# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 20420

## ADMINISTRATIVE DOCUMENTS

## PATENT INFORMATION

U.S. Patent No. 5,108,363 was submitted in the New Drug Application 20-420, December 20, 1993. Since this filing three patents have been issued for the use of Arbutamine. U.S. Patent No. 5,495,970, 5,286,252 and 5,234,404 are described in the next section.

## PATENT INFORMATION

1. U.S. Patent No. 5,495,970

| | |
|---|---|
| Entitled: | 1-(3,4-Dihydroxypenyl)-2-(4-(4-Hydroxyphenyl)Butaylamino)Ethanol |
| Filed: | December 15, 1994 |
| Issued: | March 7, 1995 |
| Foreign Fillings: | Canada |
| Expiration Date: | March 7, 2012 |
| Type of Patent: | Method of Diagnosis |
| Assignee: | Gensia, Inc. |

2. U.S. Patent No. 5,286,252

| | |
|---|---|
| Entitled: | Diagnosis, Evaluation and Treatment of Coronary Artery Disease by Exercise Simulation Using Closed Loop Drug Delivery of an Exercise Simulation Agent Beta Agonist |
| Filed: | December 11, 1990 |
| Issued: | February 15, 1994 |
| Foreign Fillings: | None |
| Expiration Date: | February 15, 2011 |
| Type of Patent: | Method of Diagnosis |
| Assignee: | Gensia, Inc. |

3. U.S. Patent No. 5,234,404

| | |
|---|---|
| Entitled: | Diagnosis, Evaluation and Treatment of Coronary Artery Disease by Exercise Simulation Using Closed Loop Drug Delivery of an Exercise Simulation Agent Beta Agonist |
| Filed: | October 11, 1991 |
| Issued: | August 10, 1993 |
| Foreign Fillings: | None |
| Expiration Date: | August 10, 2010 |
| Type of Patent: | Method of Diagnosis |
| Assignee: | Gensia, Inc. |

The undersigned certifies that U.S. Patent Number 5,395,970, 5,286,252 and 5,234,404 covers the use of Arbutamine which is the subject of New Drug Application 20-420 for which approval is being sought.

Alan Timms, Ph.D.
Vice President of Research and Development
Gensia, Inc.

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-420 Trade (generic) names Gen ESA (arbutamine) System

Check any of the following that apply and explain, as necessary, on the next page:

__f__ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__X__ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Signature of Preparer

9/9/94
Date

cc: Orig NDA
HFD-___/Div File
NDA Action Package

Exhibit

MAY 14 1997

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 14, 1997

FROM: Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Arbutamine, NDA 20-420 (GenESA System)

TO: Dr. Lipicky

We are at the end of a long trip and have learned a lot about the properties and evaluation of substitutes for exercise testing, including the uncomfortable observation that it is not wholly clear what clinical purpose exercise testing and its substitutes serve. Your feeling that arbutimine should have been studied for some endpoint other than predicting 50% occlusion is understandable enough, but I'm not sure we know a good alternative, and I am satisfied that we've defined a population in which the GenESA test is useful in helping decide whether to perform angiography.

A difficulty, as you note, is that while we always knew positive and negative predictive values of a test would vary with the prevalence of CAD (and therefore required some assessment of the population that would benefit from the test) we didn't fully appreciate that sensitivity and specificity would also vary with prevalence because high and low prevalence populations were different. Results of all trials in patients with CAD are shown in tables 1-6. Thus, although specificity was very high in a low risk population (virtually no false positives), specificity in sick (high risk for CAD) populations (studies 123/127) was very poor, about 31% in study 123 (echo) and 25% in study 127 (thallium). Among other things, this meant that, compared to just doing angiograms in everyone in this high risk population (127/143 and 112/120 patients had positive angios in studies 123 and 127), use of the test got in the way. In study 123, e.g., with a sensitivity of 76%, of 127 patients with coronary disease there were 38 false negatives and 89 true positives; with

specificity of 31%, among 16 patients without disease, there were five true negatives and 11 false positives. Overall, then, if the "advice" of the test had been followed 38 patients with disease would not have been angio'd and 11 patients without disease would have been angio'd, an "error rate" of ($38^{FN}$ + $11^{FP}$)143 or 34%, compared with an "error rate" of 16/143 or 11% if you just angio'd everyone. Results with thallium in study 127 were better, with an error rate of 17.5% using the test to decide vs a 7% rate from, just testing everyone (8/120=7%). The question thus was: "who would this help."

A less high CAD-risk population gives the test more "opportunity" to provide information, so that study 141 was relatively informative. In this more mixed population, testing everyone would give a relatively high rate of negative tests. This leads me to the view that we need to convey something of the test's usefulness, in various settings, at identifying patients with 50% stenoses. This probably will require more than one display of results.

The conditional probability analyses, either grouped as Low, Intermediate or High (Rodin), deciles (Fenichel) or shown as a continuous curve (Lipicky) imply that one always gains at least some information from a positive or negative test. That is, in a sense, true, but it is also true that in some settings, most test results are wrong (Echo in 141; 107/181 outcomes are false with respect to angio) and in others it is pretty close (141 Sestimibi, 31/86 results are wrong). Moreover, as I noted earlier, in high probability patients, depending on medical behavior, you may make fewer errors by just assuming a positive angiography result. This leads me to think we should present results two ways, considering, as best we can, study 127 to be a high risk population and 141 a more intermediate risk. Note that results in 141 with thallium and sestamibi are quite close; and rather better at specificity and worse at sensitivity than thallium in 123 (there is no other sestamibi data). I appreciate Dr. Rodin's reluctance to assert too strongly that sensitivity and specificity are population (pre-test likelihood)-related without clear evidence and yet the available data suggest it is so (and it is not really surprising). Similarly, although predictive values are prevalence-dependant, that is their virtue as well as their defect; we can make sure the label makes clear that high positive predictive value is almost always accompanied by low negative predictive value in the high prevalence situation.

I agree that we cannot now label Arbutamine for use with echo and the letter should make this clear. The 123 results show poor specificity

while 141 central results show poor sensitivity. I do not believe that use of the local readings (unblinded, subject to influence of other test and angiograms) is appropriate for study 141. There is nothing implausible about the idea that Arbutamine could have different effects on echo measures and radionuclide measures.

Robert Temple, M.D.

cc:
Orig.
HFD-110
HFD-110/GBuehler
HFD-110/RFenichel

Table 1

| Study | Assessment Method | Sensitivity TP/(TP+FN) | Specificity TN/(TN+FP) | Pos Predictive TP/(TP+FP) | Neg Predictive TN/(TN+FN) |
|---|---|---|---|---|---|
| 123 | Echo | 97/127(76%) | 5/16 (31%) | 97/108(90%) | 5/35(14%) |
| 127 | Thallium | 97/112(87%) | 2/8 (25%) | 97/103(94%) | 2/17(11%) |
| 141 | Thallium | 10/16 (63%) | 7/12 (58%) | 10/15(67%) | 7/13(54%) |
| 141 | Sestimibi | 41/65 (63%) | 14/21 (67%) | 41/48(85%) | 14/38(37%) |
| 141 | Echo | 43/132(30%) | 31/39 (80%) | 43/51(84%) | 31/130(24%) |

Table 2

141 Thallium

| | | Angio + | Angio - | |
|---|---|---|---|---|
| Thallium | + | 10 | 5 | 15 |
| | - | 6 | 7 | 13 |
| | | 16 | 12 | |

Positive Predictive Fraction (TP/TP+FP): 10/15 = 67%

Negative Predictive Fraction (TN/TN+FN): 7/13 = 54%

Table 3

127 Thallium

| | | Angio + | Angio - | | |
|---|---|---|---|---|---|
| Thallium | + | 97 | 6 | 103 | n=20 |
| | - | 15 | 2 | 17 | |
| | | 112 | 8 | | |

Positive Predictive Fraction (TP/TP+FP): 97/103 = 94%

Negative Predictive Fraction (TN/TN+FN): 2/17 = 12%

Table 4

141 Sestimibi

Angio

| Sestimibi | + | - | |
|---|---|---|---|
| + | 41 | 7 | 48 |
| - | 24 | 14 | 38 |
| | 65 | 21 | |

Positive Predictive Fraction (TP/TP+FP): 41/48 = 85%

Negative Predictive Fraction (TN/TN+FN): 14/38 = 37%

Table 5

141 Echo

| | | Angio + | Angio - | |
|---|---|---|---|---|
| Echo | + | 43 | 8 | 51 |
| | - | 99 | 31 | 130 |
| | | 142 | 39 | |

Positive Predictive Fraction (TP/TP+FP): 43/51 = 84%

Negative Predictive Fraction (TN/TN+FN): 31/130 = 24%

Table 6

123 Echo

| | | Angio + | Angio - | |
|---|---|---|---|---|
| Echo | + | 97 | 11 | 108 |
| | - | 30 | 5 | 35 |
| | | 127 | 16 | |

Positive Predictive Fraction (TP/TP+FP): 97/108 = 90%

Negative Predictive Fraction (TN/TN+FN): 5/35 = 14%

Robert Temple, M.D.

DF Buckley

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: APR 12 1995

FROM: Director, Office of Drug Evaluation I, HFD-100

SUBJECT: Arbutamine, NDA 20-420

TO: Dr. Raymond Lipicky, HFD-110

I had a few further thoughts on this application.

1. Safety

In only 625 patients there were 2 VT/VF and an AF leading to VF, 3 other AF (2/3 needed hospitalization) and 1 AMI, about 1% of patients. Those results were attained without reaching the desired HR most of the time (but since sensitivity was already high and specificity already low perhaps they don't need a greater heart rate; perhaps arbutamine's inotropic effect, makes a greater contribution to ventricular dysfunction than we are used to or perhaps the fall in diastolic pressure leads to especially poor perfusion). At first glance, it is difficult to see what could make this risk acceptable.

If, in fact, it really is necessary to achieve the specified HR, the steep D/R, together with an 8 minute half-life, could be a real problem. It's not that an infusion program could not possibly account for all that, but it definitely would need to. This, as you point out, would require very good characterization of the time course of HR response (and, I'd say, of the BP and dp/dt response too).

We need to be sure, even while advising the sponsor that specificity needs to be defined, that they come to grips with this later, but potentially insoluble, problem.

2. Specificity

In study 128 (healthy), the angiogram is presumed normal (not a bad presumption) and all positive tests are considered false positives. The estimate of false positive (FP) rate should be conservative, i.e., high (if some angios would actually have been positive, then the FP rate would be reduced and specificity, 1-FP rate, would go up). The normalcy rate (negative test/all tests) is almost equivalent to specificity (because all angios are presumed negative, all tests = number with negative angios) and, on its face looks good at 90% (MOR p. 13).

Unfortunately, the 6/58 false positive rate in study 128, and 52/58 - specificity, almost 90%, is a lot better than the results in study 127, a far more relevant situation (also, a situation where the preferred outcome of the test is not knowable in advance, eliminating the chance of biased interpretation, and where, as Dr. Rodin points out on p. 34 of the MOR, the simultaneous assessment of sensitivity and specificity provides "checks and balances").

Do you (or Drs. Fenichel or Rodin) have a plausible explanation for the contrast between EKG and other modalities? There was rather good specificity for EKG found in study 122 (and for EUG in studies 123 and 127), but sensitivity of the whole test, whether with arbutamine or exercise, was poor, about 50%). In contrast, there was poor specificity in studies 123 (2D-echo) about 30% (worse than exercise, 55%) and 127 (thallium), about 25% (n=8). Dr. Rodin suggests (MOR p. 64) that arbutamine may induce a supra-physiologic (beyond exercise) perturbation of coronary flow and/or increase in oxygen demand, a perturbation not predicted by HR alone. Presumably, this is manifested more by ventricular muscle effects than by local hypoxia (ECG).

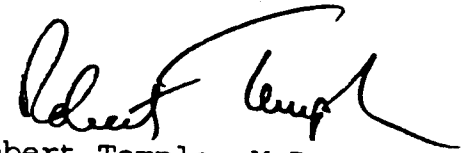
3. Approvability

Dr. Rodin's evaluation is interesting (and his review is very lucid on the definitions used in evaluating diagnostic tests). He distinguishes between use of a test to exclude CAD (the test can do this because the ensitivity is high; i.e., the false negative rate is low so if the test s negative CAD is unlikely) but not to include the diagnosis (specificity is low, i.e., false positive rate high). Although this seems possible, it is not clear how useful this would be. In a population that presents a diagnostic problem, there would presumably be a fair rate of patients with no CAD, say 50%. The test would be to find the ones to angio. But, if study 127's point estimate is used, the 25% specificity would mean that only 25% of the half of all patients with (or who would have) negative angiograms would be correctly characterized. Fully 75% of that half (or 37.5% of all patients) would be sent for a needless angiogram. Of the half with angiographic lesions, 86% (43% of all patients) would be sent for angiogram, but 14% would not. All in all 14% and 37.5%, or 51% would get the wrong answer, not too satisfactory.

Specificity at that level makes this at best a marginal product; certainly specificity needs to be defined; no one can use the test effectively without these data.

4. Gender

As we discussed, including more women would yield, probably, a group with more "true negatives" in it.



Robert Temple, M.D.

## APPLICATION SUMMARY

NDA 20-420 GenESA System (arbutamine) for Intravenous Infusion

Gensia, Inc.
9360 Towne Centre Drive
San Diego, CA 92121

FEB 16 1994

Date of Submission: December 20, 1993

Date of Receipt: December 21, 1993

The indication sought is an adjunct to echocardiography or radionuclide myocardial perfusion imaging for evaluation of patients with known or suspected coronary artery disease. The use of the GenESA system with ECG alone, given the rate of false negative and positive results, should only be considered in patients who cannot exercise adequately.

The GenESA System combines the catecholamine, arbutamine, with a closed-loop, computer-controlled drug delivery system to elicit acute cardiovascular responses similar to those produced by exercise. The application will require a combined review from the Division of Cardio-Renal Drug Products (CDER) for safety and efficacy of the drug product and General Hospital Products Division (CDRH) for safety and efficacy of the device. Appropriate sections of the application have been provided to CDRH for review. The entire application (drug and device) is contained in the archival volumes of the submission submitted to CDER. The Division of Cardio-Renal Drug Products has been designated as the lead review division.

The firm has been in contact with the Agency throughout the development of this product. On July 12, 1990 they met with the Division of Cardio-Renal Drug Products and members of CDRH to discuss the concept of the drug/device submission. An end of Phase II meeting was held on December 5, 1991, again with representatives from both centers. Pre-NDA meetings to discuss the device section of the application were held on January 27, 1993 and October 13, 1993; a pre-NDA meeting to discuss the CANDA section of the submission was held on November 3, 1993. A Pre-NDA meeting was scheduled in November, 1993 but when it became apparent that little could be said that would influence the NDA submission, the meeting was canceled. Dr. Rodin, however, clarified many points as a result of reading the pre-meeting package for the canceled meeting. He has been in touch with the firm on and off since November, 1993.

The assigned reviewers for this application are:

| | | |
|---|---|---|
| **MEDICAL** | - | Dr. Rodin |
| **PHARMACOLOGY** | - | Dr. DeFelice |
| **CHEMISTRY** | - | Dr. Short |
| **BIOPHARM** | - | Dr. Borga |
| **STATISTICS** | - | Dr. Mahjoob |
| **CDRH** | - | Mr. Dillard and Mr. Ulatowski |

The reviewers from CDER were informally polled.

Dr. Rodin stated that three studies have been submitted that could qualify as major. He has contacted Mr. Dillard of CDRH regarding the individual studies to be reviewed by each center.

Dr. Short stated that the submission was well organized and appeared to be complete.

Dr. Mahjoob stated that the application could be filed. The firm has provided him the CANDA hardware and data.

Dr. Borga has concerns about the whether the Pharmacokinetic data is adequate. There is a question as to whether this is a filing or approvability issue. The Division of Biopharmaceutics would like to discuss the issue with Dr. Lipicky at the filing meeting.

Dr. DeFelice has not expressed any concern about the filability of the application.

**SUMMARY**

The application appears to be well organized. The table of contents appears to be adequate (no complaints received to date). Debarment certification was provided. EA also appears to be of sufficient weight. From comments received to date, it appears that the application should be filed.

Gary Buehler 2/11/94
Gary Buehler, CSO

Orig NDA
HFD-110
HFD-110 SBenton
HFD-111 GBuehler

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPLICATION SUMMARY AND LABELING REVIEW

SEP 9 1997

NDA 20-420 GenESA (arbutamine hydrochloride) System

Sponsor: Gensia Automedics, Inc.
San Diego, CA 92121

**BACKGROUND**

On May 12, 1997, an approvable letter issued to Gensia for the GenESA application. The letter specified minor device deficiencies and request FPL. It also contained a discussion of the firm's request to use the GenESA system with echocardiography, stating that they may want to discuss the issue further.

On June 11, 1997 Gensia met with Dr. Temple and Division reviewers to discuss the approvable letter. At that meeting, the decision was made to grant the firm the additional indication of use of the GenESA system with echocardiography. The labeling draft was also discussed. Labeling revisions were made in the period between the June 11 meeting and early July. Drs. Temple and Fenichel reviewed the drafts and a final draft was forwarded to the firm. Dr. Wolters and Short also reviewed the draft labeling and comments were also forwarded to the firm. On July 16, FPL was submitted that incorporated the comments of the Division reviewers and Dr. Temple.

**APPROVAL ISSUES**

Labels and packaging were also submitted for review. Drs. Wolters and Short had the following revisions for the packaging (that also impacted on the package insert) that they agreed could be made at the next printing:

1. The product name should be expressed as follows on all labeling and labels:

   GenESA (arbutamine hydrochloride injection)
   0.05 mg/mL
   for Intravenous Infusion with the GenESA Device

2. The following sentence should be added at the end of the **DOSAGE AND ADMINISTRATION** section of the labeling:

   Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

The firm was also requested to remove the incomplete statement under the Syringe and Plunger Rod Assembly section (second bullet).

These statements will be forwarded to the firm in the approval letter.

**DEVICE REVIEW**

Mr. Trinh has reviewed the deficiencies sent to the firm in the approvable letter and found the

responses by Gensia acceptable. Gensia has submitted the Summary of Safety and Efficacy (SSE) to the Division of Dental, Infection Control and General Hospital Devices, HFZ-480 for review and concurrence. This package was forwarded to the Center Director (Dr. Susan Alpert) for sign off.

CDRH has decided to prepare their own approval letter. The letter will be signed off by Dr. Alpert (but not dated) and forwarded to me. I will send the signed letter to Dr. Temple's office to be dated when the CDER approval letter is signed

**ADVERTISING/PROMOTION**

Advertising/Promotional material has been submitted to DDMAC. Mr. Rumble has been in contact with Gensia regarding their submission.

**SUMMARY**

The FPL submitted was reviewed and found to be in accordance with the draft sent to the firm and subsequent discussions with Agency reviewers and Dr. Temple with the following exception:

> Under **OVERDOSAGE**, the phrase "...due to excessive dosing..." was omitted from the sentence "The symptoms of toxicity *due to excessive dosing* are those of catecholamine excess..." Gensia recognized this omission; they stated that the phrase will be inserted at next printing.

An approval letter will be forwarded to Dr. Temple's office for signature.

Gary Buehler 9/9/97
Gary Buehler
Project Manager

Orig NDA
HFD-110
HFD-110 GBuehler
HFD-110 SBenton

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION — **Public Health Service**
Division of Cardio-Renal Drug Products

**Memorandum**

**DATE** : JAN 27 1995

**FROM** : Director, Division of Cardio-Renal Drug Products, HFD-110

**SUBJECT:** NDA 20-420, arbutamine, GenESA System, Transmittal memo addendum

**TO** : Director, Office of Drug Evaluation I, HFD-100

I am adding to these thoughts to my previous memorandum and to the consideration of the GenESA System. All of these addenda are related to comparing the results of the adenosine NDA, for the same indication, to that of the GenESA System. I do this for purposes of refreshing both your memory and mine and because some of the numbers calculated for the GenESA system were not present in the reviews, so they could not be looked up even if you or I wanted to. Dr. Nuri, the original statistical reviewer has performed the requisite calculations.

All of the studies were conducted using imaging techniques. Thus the test mode was imaging and the adjuncts to imaging were either exercise or All comparisons to angiography are comparisons between angiography (with 50% narrowing of a coronary artery being the cut-off for positive angiography) and thallium scans with exercise or thallium scans with There were, arbitrarily (apparently for purposes of conforming to the letter of the law) 2 separate studies each producing almost identical numbers. For purposes of summary, I have combined the 2 studies (including Dr. Mohuidden's data) into one result. This is shown in the following 2 X 2 table (with margins calculated).

| | | Thallium/Exercise | | |
|---|---|---|---|---|
| | | Abnormal | Normal | Total |
| Angio. Result | >50% | 100 | 56 | 156 |
| | <50% | 13 | 24 | 37 |
| | Total | 113 | 70 | 193 |

| | | Thallium | | |
|---|---|---|---|---|
| | | Abnormal | Normal | Total |
| Angio Result | >50% | 100 | 56 | 156 |
| | <50% | 17 | 20 | 37 |
| | Total | 117 | 76 | 193 |

A couple of major difference in the data base that would support approval are obvious. The sample size for was about 3 times the sample size for the GenESA System and the number of patients that had normal angiograms (< 50% narrowing) was 37, about an order of magnitude greater than that submitted for the GenESA System using the test modality. The comparable estimates of the various parameters of interest (all just with respect to thallium testing with the comparison being to angiograms) are in the following table. The abbreviation NE, in the following table indicates that no reliable point estimate is able to be calculated because of too few observations.

| | | GenESA System | |
|---|---|---|---|
| | 95% Confidence Bounds | | |
| | Estimate | Lower | Upper |
| Sensitivity | | | |
| Specificity | | | |
| Concordance | | | |
| Positive Predictive Value | | | |
| Negative Predictive Value | | | |
| Kappa | | | |

| | 95% Confidence Bounds | |
|---|---|---|
| Estimate | Lower | Upper |

This comparison of numbers between something that we are about to approve and the GenESA System application which we the Division is recommending not be approved simply emphasizes the rationale behind our not-approval recommendation. Sorry for having to have this be an addendum to my original transmittal memorandum, but the calculations for were not available at the time of writing the previous transmittal memo.

As my transmittal memorandum was being circulated within the Division.the following additional information regarding literature estimates of adverse effects became known.

The mortality data cited for were obtained from the safety review of the original . dated 5/3/91, at which time there were no deaths. Dr. Rodin has brought to my attention that a more recent (mid 1993) point estimate for the mortality associated with

Likewise, the point estimate for mortality for dated 4/1/93, which according to Dr. Rodin's contains only premarketing experience. According to Dr. Rodin's compilation, 8 deaths have been reported in the United States since the approval o of which three linked to myocardial infarction and two were listed as sudden death/cardiac arrest.

I don't know how accurate this is and have not verified its accuracy myself. At face value it does not change considerations at all.

Otherwise, there is nothing new.

Raymond J. Lipicky, M.D.

cc
Orig.
HFD-110
HFD-110/CSO
HFD-110/RLipicky

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Consult #283 (HFD-110)

GenESA Arbutamine Injection 0.05 mg/mL

A review revealed no names which look or sound like the proposed name, although some concern was expressed about the proposed name sounding like the company name. The committee opposes the use of the company name for a proprietary name. However, since in this case the proposed name is not exactly the same as the company name, the committee has no reason to find the name unacceptable on that basis.

Some concern was expressed that "ESA" appearing in capital letters would constitute puffery, or be viewed as promotional or fanciful in nature. It was noted that this product is to be used with a computerized infusion device and the letters stood for Exercise-Simulated Algorithm, which does not seem to be related to the efficacy of this product. Based on this the Committee has no reason to find this stylized presentation of the name unacceptable.

The committee has no reason to find the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

Yana Ruth Mille, Chair 3/25/94