Enfuvirtide (Fuzeon™) Criteria for Use

VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

The following recommendations are dynamic and will be revised as new clinical data become available. These guidelines are not intended to interfere with clinical judgment. Rather, they are intended to assist providers in making the best clinical decisions that result in high quality, consistent, cost-effective care.

I. Overview

Enfuvirtide (Fuzeon™) is the first of the fusion inhibitor class of antiretroviral (ARV) medications approved for the treatment of HIV infection. Enfuvirtide, a 36-amino acid protein, acts by blocking viral binding to CD4+ lymphocytes. Its complex molecular structure necessitates that it be administered parenterally. The efficacy of enfuvirtide has been studied in two placebo-controlled, Phase III clinical trials. Both trials were designed to determine the potential benefit of using enfuvirtide in combination with other antiretrovirals (ARV) in patients previously exposed to all three ARV drug classes or in those with documented resistance to all three classes and HIV viral loads ≥ 5,000 copies/ml (studies T20-301 (*TORO-1, conducted in North and South America*), and T20-302 (*TORO-2, conducted in Europe and Australia*). Median baseline CD4+ lymphocyte counts were ≤ 100 in all treatment arms with median time of ARV treatment history of 7 – 7.4 years. The backbone ARV regimen that accompanied enfuvirtide/placebo was selected by the local physician using prior treatment history and baseline genotype and phenotype results (backbone regimens contained 3-5 FDA approved medications). Patients were randomized (2:1) to receive enfuvirtide or placebo for a minimum of eight weeks. Patients receiving placebo who experienced virologic failure at weeks 8 or 48 were allowed to switch to active drug. The intent-to-treat response at Study week 24 for the two studies is shown below.

Outcome	TORO-1 (T20-301)		TORO-2 (T20-302)	
	Enfuvirtide	Placebo	Enfuvirtide	Placebo
≥ 1 log decrease from baseline*	52%	29%	43%	21%
HIV RNA < 400 copies/ml*	37%	16%	28%	14%
HIV RNA < 50 copies/ml*	20%	7%	12%	5%
Median CD4 change (cells/mm^3)	76	32	65	38

* All differences were statistically significant and measured at Week 24

The development of resistance to enfuvirtide in the clinical setting occurs although the impact of this on the drug's utility is currently not fully understood.

Tolerance and Side Effects

Nearly 100% of all patients develop some type of local injection site reaction that may include pain, pruritis, erythema, induration, nodule and cyst formation. In the clinical trials, 3% of patients discontinued therapy due to injection site reactions. Mean duration of the site reaction was ≤ 7 days. Eosinophilia was seen in 10% of patients receiving enfuvirtide and 2% on placebo. Hypersensitivity reaction was seen following rechallenge with enfuvirtide, although eosinophilia was not associated with these events. Bacterial pneumonia was seen with greater incidence in patients on enfuvirtide, and while a clear relation to the drug has not been determined, clinicians should be alert for this event. Other side effects (< 5% incidence) included sinusitis, peripheral neuropathy, insomnia, and anxiety.

Drug Availability

Given the complexity of producing this 36-amino acid peptide, there will be limited worldwide drug availability for the first year following FDA approval. The manufacturer has established a procurement process to assure continued drug access for anyone initiated on enfuvirtide therapy. The details for this system can by found at the PBM intranet Web site http:/vaww.pbm.med.va.gov and the Public Health Strategic Health Care Group intranet Web site, http://vaww.vhaco.va.gov/phshcg/.

II. Patient Selection for Enfuvirtide Treatment

VA clinicians considering the use of enfuvirtide are requested to apply a series of drug use criteria to each patient considered as a candidate for therapy. The criteria were designed from the clinical information available to date for enfuvirtide including safety, tolerability, and efficacy.

1) Documented virologic failure (HIV-RNA levels over 5,000 copies/mL) to or intolerance of at least two previous HAART regimens, including prior treatment with drugs from at least 2 classes of antiretroviral agents (nucleoside analogue reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors).

   The studies presented to date on enfuvirtide have been in heavily pre-treated patients with relatively low CD4 lymphocyte counts. Consistent with data published for many other antiretrovirals used in heavily pretreated patient populations, patients with lower CD4 lymphocyte counts (< 100 cells/mm^3) and higher HIV viral loads ($\geq$ 40,000 copies/ml) experienced smaller improvements in these surrogate markers. The exact placement of enfuvirtide in a progression of regimens (i.e. as the second or fifth regimen) has not been determined in clinical trials. Therefore, the VHA cannot currently recommend the use of enfuvirtide in *drug naïve patients or in those who have multiple regimen options remaining after failing an initial regimen* given the lack of clinical efficacy data. Resistance testing (see #2 below) should be used where possible to evaluate treatment options for enfuvirtide therapy candidates.

and

2) Ability to construct a multi-drug regimen that includes at least one other active anti-retroviral drug in addition to enfuvirtide. Activity of other agents should be assessed prior to initiating treatment with enfuvirtide using appropriate resistance testing. Resistance testing should be performed while the patient remains on the failing regimen whenever possible and interpreted in the context of the patient's antiretroviral treatment history and of prior resistance tests.

   Two phase III clinical trials provided evidence that the virologic impact of enfuvirtide is greater when at least one other antiretroviral used in the patient's regimen showed potential activity against the patient's virus (i.e., no evidence of resistance using genotypic testing). The table below shows pooled results from the two phase III trials.

Number of Active Drugs at Baseline*	Change in HIV RNA from Baseline (log_{10}) – Week 24	
	Enfuvirtide	Placebo
0	- 0.9	- 0.1
1	- 1.4	- 0.6
2	- 2.0	- 1.0
3	- 2.1	- 1.7
4	- 2.1	- 1.3
5	- 2.0	- 1.0

* Active status determined by genotypic testing

   Appropriate resistance testing may include genotypic tests results and/or phenotypic tests (true or virtual) demonstrating reduced susceptibility of the patient's virus to specific ARVs. The presence of a resistance mutation at any point during the patient's treatment history is likely to predict impaired response to a particular agent, regardless of whether the mutations persists in more recent resistance testing.

   Active drug may include medication(s) in the patient's current regimen or medications to be switched to in the next regimen. Enfuvirtide should be added to an existing, failing regimen only if there is evidence that one or more drugs in that regimen may retain activity, and no other active drugs are available. In clinical trials, the combination of enfuvirtide with multiple drugs to which resistance had developed resulted in significant

but smaller declines in viremia. When no other active drugs are available, the use of such a regimen may be clinically appropriate.

Clinicians should be aware that current resistance testing *does not* test for the likelihood of enfuvirtide activity or resistance. Resistance testing is to be used in determining a reasonable backbone ARV regimen to be combined with enfuvirtide. There are preliminary data linking enfuvirtide resistance to specific mutations of the viral genome, but clinical tests to detect enfuvirtide resistance are not currently available.

and

3) Patient has a history of good medication adherence, appointment attendance, and competent use of local prescription refill process. In addition, the patient must be able to manage drug reconstitution and injection or have a reliable caregiver who can perform these functions.

Given the complexity of twice daily injections with enfuvirtide, clinicians should feel confident that the patient is able to take the medication *as prescribed*. Medication adherence is difficult for clinicians to assess reliably. Frequently missed appointments and late refills of prescribed antiretrovirals may indicate potential problems with adherence.

III. Clinical Response Follow up

Clinical follow up of virologic response to an enfuvirtide-containing regimen should be tailored for each patient. This includes monitoring CD4+ lymphocyte counts, HIV viral load, and performing the appropriate safety laboratory tests relative to the ARV backbone, co-morbid disease, and co-administered medications prescribed to the patient. The clinician and patient should make the decision of when enfuvirtide therapy should be stopped secondary to intolerance, adverse events, clinical or virologic failure.

Patients should be assessed for virologic response twelve weeks (3 months) following initiation of the enfuvirtide-containing regimen. Response should be > 1 $\log_{10}$ decline in HIV viral load from pre-enfuvirtide levels. Patients who do not reach this level of response should be reassessed for possible therapeutic changes. The new regimen may or may not continue to include enfuvirtide. Improvements in immunologic status (increased CD4 lymphocyte counts) despite suboptimal virologic response may be considered in decisions regarding continued use of enfuvirtide. If there is neither virologic nor immunologic improvement after six months of therapy, discontinuation of treatment with enfuvirtide should be strongly considered.

IV. Cost of Therapy

The most commonly prescribed three-drug ARV combinations in VHA during calendar year 2002 had a 30-day equivalent cost in the range of $593 to $777. The 30-day cost for enfuvirtide alone is $1266. As with all ARVs, enfuvirtide is to be prescribed in addition to other anti-HIV medication as part of a multi-drug regimen. Since enfuvirtide is FDA-approved for treatment-experienced patients, it is expected that many patients will receive greater than four ARVs (including enfuvirtide) in an attempt to control viral replication. Therefore, the average cost of an enfuvirtide-containing regimen is projected to range from $1,617 to $2,243 per 30-day supply.

V. Summary Advice on Addition of Enfuvirtide to an ARV Regimen.

To date, VHA has placed all FDA-approved ARVs on the national formulary. VHA's HIV clinicians are able to choose the best-available ARV regimen for an individual patients based on the patient's clinical status, their past experience with ARVs, the risks of side effects, and an expectation of tolerance and a potential for benefit. Enfuvirtide is more complicated to administer and more costly than any other single ARV available. Because of this, VA HIV clinicians must carefully weigh the potential risks and benefits of this particular medication when considering adding or changing to an enfuvirtide-containing regimen.

References

DHHS Guidelines - http://www.aidsinfo.nih.gov/guidelines/

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Prepared by: Larry Mole, PharmD.
Reviewed by: Public Health Strategic Health Care Group (PHSHG) and the HIV Treatment Advisory Panel