside cell's nucleus. Each chromosome is itself divided into thousands of smaller segments, called genes.

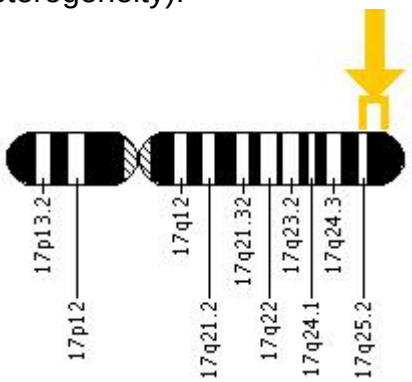
Among the 23 pairs of chromosomes, one pair, called sex chromosomes, determines a person's gender. The other 22 pairs, called autosomes, determine all other non-gender-related traits.

Because genes are a part of chromosomes, they also come in pairs - during reproduction, each parent passes on a copy of half of their genetic material to their offspring.

Each gene pair works together to control a specific function or activity within the cell. Some have relatively small significance, such as defining a person's hair or eye color, while others control important cellular activities, such as the production of vital enzymes needed for healthy functioning.

A gene mutation is a permanent alteration in a gene. Disease results from the gene's inability to produce a protein the body needs for normal functioning. The altered diseases produced by gene mutations can be mild, severely debilitating, or fatal.

The gene that causes Pompe disease is called GAA and is located on chromosome 17, which is an autosomal chromosome. (More on this under the section titled Genetic Heterogeneity).



There are many different defects, or mutations, that can affect the GAA gene. Most people with Pompe disease inherit two different GAA gene mutations, one from each of their parents. Researchers have already identified approximately 300 distinct mutations (although not every one of these always causes Pompe disease), and more continue to be found.

For more detailed information about genetic heterogeneity go to the Pompe Center, Erasmus MC Rotterdam website (http://www.pompecenter.nl/en/?Disease)

Q: What does it mean to be a carrier of Pompe disease?

A: The term "carrier" is used for any person who is symptom-free (or has only very mild symptoms) despite having a medical condition. Carriers of Pompe disease have one bad copy of the GAA gene. The one good copy of the GAA gene allows for the

production of enough enzymes to keep cells functioning properly. A carrier's enzyme activity is usually somewhat lower than normal, but they usually do not experience any symptoms.

Q: Does Pompe Disease affect one ethnic group more than others?

A: Research has shown that Pompe disease is pan-ethnic—it occurs in people of all ethnicities and races. There does appear to be a slightly higher incidence rate in certain groups:

- In infants, the disease has a higher frequency among African-Americans and people from southern China and Taiwan.
- Among adults, the disease has a higher frequency in the Netherlands.

In addition, specific gene mutations have been found to be more common in certain ethnic groups or nationalities. It's still unclear exactly why these higher frequencies exist in certain groups, although the disease's genetic basis and family inheritance patterns are likely major contributing factors.

Q: How do you inherit Pompe disease?

A: Pompe disease is a genetic disorder, passed down from parent to child in an autosomal recessive manner. Autosomal recessive diseases are relatively rare, because to get Pompe disease you must inherit one bad copy of the gene from both parents, not from just from one parent. So that means both parents must have at least one bad copy of the gene.

Read more at http://www.wrongdiagnosis.com/genetics/recessive.htm?ktrack=kcplink

Inheritance Scenarios:

- If one parent has Pompe disease and the other parent is unaffected:
  - There is a 100% chance the child will be a carrier. The parent with Pompe disease has two bad copies of the gene, so the child will always get one bad copy of the gene from that parent, and one good copy of the gene from the parent who is unaffected.
- If one parent has Pompe disease, and the other parent is a carrier:
  - There is a 50% chance the child will get Pompe disease. The child will get one bad copy of the gene from the parent with Pompe disease, and a 50% chance of getting a second bad copy of the gene from the parent who is a carrier.
  - There is a 50% chance the child will be a carrier. The child will get one bad copy of the gene from the parent with Pompe disease, and a 50% chance of getting one good copy of the gene from the parent who is a carrier.

Supported by an Unrestricted grant from genzyme
August 2005 **Code 010**
Rev Aug 2011

- If one parent is a carrier of Pompe disease and the other parent is unaffected:
  - There is no chance the child will get Pompe disease. The child will always get one good copy of the gene from the parent who is unaffected and 50% chance of getting a second good copy of the gene from the parent who is a carrier.
  - There is a 50% chance the child will be a carrier. The child will always get one good copy of the gene from the parent who is unaffected and 50% chance of getting one bad copy of the gene from the parent who is a carrier.
- If both parents are carriers, each child born to them has a:
  - 25% chance of having the disease
  - 50% chance of being a carrier of the disease
  - 25% chance of neither having the disease nor being a carrier of the disease

Q: Are there tests to determine if my partner and I are Pompe carriers?

A: The only way to know for sure if someone is a carrier of the genetic mutation that causes Pompe disease is by doing DNA testing, or direct mutation analysis (also called genotyping). This involves taking a sample of blood, separating the DNA from the cells, and then looking for the specific mutations that are known to cause Pompe disease. Molecular testing of DNA mutations is possible because more than 150 mutations of the GAA gene have been identified in people with Pompe disease. Some of these mutations are limited to particular ethnic groups.

Since Pompe disease is so rare and the risk for being a carrier is so small, carrier testing is not done unless there is a family member with the disease whose mutations are known. Mutation analysis is the only way to identify carriers, who do not have the disease, but "carry" the gene defect and may pass it on to their own children - so it's particularly important to identify carriers within families with a history of the disease.

Q: If I should be pregnant now, is there a way to find out if my unborn child has Pompe disease?

A: Yes, there are prenatal screening tests that can be done early in pregnancy to see if your fetus (unborn child) is affected with Pompe disease.

Chorionic villus (tiny finger-shaped growths found in the placenta) *sampling,* or CVS, is done between the 10th and 12th week of pregnancy. This test involves taking a small sample of tissue from the growing placenta (an organ that connects the developing fetus to the uterine wall to allow nutrient uptake, waste elimination, and gas exchange via the mother's blood supply) and measuring enzyme activity.

Prenatal testing is also available by enzyme analysis in amniocytes (amniocyte is a cell of a fetus which is suspended in the amniotic fluid) taken from the amniotic fluid

Supported by an Unrestricted grant from genzyme
August 2005 **Code 010**
Rev Aug 2011

(amniocentesis). An amniocentesis can be performed as early as the 12th week of pregnancy and can provide results as quickly as a few days. This test checks for enzyme activity and allows for DNA analysis by testing cells taken from fluid in the womb.

DNA testing may also be done to compare the DNA from the fetus with the DNA of the parents or an affected brother or sister.

The results of these prenatal tests can help guide choices about the pregnancy and prepare for the baby's arrival.

In summary, for prenatal diagnosis:

- Molecular testing is the preferred method when both mutations are known
- Enzyme analysis in chorionic villus samples is preferred when molecular testing is not feasible, or when enzyme analysis is an adjunct to molecular testing,
- Confirmation in amniocytes (cell of a fetus which is suspended in the amniotic fluid) may be considered if mutations are known.

Q. My healthcare provider has advised me to get genetic counseling before I get pregnant. What is a Genetic Counselor?

A: Genetic counselors are health care professionals with unique specialized graduate degrees and experience in the areas of both medical genetics and counseling. Genetic counselors work as members of a health care team, providing risk assessment, education and support to individuals and families at risk for, or diagnosed with, a variety of inherited conditions, like Pompe disease. Genetic counselors also interpret genetic testing, provide supportive counseling, and serve as patient advocates.

If you or a family member has Pompe disease, or a carrier for Pompe disease, genetic counseling can help you understand your chances for having a baby with the disease. Meeting with a genetic counselor **before you get pregnant** will help you sort out all the issues that may affect your decision to have children:

A genetic counselor will be able to:

- Explain family inheritance patterns and identify potentially at-risk individuals.
- Provide balanced information about what genetic testing involves, in order to support decisions about who to test
- Help family members cope with positive test results.
- Provide guidance on genetic issues such as family planning and prenatal testing.

If you are already pregnant the genetic counselor can talk to you about prenatal testing for your unborn child. Should you choose to go ahead with genetic testing; the genetic counselor will help you make appointments for the tests and provide the support you need once you get the test results back. For example, if you find out your unborn child is affected by Pompe disease, the genetic counselor can help you explore your options and cope with the difficult choices ahead of you. Since the process of getting

Supported by an Unrestricted grant from genzyme
August 2005 **Code 010**
Rev Aug 2011

tested and waiting for results takes time, it is important to seek genetic counseling as early as possible.

Q: Should I be treated with lumizyme if I become pregnant?

A: Animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women at this time to confirm this. So Lumizyme should only be used during pregnancy if clearly needed.

The Lumizyme Prescribing Information document states the following:

Teratogenic Effects (definition below): **Pregnancy Category B**. Reproduction studies have been performed in pregnant mice at intravenous doses up to 40 mg/kg/day (plasma AUC of 64.6 mg•min/mL, 0.4 times the human steady-state exposure at the recommended bi-weekly dose) and in pregnant rabbits at intravenous doses up to 40 mg/kg/day (plasma AUC of 85 mg•min/mL, 0.5 times the human steady-state exposure at the recommended bi-weekly dose) and have revealed no evidence of impaired fertility or harm to the fetus due to alglucosidase alfa. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Lumizyme should be used during pregnancy only if clearly needed. Women of childbearing potential are encouraged to enroll in the Pompe Registry

Teratology is the study of abnormalities of physiological development. It is often thought of as the study of birth defects (congenital anomalies).

Labor and Delivery
Information on the effect of Myozyme/Lumizyme (USA) on labor and delivery is unknown. Pregnant women are encouraged to enroll in the Pompe Registry.

Nursing Mothers
It is not known whether Myozyme/Lumizyme (USA) is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Myozyme/Lumizyme (USA) is administered to a nursing woman. Nursing women are encouraged to enroll in the Pompe Registry.

http://www.lumizyme.com/pdfs/lz_pi.pdf.

If you are interested in learning more about Pregnancy Categories, please refer to Attachment 1.

Q: Can I get pregnant if I have Pompe disease?

A: Pompe disease does not appear to affect fertility (the ability to conceive a child). Women diagnosed with Pompe disease also do not seem to have a higher risk for miscarriage (loss of the pregnancy). However, if one partner has severe muscle weakness, scoliosis (curvature of the spine), or contractures (muscle tightness), having sexual intercourse may be difficult. If you are concerned about your risk for having a child with Pompe disease because you and your partner are both carriers, you may want to consider other options, such as adoption or conception with donor eggs or

Supported by an Unrestricted grant from genzyme
August 2005 **Code 010**
Rev Aug 2011

sperm. It is important to explore these choices with your healthcare provider and with a genetic counselor so that you can make informed decisions.

Q: I have Pompe disease and I want to start a family. How will pregnancy affect my health?

A: Although having Pompe disease should not affect your ability to get pregnant or carry a pregnancy to term; there are some health concerns to be aware of, especially if you are severely affected.

Weight gain: The biggest concern is the extra weight you will gain when you are pregnant. If you already have a lot of muscle weakness, the weight you gain during your pregnancy can cause lower back pain and make it harder to walk or keep your balance. Scoliosis can make these problems worse. You may need to use a wheelchair as you get further along in the pregnancy.

Breathing: Whether your muscle weakness is mild or severe, you may have more trouble breathing as you gain weight. Be sure to tell your healthcare provider if you notice these symptoms: shortness of breath, morning headaches, fatigue, dizziness, confusion, or sleeping problems. Using a ventilator may help you breathe more easily. Because of these concerns, you will need to be seen by both a healthcare provider who treats high risk pregnancies and one who treats your Pompe disease. It is important to have these doctors work together to manage your care.

Delivery: If muscle weakness or scoliosis is severe, your baby may need to be delivered through the abdomen instead of the vagina. This is called a *Cesarean section* (C-section). If a C-section must be performed, it will be necessary to plan in advance for the anesthesia you may need (see the handouts *Common health concerns* and *Breathing problems in Pompe disease).*

Recovery: After the baby is born, it may take longer for you than for others to recover and lose the extra weight you gained. It may also be hard to lift, carry, or nurse your newborn. Be prepared to seek advice from other Pompe parents and your healthcare team, and to get help at home if you need it.

Where to Learn More:
These groups can help you find answers to any other questions you may have about pregnancy or family planning issues related to Pompe disease.

- **International Pompe Association** (IPA) is a global federation of Pompe disease patient groups. The IPA helps patients, family members, and healthcare providers from around the world share their experiences and knowledge across continents and cultures. To find the contact for your country, visit the IPA Web site at www.worldpompe.org
- **Muscular Dystrophy Association** (MDA): The MDA offers fact sheets on genetic testing, inheritance patterns, and pregnancy for people affected by neuromuscular diseases. Visit www.muscular-dystrophy.org and click on “Information and Resources”

Supported by an Unrestricted grant from genzyme
August 2005 **Code 010**
Rev Aug 2011

- **National Society of Genetic Counselors** (NSGC) has an online directory of genetic counselors in the United States and around the world. To search the listings, visit www.nsgc.org and click on "Find a Counselor". http://www.nsgc.org
- The **Pompe Center at Erasmus Medical Center** in the Netherlands maintains the most up-to-date record of mutations that have been identified for the GAA gene. To learn about advances in research, treatment, and genetic testing for Pompe disease, visit the Pompe Center Web site at www.pompecenter.nl
- **American College of Medical Genetics (ACMG) Practical Guidelines:** Pompe Disease Diagnosis and Management Guideline 2006. Vol. 8. No. 5. The ACMG guidelines were designed as an educational resource for physicians and other health care providers.
- The Genzyme Corporation's **Pompe Community website** www.pompe.com: offers the Pompe community comprehensive information on the disease, as well as resources and support to help manage the challenges it may bring.

- **Pompe Pregnancy Sub-Registry (Observational Study):** The objective of this study is to track pregnancy outcomes in women with Pompe Disease and to follow infants born to women with Pompe Disease. http://www.clinicaltrials.gov/
- **Pompe Lactation Sub-Registry (Observational Study):** The objective of this study is to determine if alglucosidase alfa is present in breast milk from mothers with Pompe Disease being treated with Myozyme® and to measure breast milk production and composition in women with Pompe Disease who receive Myozyme®. http://www.clinicaltrials.gov/
- **Know Your Genes:** A Genetic Disease Foundation www.knowyourgenes.org/genes101.shtml
- The **Global Genes Project™** exists to unify, support, build awareness and raise much needed funds for those affected by rare disease. The Global Genes Project™ campaign will broadly promote the needs of the rare disease community as a whole, engaging the general public, garnering corporate support under the unifying symbol of hope ~ the blue denim ribbon. www.globalgenesproject.org
    - The following videos have been developed by some of the Global Genes Project rare disease partners to you help you better understand Genetics:
        - Genetics 101 Part 1: What are genes? Produced by 23andMe
        - Genetics 101 Part 2: What are SNPs? Produced by 23andMe
        - Genetics 101 Part 3: Where do your genes come from? Produced by 23andMe
        - Genetics 101 Part 4: What is phenotype? Produced by 23andMe
        - What Genes Means! Produced by JeansforGenes

References:

- **ACMG Practical Guidelines:** Pompe Disease Diagnosis and Management Guideline 2006. Vol. 8. No. 5
- www.pompe.com
- http://en.wikipedia.org/wiki/Pregnancy_category
- http://www.tga.gov.au/docs/html/medpreg.htm
- http://www.safefetus.com/fda_category.asp
- http://www.wrongdiagnosis.com/genetics/index.htm
- http://www.pompecenter.nl/en/?Disease

Supported by an Unrestricted grant from genzyme
August 2005 **Code 010**
Rev Aug 2011

ATTACHMENT 1: Pregnancy Categories

Pregnancy Categories:

The pregnancy category of a pharmaceutical agent is an assessment of the risk of fetal injury due to the pharmaceutical, if it is used as directed by the mother during pregnancy. It does *not* include any risks conferred by pharmaceutical agents or their metabolites that are present in breast milk.

Every drug has specific information listed in its product literature. In the UK, while no preset categories are applied, the British National Formulary gives a table of drugs to be avoided or used with caution in pregnancy, and does so using a limited number of key phrases.

In 1979, the United States Food and Drug Administration (FDA) introduced a classification of fetal risks due to pharmaceuticals. This was based on a similar system that was introduced in Sweden one year earlier.

United States FDA Pharmaceutical Pregnancy Categories

Pregnancy Category A: Adequate and well-controlled human studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

Pregnancy Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.

Pregnancy Category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Pregnancy Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Pregnancy Category X: Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

One characteristic of the FDA definitions of the pregnancy categories is that the FDA requires a relatively large amount of high-quality data on a pharmaceutical for it to be defined as Pregnancy Category A. As a result of this, many drugs that would be

considered Pregnancy Category A in other countries are allocated to Category C by the FDA. [1]

References:
http://www.safefetus.com/fda_category.asp
http://en.wikipedia.org/wiki/Pregnancy_category

Australia's Pregnancy Categories

Australia has a slightly different pregnancy category system from the United States - notably the subdivision of Category B. The system, as outlined below, was established by the Congenital Abnormalities Sub-committee of the Australian Drug Evaluation Committee (ADEC).

Pregnancy Category A: Drugs which have been taken by a large number of pregnant women and women of childbearing age without an increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

Pregnancy Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Pregnancy Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

Pregnancy Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Pregnancy Category C: Drugs which, owing to their pharmaceutical effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

Pregnancy Category D: Drugs which have caused are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Pregnancy Category X: Drugs that have such a high risk of causing permanent damage to the fetus that they should NOT be used in pregnancy or when there is a possibility of pregnancy.

[1] http://www.safefetus.com/fda_category.asp; http://en.wikipedia.org/wiki/Pregnancy_category

Supported by an Unrestricted grant from genzyme
August 2005 **Code 010**
Rev Aug 2011

The sub-categories of Category B, while offering additional information which may be of benefit in evaluating the risk vs benefit, presents its own problem of data reliability - since human data is lacking or inadequate, the subcategories are based on animal data. Furthermore, allocation of a drug in Category B does not necessarily imply greater safety than Category C.

Drugs in Category D are not absolutely contraindicated in pregnancy, unlike Category X. In some cases Category D was assigned to a drug on the basis of suspicion.[2]

http://www.tga.gov.au/hp/medicines-pregnancy-categorisation.htm

Germany's Pregnancy Categories

Gr 1: Extensive human testing and animal studies have not shown that the drug is embryotoxic / teratogenic.

Gr 2: Extensive human testing of the drug have not shown that the drug is embryotoxic / teratogenic.

Gr 3: Extensive human testing of the drug has not shown that the drug is embryotoxic / teratogenic. However, the drug appears to be embryotoxic / teratogenic in animals.

Gr 4: There have been no adequate and well-controlled studies of the drug's effects on humans available. Animal studies have shown no embryotoxic/teratogenic effects.

Gr 5: There have been no adequate and well-controlled studies of the drug's effects on humans available.

Gr 6: There have been no adequate and well-controlled studies of the drug's effects on humans on pregnant women. Animal studies have shown embryotoxic/teratogenic effects.

Gr 7: There is a risk that the drug is embryotoxic / teratogenic to the human fetus, at least in the first trimester.

Gr 8: There is a risk that the drug is toxic to fetuses throughout the second and third trimester.

Gr 9: There is a risk that the drug causes prenatal complications or abnormalities.

Gr 10: There is a risk that the drug causes hormone specific action on the human fetus.

Gr 11: There is a known risk that the drug is a mutagen/carcinogen.[3]

http://en.wikipedia.org/wiki/Pregnancy_category

[2] http://www.tga.gov.au/docs/html/medpreg.htm
[3] http://en.wikipedia.org/wiki/Pregnancy_category

Supported by an Unrestricted grant from genzyme
August 2005 **Code 010**
Rev Aug 2011