

Revised Guidance to the U.S. Fabry Community:
Management of Fabrazyme® (agalsidase beta for injection) Supply

Temporary Conservation of Fabrazyme Supply for the Remainder of 2009

Prepared by the U.S. Fabrazyme Stakeholders Working Group* (meeting held September 23, 2009)

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*The Fabrazyme Stakeholders Working Group (FSWG) includes representatives of the Fabry Support and Information Group (FSIG), the National Fabry Disease Foundation (NDFD), the Fabry Registry North American Board of Advisors, and Genzyme Corporation. Please note that some individuals who participated in the FSWG are employees of Genzyme and other individuals or their institutions or organizations receive or have received funding from Genzyme for research, educational activities, and other purposes.

Summary of Revised Guidance*

1. Because of various factors affecting Fabrazyme re-supply*, the current inventory of Fabrazyme must be spread over the remainder of 2009. Therefore, Fabrazyme shipments will be reduced to 30% of expected demand until the end of 2009.
2. In order to achieve this reduction, for the remainder of the year all patients will be allocated the equivalent of two bi-weekly infusions at their usual dose.
3. The FSWG recommends that patients spread their allotment of Fabrazyme over multiple infusions in order to minimize the time without treatment.*
4. Treatment-naïve patients or patients returning to therapy after an interruption of two months or longer should delay starting Fabrazyme until 2010.
5. Patients in clinical trials should adhere to the study protocol.
6. Patients should, at minimum, be monitored by obtaining an antibody level at baseline, and then every three months during 2010 and every 6 months thereafter until two consecutive negative results are obtained. Additionally, patients should undergo plasma GL-3 testing at baseline and every 3 months until normalized. These recommendations are consistent with those from the Fabry Registry.
7. Patients, if already enrolled, should have clinical data collected and entered into the Fabry Registry.

* Additional information and discussion follow

Additional Information

1. The table on the following page presents two examples of how Fabrazyme allocation can be distributed. Example 1 shows regimens that spread the allocation over 3 to 4 infusions. Example 2 illustrates receiving two infusions at the usual dose.
2. Physicians will have the option of receiving Fabrazyme in a single shipment, or in two separate shipments, depending on physician/patient preference. This will allow for maximum dosing flexibility within the limitations of fixed vial sizes (5 mg and 35 mg) and the available proportion of each vial size.
3. Each patient's individual treatment regimen is ultimately at the discretion of the treating physician. Patients are encouraged to speak with their physicians about their treatment regimen.
4. There is limited evidence in the literature on the use of Fabrazyme at doses lower than the recommended 1mg/kg biweekly. A study evaluating the use of 0.3 mg/kg as a maintenance dose following an initial 1 mg/kg dose schedule has been published (Lubanda et al, *Genet Med*, 2009).

Dosing Examples

Usual Biweekly Dose	Total Available Dose Oct-Dec	Example 1: Three - Four Infusions				Example 2: Two Full Doses	
		Infusion Number - mgs/infusion				Infusion Number - mgs/infusion	
		1	2	3	4	1	2
5mg	10mg	Not an Option				5mg	5mg
10mg	20mg	5mg	5mg	5mg	5mg	10mg	10mg
15mg	30mg	10mg	10mg	5mg	5mg	15mg	15mg
20mg	40mg	10mg	10mg	10mg	10mg	20mg	20mg
25mg	50mg	15mg	15mg	10mg	10mg	25mg	25mg
30mg	60mg	15mg	15mg	15mg	15mg	30mg	30mg
35mg	70mg	35mg	15mg	10mg	10mg	35mg	35mg
40mg	80mg	35mg	35mg	10mg		40mg	40mg
45mg	90mg	35mg	35mg	20mg		45mg	45mg
50mg	100mg	35mg	35mg	30mg		50mg	50mg
55mg	110mg	35mg	35mg	20mg	20mg	55mg	55mg
60mg	120mg	35mg	35mg	35mg	15mg	60mg	60mg
65mg	130mg	35mg	35mg	35mg	25mg	65mg	65mg
70mg	140mg	35mg	35mg	35mg	35mg	70mg	70mg
75mg	150mg	40mg	40mg	35mg	35mg	75mg	75mg
80mg	160mg	40mg	40mg	40mg	40mg	80mg	80mg
85mg	170mg	45mg	45mg	40mg	40mg	85mg	85mg
90mg	180mg	50mg	50mg	50mg	30mg	90mg	90mg
95mg	190mg	50mg	50mg	50mg	40mg	95mg	95mg
100mg	200mg	50mg	50mg	50mg	50mg	100mg	100mg
105mg	210mg	70mg	70mg	35mg	35mg	105mg	105mg
110mg	220mg	70mg	70mg	40mg	40mg	110mg	110mg
115mg	230mg	70mg	70mg	45mg	45mg	115mg	115mg
120mg	240mg	70mg	70mg	50mg	50mg	120mg	120mg
125mg	250mg	70mg	70mg	55mg	55mg	125mg	125mg
130mg	260mg	70mg	70mg	60mg	60mg	130mg	130mg
135mg	270mg	70mg	70mg	65mg	65mg	135mg	135mg
140mg	280mg	70mg	70mg	70mg	70mg	140mg	140mg

Patients on weekly infusions will be shipped the equivalent of four infusions in order to achieve the 30% allocation.

If considering Example 1, while prescriptions will not change, there will be a need to update infusion orders for all patients. Of particular note, it is important to ensure that the infusion nurse is aware of these changes, especially for patients receiving home infusions.

Background

Throughout this temporary period of Fabrazyme shortage, the following fundamental guiding principles have been used to make decisions and formulate recommendations:

1. All decisions and recommendations should be designed to minimize risk to patients and should be based on best available evidence and experience
2. All countries and regions should participate in an equitable manner proportional to their normal demand
3. All decisions and recommendations should be made without reference to the commercial or charitable status of patients

On June 16, 2009, in response to a viral contamination at the plant where Fabrazyme is manufactured, Genzyme communicated that the facility was to be shut down and sanitized, causing an interruption in production and a temporary Fabrazyme shortage. On June 29, 2009, the Fabrazyme Stakeholders Working Group (FSWG) issued a *Guidance to the Fabry Community on the Management of Fabrazyme Supply* to conserve the supply of Fabrazyme to avoid a complete depletion during this period. Additional information on the Fabrazyme shortage is available online at www.genzyme.com/supplyupdate.

The initial *Guidance* was expected to reduce the use of Fabrazyme to approximately 80% of normal levels, which would be achieved by asking all patients to miss the equivalent of two doses, either by skipping two full infusions or receiving a half-dose for four infusions. This guidance of 80% was based on the assumptions that the recommendations would be quickly and widely adopted and that newly produced Fabrazyme would be available in mid- to late-November. As these assumptions had some uncertainty, the *Guidance* noted that the “recommendations may be subject to change if the guidance is not widely adopted or if Fabrazyme production timelines need to be revised.”

As of September 22, 2009, based on ordering patterns for Fabrazyme in the U.S., the Fabry community has been successful in reducing demand for Fabrazyme to less than 80% of normal, indicating most patients quickly and completely altered their treatment regimen according to the guidance.

However, due to factors affecting Fabrazyme re-supply, the original guidance will not be sufficient to avoid a complete depletion of the medication. Three major factors are driving the need for longer and more stringent dose conservation:

1. **Delayed Reactor Starts:** Fabrazyme bioreactors started later than initially planned due to extension of the time needed to fully sanitize the plant and perform preventative maintenance.
2. **Lower Initial Output:** Production out of these first bioreactor runs is at the low end of the range of Genzyme’s manufacturing experience and will not compensate for the delay in bioreactor starts.
3. **Lower Processing Efficiency:** In an effort to expedite supply, Genzyme is manufacturing smaller batches, which is a less efficient process.

Together, the end result of these three factors is that despite the Fabry community’s success in achieving dose conservation to date, Fabrazyme inventories will be lower than expected in the last three months of this year and new material is projected to become available later than originally anticipated.

As of today, there is sufficient inventory to cover 80% of forecasted demand for October, the last remaining month of our initial dose conservation plan. Now this inventory must be spread over three months to last through the end of 2009. Therefore, it is necessary that Fabrazyme shipments be reduced to 30% of forecasted demand until the end of 2009.

Based on this new information, the FSWG met for a second time on September 22, 2009, and developed this *Revised Guidance* that would reduce Fabrazyme use to 30%. In order to reach this reduction, each patient will be allocated an amount of Fabrazyme that is the equivalent of two of the seven doses that would normally take place in the 14 weeks remaining in the year.

Genzyme will ship either the full allocation (i.e. equivalent of two full doses) in a single shipment in early October, or ship the equivalent of one full dose per patient during two specified periods of time, depending on physician/patient preference. Regardless of which option is chosen, the actual scheduling, dose, and frequency of Fabrazyme infusions should be determined by each patient in consultation with his or her physician.

In order to minimize prolonged treatment interruptions, the FSWG recommends spreading each patient's allotment of Fabrazyme over 3 or 4 infusions. To assist physicians in determining a dosing schedule for their patients that, the FSWG has developed the table on the previous page. To use the table, first locate the usual dose for each patient, and then follow that row horizontally for the recommended schedule of infusions. When reviewing this table, it should be noted that Fabrazyme is supplied as 35 mg and 5 mg vials, and that 5 mg vials are in limited supply.

Monitoring

Patients should be monitored by obtaining an antibody level at baseline, every three months during 2010, and every six months thereafter until two consecutive negative results are obtained (also consistent with the recommended schedule of assessments in the Fabry Registry- see below). The impact of prolonged treatment interruption on the subsequent development of infusion reactions antibodies is unknown and as a precaution, treating physicians should assess whether infusion rates may need to be prolonged upon restart. Additionally, the FSWG recommends a plasma GL-3 level at baseline and every three months thereafter until normalized. Genzyme provides antibody and plasma GL-3 testing free of charge. To order test kits please call 1-800-745-4447, option #1. For additional information about antibody testing or how to send in a sample without a test kit, please call Medical Information at 1-800-745-4447, option #2.

These monitoring recommendations represent a minimal set of tests for assessing disease status and should be tailored to each patient's clinical status as determined by his or her physician. Because Fabry disease is a highly heterogeneous and multi-systemic disorder, additional monitoring studies should be conducted as appropriate during the period of temporary Fabrazyme shortage.

The Fabry Registry

Physicians who have previously enrolled their patients in the Fabry Registry are encouraged to collect and enter data on these patients into the Registry. Because there is limited published data on the clinical effects of dose reductions or treatment interruptions, the collective data from many patients may provide valuable answers to these important unanswered questions through future analyses.

Additional information about the Fabry Registry is available online at www.fabryregistry.com or by telephone at 1-800-745-4447, x15500.

General Guidance

- The recommendations may be subject to change and the ongoing availability of Fabrazyme and the timing of new supply of Fabrazyme cannot be guaranteed.
- The recommendations should be continued until notification by Genzyme that adequate supply has been restored.
- At the end of this temporary Fabrazyme shortage, it is recommended that all patients should resume their previously prescribed dosage regimen.