CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-732

Chemistry Review(s)

Memo to File

From: Suong Tran, PhD, Chemist, co-located in HFD-580
Through: Moo-Jhong Rhee, PhD, Chemistry Team Leader, co-located in HFD-580
To: NDA 21-732 (histrelin implant)
Date: 8-OCT-2004
Subject: Addendum to Chem. Rev. #2, Final

- The chemistry recommendation of APPROVABLE was placed on file (DFS) on 23-SEP-2004 (Chem. Review #2).
- The Office of Compliance issued the overall recommendation "Acceptable" for the NDA on 4-OCT-2004.
- The Division found the proposed proprietary name "Vantas" to be acceptable (refer to the Medical Officer Team Leader's review by M. Hirsch). The final packaging labels submitted on 8-OCT-2004 are acceptable. All revisions were made as requested by FDA (refer to the Chem. Review #2 and communications between the Project Manager N. Crisostomo and the applicant regarding the logo "Vantas").
- The final packaging insert submitted on 7-OCT-2004 is acceptable. All revisions were made as requested by FDA (refer to the Chem. Review #1).
- There is no other pending issue with respect to the Chemistry, Manufacturing, and Controls review of NDA 21-732.

CONCLUSION:
From the Chemistry perspective, NDA 21-732 is recommended for APPROVAL.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Suong Tran
10/8/04 10:50:11 AM
CHEMIST

revised per your discussion

Moo-Jhong Rhee
10/8/04 11:30:03 AM
CHEMIST
I concur

NDA 21-732

Vantas
(histrelin implant)

Valera Pharmaceuticals, Inc.

Reviewer: Suong Tran, PhD

Division of Reproductive and Urologic Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-732

2. REVIEW #: 2

3. REVIEW DATE: 22-SEP-2004

4. REVIEWER: Suong Tran, PhD

5. PREVIOUS DOCUMENTS: none

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document/DFS Date
Amendment	22-JUL-2004
Amendment	9-AUG-2004
Amendment	19-AUG-2004
Amendment	19-AUG-2004
Amendment	1-SEP-2004
Amendment	7-SEP-2004
Amendment	8-SEP-2004
Amendment	9-SEP-2004

7. NAME & ADDRESS OF APPLICANT:

Valera Pharmaceuticals, Inc.
8 Clarke Drive
Cranbury NJ 08512

8. DRUG PRODUCT NAME/CODE/TYPE:

Full Name: Vantas™ (histrelin implant)
Proprietary Name: Vantas™
Non-Proprietary Name (USAN): histrelin
Code Name/# (OGD only): Not Applicable
Chem. Type(ONDC only): 3
Submission Priority(ONDC only): S

9. LEGAL BASIS FOR SUBMISSION: Not Applicable

10. PHARMACOL. CATEGORY: Palliative treatment of advanced prostate cancer

11. DOSAGE FORM: implant (reservoir system)

12. STRENGTH/POTENCY: 50 mg histrelin acetate per implant

13. ROUTE OF ADMINISTRATION: subdermal

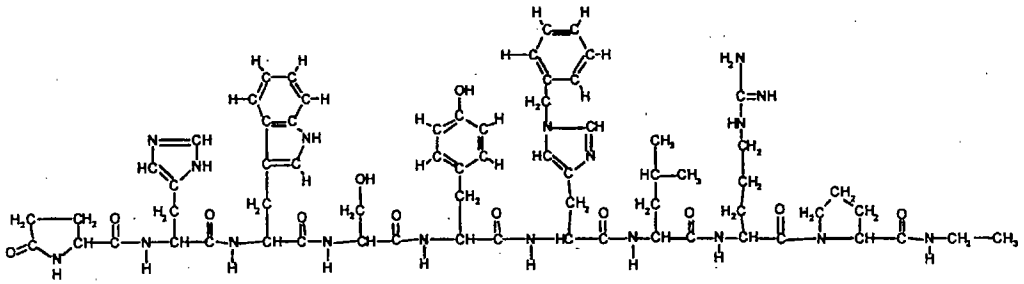
14. Rx/OTC DISPENSED: _x_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

____SPOTS product – Form Completed

_x_Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Histrelin (USAN):
5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-Nt-benzyl-D-histidyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide
CAS-76712-82-8
Molecular formula: $C_{66}H_{86}N_{18}O_{12}$ ($C_{66}H_{86}N_{18}O_{12}$ x 2 CH_3COOH as histrelin acetate)
Molecular weight: 1323.50 (1323.5 + 120.2 = 1443.70 as histrelin acetate)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW COMPLETED	COMMENT
[redacted]	II	[redacted]	Histrelin acetate	1	Adequate	9-AUG-2004	By S. Tran
[redacted]	III	[redacted]	[redacted]	4	N/A	N/A	N/A

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted

6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: none

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	*Not Applicable*		
EES	**Ongoing review by Compliance**		
Pharm/Tox	Acceptable impurities and residual raw materials limits	14-SEP-2004	K. Raheja
Biopharm	Acceptable Elution Rate (19-AUG-2004 amendment)	23-AUG-2004	S. Apparaju
LNC	*Not Applicable*		
Methods Validation	Package will be sent to FDA labs.		
EA	*Not Applicable*		
Microbiology	Acceptable microbiology quality	21-SEP-2004	J. McVey
CDRH	Acceptable implantation device/trocar	23-AUG-2004	V. Hibbard

19. ORDER OF REVIEW (OGD Only) Not Applicable

The Executive Summary

Recommendations

A. Recommendation and Conclusion on Approvability

The final recommendation from Chemistry is approvable pending a satisfactory recommendation from the Office of Compliance for the GMP status of manufacturing and testing facilities.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug product –

- Vantas is a reservoir drug release system for subdermal implantation. It consists of a histrelin drug core inside a non-biodegradable polymeric shell, measuring 3.5 cm x 3 mm.
- Name: Vantas (histrelin implant)
- Strength: 50 mg histrelin acetate per implant
- Dosage form: implant (reservoir system)
- Indication: palliative treatment of advanced prostate cancer
- Formulation: The Vantas implant consists of a 50 mg histrelin acetate drug core inside a non-biodegradable, 3.5 cm by 3 mm, cylindrical hydrogel reservoir. The drug core also contains the inactive ingredient stearic acid NF. The hydrogel cartridge is composed of 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, trimethylolpropane trimethacrylate, benzoin methyl ether, Perkadox-16, and Triton X-100. Each cartridge is sealed with a plug composed of 2-hydroxyethyl methacrylate, trimethylolpropane trimethacrylate, benzoin methyl ether, and Perkadox-16. The implant is stored in 2 mL of 1.8% sterile sodium chloride.
- Packaging (from the outside in): a carton contains 2 cartons, one for the implant and one for the implantation kit.
    - The implant carton has the statement "Open immediately Refrigerated content enclosed" prominently displayed. Inside the implant carton are a cold pack for refrigerated shipment and a carton containing an amber plastic pouch. Inside the pouch is a USP Type I glass vial with a teflon-coated stopper and an aluminum seal, containing the implant immersed in 2 mL of 1.8% sterile sodium chloride.

- The implantation kit carton contains one each of the following: implantation device, scalpel, syringe, needle, mosquito clamp, betadine swab, alcohol swab, fenestrated drape, antiseptic ointment, gauze sponge, surgical closure strip package, vicryl coated suture package, elastoplast package, and ampule of lidocaine HCl 1% with epinephrine. The implantation device is reviewed by CDRH (ongoing), and the other products (individually packaged) in the implantation kit are commercially available.

- The primary stability batches are the three production-scale lots 508, 510, and 511 (all used in the pivotal clinical protocol 301). Data are provided in the NDA for periods of up to 24 months at 2-8 °C, 6 months at 25 °C, and 12 months at 40 °C.

Drug substances –

- USAN: histrelin
- The drug substance is histrelin acetate, a synthetic nonapeptide derived from the natural decapeptide LHRH( ). Reference is made to Drug Master File ( ) for all chemistry reviews of the drug substance. Due to the confidentiality nature of Drug Master Files, review issues regarding the drug substances cannot be divulged in this NDA review. Reference is made to the chemistry reviews of the Drug Master Files for details.

B. Description of How the Drug Product is Intended to be Used

- Dosage administration: subdermal implantation for 12-month use
- Daily dose: approximately 50 µg/day is released from the implant (by diffusion through the non-biodegrable polymer cartridge)
- Shelf life: 24 months under refrigerated conditions

C. Basis for Approvability or Not-Approval Recommendation

- The initial review by this chemist found several deficiencies in the NDA. They included the following: broad impurity and drug release criteria, unclear information on reprocessing, incomplete information on certain solvents and reagents, incomplete system suitability testing used in the impurity test method, missing information on the development of the hydrogel (e.g., optimization of the composition and controls, optimization of hydration and storage), among other issues. Subsequently, per FDA's requests for additional information, the applicant submitted amendments (dated 9-AUG-2004, 19-AUG-2004, 8-SEP-2004) which satisfactorily resolved the chemistry deficiencies.
- Revisions made to the packaging labels by this chemist and DMETS were sent to the applicant, who implemented all of them (9-AUG-2004, 1-SEP-2004 amendments, and final mock-ups in the 7-SEP-2004 amendment). Revisions made by this chemist to the packaging inserts will be sent electronically by the Division along with other revisions made by the Division.
- The implantation device (or trocar) was found to be acceptable by the Center for Devices and Radiological Health on 23-AUG-2004 (V. Hibbard).
- The elution rate submitted in the 19-AUG-2004 amendment was found to be acceptable by the Clin. Pharm. reviewer on 23-AUG-2004 (S. Apparaju).

- The sterility assurance of the drug product was found to be acceptable by the Microbiology reviewer (J. McVey) on 21-SEP-2004.
- The safety of specified impurities ([ ] and residual raw materials ([ ] was found to be acceptable by the Pharm. Tox. reviewer (K. Raheja) on 14-SEP-2004.
- A recommendation on the GMP status of facilities is pending from the Office of Compliance.
- The chemistry recommendation is approvable pending a satisfactory recommendation from the Office of Compliance.

Administrative

A. Reviewer's Signature

Electronically captured in DFS

B. Endorsement Block

Electronically captured in DFS

C. CC Block

Electronically captured in DFS

12 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Suong Tran
9/22/04 11:12:44 AM
CHEMIST

paper sign-off 9/22/04

Moo-Jhong Rhee
9/23/04 11:45:15 AM
CHEMIST
I concur

NDA 21-732

Vantas
(histrelin subdermal implant)

Valera Pharmaceuticals, Inc.

Reviewer: Suong Tran, PhD

Division of Reproductive and Urologic Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-732

2. REVIEW #: 1

3. REVIEW DATE: 15-JUN-2004

4. REVIEWER: Suong Tran, PhD

5. PREVIOUS DOCUMENTS: none

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document/DFS Date
Original	12-DEC-2003
Amendment	2-FEB-2004
Amendment	25-MAR-2004
Amendment	30-APR-2004

7. NAME & ADDRESS OF APPLICANT:

Valera Pharmaceuticals, Inc.
8 Clarke Drive
Cranbury NJ 08512

8. DRUG PRODUCT NAME/CODE/TYPE:

Full Name: Vantas™ (histrelin subdermal implant)
Proprietary Name: Vantas™
Non-Proprietary Name (USAN): histrelin
Code Name/# (OGD only): Not Applicable
Chem. Type(ONDC only): 3
Submission Priority(ONDC only): S

9. LEGAL BASIS FOR SUBMISSION: Not Applicable

10. PHARMACOL. CATEGORY: Palliative treatment of advanced prostate cancer

11. DOSAGE FORM: implant (reservoir system)

12. STRENGTH/POTENCY: 50 mg histrelin acetate per implant

13. ROUTE OF ADMINISTRATION: subcutaneous

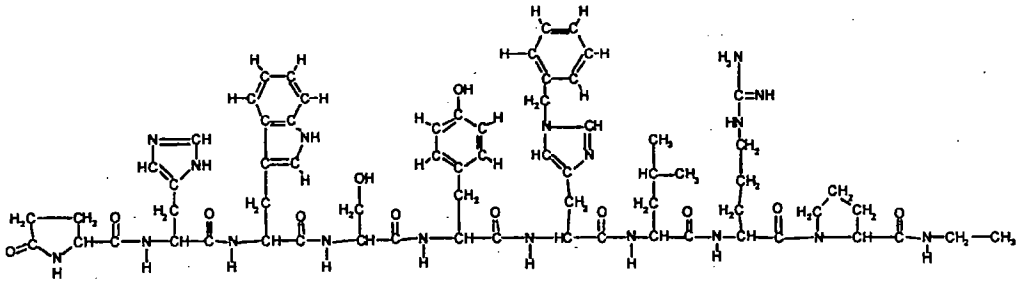
14. Rx/OTC DISPENSED: _x_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

____SPOTS product – Form Completed

__x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Histrelin (USAN):
5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-Nt-benzyl-D-histidyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide
CAS-76712-82-8
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Molecular weight: 1323.50 (1323.5 + 120.2 = 1443.70 as histrelin acetate)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW COMPLETED	COMMENT
[redacted]	II	[redacted]	Histrelin acetate	1	Inadequate	12-APR-2004	By S. Tran
[redacted]	III	[redacted]	[redacted]	4	N/A	N/A	N/A

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6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: none

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	*Not Applicable*		
EES	**Ongoing review by Compliance**		
Pharm/Tox	**Ongoing review by Pharm.Tox.**		
Biopharm	**Ongoing review by Clin.Pharm.**		
LNC	*Not Applicable*		
Methods Validation	Package will be submitted to FDA labs after test methods are finalized.		
DMETS	**Ongoing review by DMETS**		
EA	*Not Applicable*		
Microbiology	**Ongoing review by Microbiology**		
CDRH	**Ongoing review by CDRH**		

19. ORDER OF REVIEW (OGD Only) Not Applicable

The Executive Summary

Recommendations

A. Recommendation and Conclusion on Approvability

The final recommendation from Chemistry is approvable pending a satisfactory response to the chemistry issues delineated in the attached draft letter and satisfactory recommendations from the Office of Compliance, Microbiology, CDRH, Pharm. Tox, and Clin. Pharm. reviewers.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Pending.

Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug product –

- Vantas is a reservoir drug release system for subcutaneous implantation. It consists of a histrelin drug core inside a non-biodegradable polymeric shell, measuring 3.5 cm x 3 mm.
- Name: Vantas (histrelin subdermal implant)
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    - The implant carton has the statement "Open immediately Refrigerated content enclosed" prominently displayed. Inside the implant carton are a cold pack for refrigerated shipment and a carton containing an amber plastic pouch. Inside the pouch is a USP Type I glass vial with a teflon-coated stopper and an aluminum seal, containing the implant immersed in 2 mL of 1.8% sterile sodium chloride.

- The implantation kit carton contains one each of the following: implantation device, scalpel, syringe, needle, mosquito clamp, betadine swab, alcohol swab, fenestrated drape, antiseptic ointment, gauze sponge, surgical closure strip package, vicryl coated suture package, elastoplast package, and ampule of lidocaine HCl 1% with epinephrine. The implantation device is reviewed by CDRH (ongoing), and the other products (individually packaged) in the implantation kit are commercially available.

- The primary stability batches are the three production-scale lots 508, 510, and 511 (all used in the pivotal clinical protocol 301). Data are provided in the NDA for periods of up to 24 months at 2-8 °C, 6 months at 25 °C, and 12 months at 40 °C.

Drug substances –

- USAN: histrelin
- The drug substance is histrelin acetate, a synthetic nonapeptide derived from the natural decapeptide LHRH by [ ]. Reference is made to Drug Master File [ ] for all chemistry reviews of the drug substance. Due to the confidentiality nature of Drug Master Files, review issues regarding the drug substances cannot be divulged in this NDA review. Reference is made to the chemistry reviews of the Drug Master Files for details.

B. Description of How the Drug Product is Intended to be Used

- Dosage administration: subcutaneous implantation for 12-month use
- Daily dose: approximately 50 µg/day is released from the implant (by diffusion through the non-biodegrable polymer cartridge)

C. Basis for Approvability or Not-Approval Recommendation

- A recommendation on the safety of specified impurities [ ] and residual raw materials [ ] is pending from the Pharm. Tox. reviewer.
- A recommendation on the elution rate is pending from the Clin. Pharm. reviewer.
- A recommendation on the implantation device is pending from the Center for Devices and Radiological Health.
- A recommendation on the sterility assurance of the drug product is pending from the Microbiology Team.
- A recommendation on the GMP status of facilities is pending from the Office of Compliance.
- The chemistry recommendation is approvable pending satisfactory recommendations from the consults listed above and a satisfactory response to issues delineated in the draft letter.
- A recommendation on the proprietary name is pending from the Division of Medication Errors and Technical Support.

Administrative

A. Reviewer's Signature

Electronically captured in DFS

B. Endorsement Block

Electronically captured in DFS

C. CC Block

Electronically captured in DFS

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On Original

52 Page(s) Withheld

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___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

CHEMISTRY NDA FILEABILITY CHECKLIST

NDA: 21-732
Applicant: Valera Pharmaceuticals, Inc.
Letter Date: 12-DEC-2003

Drug Name: Vantas (histrelin subdermal implant)

IS THE CMC SECTION OF APPLICATION FILEABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		No CFNs.
5	Is a statement provided that all facilities are ready for GMP inspection?	X		All facilities are listed.
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		Partial information is included.
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?	X		The sterilization validation report is in Vol. 12 of the CMC section.

Comments:

- NDA is acceptable for filing.
- The dosage used in the pivotal clinical study 301 is 50 mg histrelin acetate per implant (not 50 mg histrelin per implant).
- The sterile drug product consists of a 50 mg histrelin acetate core inside a non-biodegradable, polymeric cartridge.
    - Sterility assurance will be reviewed by the Microbiology reviewer.
    - Toxicology information on the polymeric cartridge will be reviewed by the Pharm./Tox. reviewer.
- Each implant is packaged in a kit that also includes one Trocar insertion device.
    - The Trocar insertion device will be reviewed by the CDRH reviewer.
- At the pre-NDA meeting on 12-AUG-2003, Chemistry and Microbiology conveyed a list of issues to Hydro Med Sciences, the sponsor of IND 40,772. From a preliminary review of the CMC section of the NDA, it is not obvious that many of these issues are addressed in the NDA. The NDA applicant should refer to the pre-NDA meeting minutes and indicate the appropriate volume and page numbers of the NDA where the Chemistry and Microbiology issues are addressed.

FILING COMMENT TO BE INCLUDED IN THE 74-DAY LETTER:

With reference to the Chemistry and Microbiology comments in the 12-AUG-2003 pre-NDA meeting minutes, indicate the appropriate volume and page numbers of the NDA where these Chemistry and Microbiology issues are addressed.

Review Chemist: Date:

Team Leader: Date:

cc: Original NDA 21-372
HFD-580/Division File
HFD-580/NCrisostomo/STran/MRhee

Have all DMF References been identified? YES

DMF #	TYPE	HOLDER	ITEM REFERENCED
[redacted]	II	[redacted]	Histrelin acetate
[redacted]	III	[redacted]	[redacted]

DRUG PRODUCT NAME

Proprietary: Vantas (histrelin subdermal implant)
Nonproprietary/USAN: histrelin

APPLICANT:

Valera Pharmaceuticals, Inc.

PHARMACOL. CATEGORY/INDICATION: palliative treatment of advanced prostate cancer

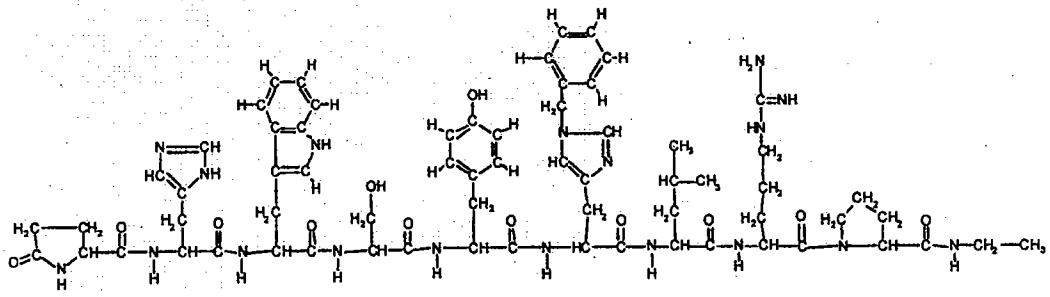
DOSAGE FORM: implant (with non-biodegradable polymer shell)

STRENGTH: 50 mg histrelin acetate

ROUTE OF ADMINISTRATION: subdermal

DISPENSED: X Rx _____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:



Histrelin (USAN):

5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-Nt-benzyl-D-histidyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide

CAS-76712-82-8
Molecular formula: $C_{66}H_{86}N_{18}O_{12}$
Molecular weight: 1323.50 (base)

3 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Suong Tran
1/8/04 11:16:22 AM
CHEMIST

revised as recommended 1/8/04

Moo-Jhong Rhee
1/8/04 11:51:23 AM
CHEMIST
I concur

NDA 21-732
Vantas™ (histrelin implant)
Valera Pharmaceuticals

Environmental Assessment

Valera Pharmaceuticals claimed for a categorical exclusion from an environmental assessment under 21 CFR 25.31(c)

See Chemistry review #2 dated September 23, 2004, page 18.

4.3 Claim for Categorical Exclusion from Environmental Assessment

This is to certify that the Histrelin Acetate Implant meets the exclusion categories under 21 CFR 25.24 as the implant will not affect the quality of the human environment and the Sponsor hereby requests a categorical exclusion from submission of an environmental assessment.