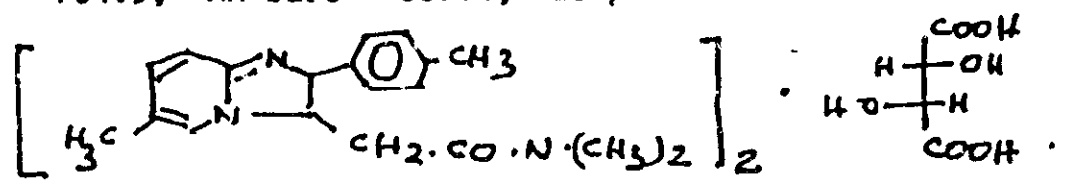
Chem

NDA 19-908 CHEMISTRY REVIEW# 5

AMENDMENTS/REPORTS/DATES: Sept 6, 91; Aug 26, 91; July 16, 91; June 20, 91; May 17, 91; April 17, 91; April 1, 91

OCT 17 1991

APPLICANT NAME/ADDRESS:
Lorex Pharmaceuticals, 4930 Oakton St, Skokie, Il 60077
DIVISION: HFD-120 REC'D. BY CHEMIST: P.Maturu, PhD, MBA
NAME OF DRUG: Ambien and Stilnox
NONPROPRIETARY NAME Zolpidem tartrate
CHEMICAL NAME AND STRUCTURE:
Imidazo(1,2-a)-pyridine-3-acetamide,
N,N,6-trimethyl-2-(4-methylphenyl)-L-tartrate (2:1); CAS# 99294-93-6
MW = 764.9; MW base = 307.4; Zolpidem ≃ 80% w/w and Tartrate ≃ 20% w/w



DOSAGE FORM: Capsule shaped film coated tablet
POTENCY: 5 and 10 mg
PHARMACOLOGICAL CATEGORY: Hypnotic
HOW DISPENSED: X (RX) (OTC)
RELATED IND/NDA/DMF(s):
US Pat 4,382,938 and Eur Pat 50,563, for Zolpidem bulk drug.
DMF
DMF
No DMF
IND for Zolpidem capsules, Lorex Pharmaceuticals.
COMMENTS
See next page for comments on 7 submissions dated Sept 6, 91, Aug 26, 91, July 16, 91, June 20, 91, May 17, 91, April 17, 91, and April 1, 91
CONCLUSIONS AND RECOMMENDATIONS
The chemistry, manufacturing, and controls for 5 and 10 mg Zolpidem tartrate film coated tablets are satisfactory and approvable. Final approval is pending 2 inputs, (1) a satisfactory CGMP inspections of 3 facilities, namely,

and (2) satisfactory methods validation by FDA labs.
Due to last minute tablet shape and color changes initiated by marketing departments the applicant had only 3 months stability data but requested 3 year expiry date. Based on 3 year stability for Zolpidem bulk drug and 3 year expiry date for Zolpidem tablets marketed in France with an identical tablet core, I have no objection in granting the applicants request for 3 year expiry date.

NAME	SIGNATURE	DATE COMPLETED
Pramod K. Maturu, PhD, MBA	P Maturu	9.29.91

Copies:
ORIG:NDA 19-908
HFD-120/Division File
HFD-007/PMaturu
HFD-120/ INIT:SBlum SWB 10/16/91
HFD-120/MMille
DOC#17 3P

APPROVABLE

Submission dated Sept 6, 1991

Listed the commitments agreed by Lorex pharmaceuticals at the meeting held at FDA, Parklawn, on Aug 28, 1991.

(a) Agreed to revise the specifications for Zolpidem tartrate drug substance. (1) To perform IR identity test for Zolpidem tartrate molecule; (2) to perform assay for tartrate portion of the drug substance with a spec based on 2:1 salt; and (3) to perform residual solvent test for methanol with a spec of NMT ppm.

(b) Agreed to revise the in process testing in synthesis. To perform a LC test that can distinguish hydroxy intermediate, chloride intermediates and Zolpidem base.

A written assurance that Zolpidem core tablet compositions are identical for the French product and for the US product. Provided the quantitative compositional differences in the film coat for the French product and for the US product.

A written assurance that Zolpidem tartrate is not a hemihydrate because the firm controls the %RH at Puerto Rican facility at less than 40% and to form Zolpidem tartrate hemihydrate the RH has to excess 70%.

Submission dated Aug 26, 91

Bioequivalency batches:

(a) Submitted batch records for the bioequivalency lots, 5 mg Zolpidem tablet lot PT-232-90 and 10 mg Zolpidem tablet lot PT-233-90, used in the bioequivalency study LSH-91.

(b) These bioequivalency batches were released based on positive identities (LC retention time), LC assays were within specs, met dissolution specs (Q= % at 30 min), an acceptable levels of bioburden (absence of E.Coli and Salmonella, NMT total aerobic organisms per gm and NMT fungi per gram).

(c) These bioequivalency batches were subjected to the following in process checks.

(1) granulation mix in Zanchetta Roto-P 600 high speed mixer and in 30 cu.ft. V-blender were sampled from 6 locations for the 2 process steps and assayed for Zolpidem content;

(2) tablet cores were checked every 20 minutes, for parameters such as, weight of 20 cores, Scheluniger hardness, thickness, friability;

(3) tablet cores were checked prior to coating for assay, content uniformity and dissolution profile;

(4) checked every 30 min check for coating settings such as inlet air temp (70-80^{o}C), outlet air temp (35-45^{o}C), exhaust air volume (1000 CFM).

(5) 135.7 kg or tablet cores of 5 mg Zolpidem lot PT-232-90 were prepared in about 24 hours (819 tablet cores per min/compression dates 12.6.90 to 12.8.90). 137.7 kg or tablet cores of 10 mg Zolpidem lot PT-233-90 were prepared in about 20 hours (956 tablet cores per min/compression dates 12.11.90 to 12.13.90).

(6) In order to use these lots for bioequivalency study, packaged 77 bottles for stability evaluation after 1 mon storage at 40°C and at 40°C-80%RH. The package configuration was 60 cc HDPE bottle/33 mm plastic CR cap/9 gm polyester coil/30 count tablets.

Submitted box labels for 10 cartons of 100 unit dose tablets with Ambien C proprietary name and without the nonproprietary name.

Submitted inspection report for Mourenx, France, facility performed in 2.89 to show the chemical unit processes for Zolpidem bulk drug were layed out well and acceptable cleaning procedures were followed to prevent cross contamination.

Submission dated July 16, 91

Submitted dissolution profiles (a) for Zolpidem tablets 5 mg lot B035 in different dissolution media, water, 0.01 N HCl, pH 8 media; and (b) for Zolpidem tablets 10 mg lot 9075 in 0.01 N HCl.

Submission dated June 20, 91

Changed trade name from Stilnox to Ambien.

Submission dated May 17, 91

Submitted revised package insert dated May 16, 91 with the following revisions.
(a) In Description section added the presence of FDC Red No 40 in 5 mg tablet; changed from imidazopyridine hypnotic agent to nonbenzodiazepine hypnotic of the imidazopyridine class.
(b) In How supplied section added NDC numbers; for 5 mg tablet, a change was made from round white film coated to capsule shaped pink film coated identified with markings of 'SN 5' on one side and '5401' on the other side; for 10 mg tablet, a change was made from oblong white scored film coated to capsule shaped white film coated identified with markings of 'SN 10' one one side and '5421' on the other; added storage condition, store below 86°F (30°C); changed from a carton of 100 unit doses to a carton of 100 unit dose in blister packs.

Submission dated April 17, 91

Submitted for 5 and 10 mg Zolpidem film coated tablets the quantitative composition and dissolution profiles in 0.01 N HCl (5, 10, 15, and 30 min/50 RPM paddle).

Submission dated April 1, 91

Provided assurance that formulation changes will not effect potency estimates of Zolpidem and method validation work.
(a) pure FDC Red No 40 showed no UV absorption from 210 to 360 nm;
(b) 5 mg Zolpidem tablet cores with and without FDC Red No 40 have identical UV maxima at 293 nm;
(c) 5 mg Zolpidem tablet cores uncoated and coated with Opadry Pink YS-1-1418 have identical UV maxima and no extra peaks were observed in LC chromatograms.

The following facilities were listed for different operations/services.
(a)
(b)
(c) had supplied the film coating solutions, Opadry Pink No Y-1-1418 and Opadry White No Y-1-7000 (DMF
(d) for packaging (DMF
(e) Plasma sample assay method for Zolpidem was developed by
(f) facilities were used for dose proportionality studies with 2.5, 5, 10, and 20 mg Zolpidem capsules in healthy subjects.

Submitted an unexcuted batch record for Zolpidem tablets with the use of the following process equipment. Zanchetta Roto P-600 high speed mixer; Kettle with agitator; Fitzmill; Oscillating granulator; Tray-oven dryer; V blender; Hi-Coater HC-130.

Raw material controls: Film coating solutions were tested by for IR/KBr identity, self sustaining film formation, heavy metals, residue on ignition, instrumental color in Cielab Units.

Revised the drug product specifications by eliminating UV identity test and by changing dissolution Q spec from Retained content uniformity by UV method, identity by TLC, and potency by LC.
LC assay: 15 X 0.46 cm Spherisorb ODS 1 5 micron column; 2 methanol 3 acetonitrile 5 buffer 0.025 M potassium phosphate monobasic at pH 5.5; 1.2 ml/min flow; 254 nm detection; retention times were 10.3 min for Zolpidem, 2.1 min for acid impurity I, 6.2 min for oxoacetamide impurity II, 9 min for benazmide impurity IV, 17 min for aldehyde impurity III.
TLC assay: Silicagel 60 F 254 plate; 70 ethyl acetate-15 heptane-15 diethylamine; 254 nm detection.

Stability data update:
(a) Provided 3 mon stability data for 5 and 10 mg Zolpidem tablets used in the bioequivalency studies packaged in 60 cc HDPE bottle-plastic CR cap. No significant changes were observed.
(b) Provided stability data for 10 mg Zolpidem tablets for 24 mon for lots 6043, 6054/30, 6055/10, packaged in PVC-Al-blister packages. No significant changes were observed.
(c) Updated the stability data for 5 mg Zolpidem tablets from 6 mon to 24 mon for lots 8035, 8036, 8037 packaged as 100s in 120 cc HDPE bottle-38 mm plastic CR cap and as 500s in 175 cc HDPE bottle-38 mm metal cap. No significant changes were observed for appearance, potency, impurities, dissolution and friability.

Provided linkage tables between clinical study no, clinical study dosage lot no, bulk drug lot no.

Bulk drug lot	Mfg	Batch size, kg	
Past/Original method of synthesis lots/			facility:
P 007-32	1982	0.25	
P 750-236-001	1982	1.7	
P 750-236-005	1983	0.3	
P 750-236-006	1983	26.8	
P 750-236-009	1984	8.3	
P 750-236-010	1984	9.2	
Current/new method of synthesis lots/			facility::
P 750-236-012	1985	4.8	
P 750-236-015	1985	58	
L 0236-002	1987	226.6	

Toxicology assessment: 4 week oral toxicity in rats was conducted to compare past method of synthesis lot P 750-236-006 with the current method of synthesis lot L 0236-025 (v1.4, p13). Test parameters were body weight, food consumption, haemtology-WBC, RBC, HB, PCV, MCV, MCH, MCHC, pla , Qt, differential cell count, blood biochemistry-Na, K, Gluc, Urea, creat, total bil, prot, alb, A/g, chol, trig, Alp, ASAT, alat, urin analysis-vol, sp gr, pH, pathology report-body organ weights and microscopic examination.

Environmental assessment:

(a) Environmental controls at Mourenx-France facility have included that nonhazardous waste water were pH adjusted and pumped into a empty gas cavern 400 meters below the surface; particulate emissions were reduced through out the facility by transporting in lined closed containers; fugitive air emissions were reduced by vacuum transportation and loading into processing equipment. Projected natural resources at Mourenx are 1700 kwh/day a 10% of total mfg power requirement.

(b) For 150 kg batch Zolpidem tablets 38.5 mg Zolpidem is released into the air, 62.5 mg is lost to waste water, a maximum concentration of 0.33 mg Zolpidem per lit was estimated in waste water discharge. Projected natural resources are kwh/day or 27% of total mfg power requirement.

(c) Zolpidem water solubility is 23 mg/ml at 20°C; octanol to water partition is 263 at pH 7.4; 50% Zolpidem is hydrolyzed to N,N,6-trimethyl-2-(4-methylphenyl) imidazo (1,2a)pyridine acetic acid at 80°C after 6 mon; 35% Zolpidem is photolyzed in day light after 1 mon (photolysis products are 5-methyl-2(4-methylbenzamido)pyridine, 6-methyl-2(4-methylphenyl)imidazo (1,2a)pyridine-3-carboxaldehyde, N,N,6-trimethyl-2(4-methylphenyl) imidazo (1,2a)pyridine-3-(2-oxoacetamide)); biological microtoxicity EC50 is 2900 mg/lit using activated sludge; about 30% biodegradation after 28 days; maximum emitted concentration (MEC) is ppm based on kg/yr proj sales, gallon water usage per persons and million US population; EC50 value for algae is mg/lit or ppm or fold safety factor over MEC.

(1) 48 hr static acute immobilization toxicity test with Daphnia magna invertebrate (120 mg/l EC 50 and 16 mg/l NOEC); 96 hr static acute toxicity LC50 to Rainbow trout vertebrate (22 mg/l EC 50 and 6.2 mg/l NOEC); Acute toxicity test EC50 with fresh water Selenastrum algae (2.2 mg/l EC 50 and 0.32 mg/l NOEC); Ready biodegradability of the test material in closed bottle test; Activated sludge respiration inhibition test - dissolved oxygen measurement (oxygen consumption mg O_2 per lit) during the inhibition of microbial respiration of the test material Zolpidem mg/lit and the reference material 3,5-dichlorophenol mg/lit.

DOC#1778P/9.29.91.

15.0 SECTION I : ANALYSIS OF DRUG SUBSTANCE : ZOLPIDEM TARTRATE

15.1 SPECIFICATIONS

DESCRIPTION : white to off-white microcrystalline powder

INFRARED SPECTRUM : the infrared spectrum exhibits absorption maxima at the same wavelengths as that of the reference spectrum (Figure 27).

HPLC IDENTIFICATION : the major peak obtained in HPLC for related substances has the same retention time as that obtained with a reference solution of zolpidem tartrate.

IDENTIFICATION OF TARTRATE : positive

CLARITY AND COLOR - APPEAREANCE OF SOLUTION : clear and almost colorless

pH : between 4.0 and 5.5

WATER CONTENT : not more than %

RESIDUE ON IGNITION : not more than %

HEAVY METALS : not more than ppm

RELATED SUBSTANCES :

Major impurity : not more than % (by weight)
Other impurities : not more than % each (by weight)
Total impurity : the sum of the areas corresponding to chromatographic peaks other than the principal peak is not more than % of the total area of all peaks observed

ASSAY : 98.5 % - 101.5 %

UNIT DOSE
BOX LABEL
5MG

Box Label-HUD 7/10/91 6:52 PM Page 1

NDC 0025-5401-34

Ambien™ C

5 mg

Store below 86°F (30°C).
10 Cartons of 100 Unit Dose Tablets

SEARLE

A09678

1 03 0905 0511 31 1

149
Box 12

UNIT DOSE
BOX LABEL
10MG

Box Label-HUD 7/18/91 6:52 PM Page 2

NDC 0025-5421-34

Ambien™ C

10 mg

Store below 86°F (30°C).
10 Cartons of 100 Unit Dose Tablets

SEARLE

A09677

1 03 0905 0511 31 1

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STABILITY EVALUATION PROTOCOL
LOREX PROTOCOL NUMBER SM-01-90

e. In order to use these lots in the bioequivalency study, Lorex requires at least one month accelerated data. This protocol is to generate these data to allow Lorex to set an expiration date for these clinical supplies. The 30 count bottle for this study is a 60 cc HDPE bottle/plastic CR cap/polyester coil.

f. Data to monitor the concurrent use of this lot in the clinical study will be generated by a separate Lorex stability study.

4. Objectives:

a. Generate at least one month accelerated data to fulfill the Lorex requirement prior to using these lots in the bioequivalency study.

b. Supply Lorex with accelerated data to allow an expiration date to be set for the clinical supplies.

5. Samples:

Manufacturing Site: Puerto Rico ✓

No. of Lots	Product	Container	Packaging Closure	Coil	Quantity/ Lots Required
1	Stilnox 5 mg	30 ct/60 cc HDPE	Plastic C/R Cap	Polyester	77 Bottles
1	Stilnox 10 mg	30 ct/60 cc HDPE	Plastic C/R Cap	Polyester	77 Bottles

6. Packaging Specifications:

Packaging Site: Puerto Rico
See Stability Packaging Instructions

Part No.	Description	Issue Date
A02353	Stilnox 5 mg	22 Feb. 90
A02356	Stilnox 10 mg	22 Feb. 90

7. Sample Storage:

Storage Site: Puerto Rico

Storage Condition	Weeks of Storage/Analytical Testing 0	4	8	13	26	Quantity/Lot to Store 30 ct. Bottle
5°C						2
30°C	ADHMP			ADHMP	*	25
40°C		ADHMP		ADHMP	*	25
40°C/80%		ADHMP	ADHMP	ADHMP	*	25

* Testing through 13 weeks is scheduled. However, enough bottles will be stored for future testing if the data are equivocal.

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manuf.

REVIEW OF CHEMISTRY AND MANUFACTURING CON LS

NDA#. 19-908

Applicant: Lorex Pharmaceuticals
Sponsor:
Address: P.O.Box 163
4930 Oakton Street
Skokie, Illinois 60077
AF#: 65-898, Synthelabo Pharmacie

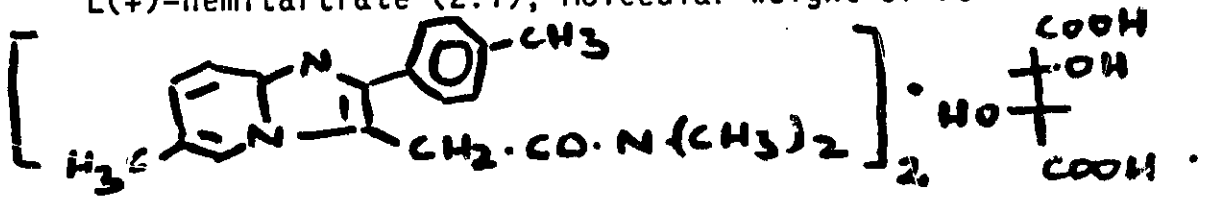
Division: HFD-120
Chemist Review: # 4
Reviewing Chemist: P.Maturu
Date Received: 4.7.89
Date Completed: 8.31.89
Received CDB: 4.1.89
Serial Number:

Product Name:
Proprietary: Stilnox
Non-proprietary: Zolpidem tartrate
Compendium:
USAN: Zolpidem tartrate
Code Name/Number: SL 80.0750-23N salt and CAS-99294-93-6
Drug Classification: Hypnotic; sedative
Patent Number: US Patent 4,382,938, May 10, 1983

Dosage Form(s) and Route(s) of Administration:
R_x. Film coated oral tablet

Pharmacological Category and/or Principal Indication:
Hypnotic; sedative

Structural Formula & Chemical Name:
N,N,6-Trimethyl-2-p-tolylimidazo(1,2a)pyridine-3-acetamide L(+)-hemitartrate (2:1); Molecular weight of 764.88.



Initial Submission: 1.26.89
Amendments(s): 3.31.89
Related Documents:
IND DMF# DMF#

Remarks:
The submission contains 'certificates of analysis in French language' for the different lots used in the European clinical studies (2.5, 5, 7.5, 10, 12.5, 15, 20, 25, 30, 35 and 40 mg capsule; 10 and 20 mg tablet; 5 mg/5 ml and 10 mg/10 ml injection. See next page for the continuation of chemists remarks.

Conclusions and Recommendations:
See enclosed updated chemists portion of letter to sponsor for chemistry deficiencies.

P Maturu
Reviewing Chemist, P.Maturu, Ph.D.

cc: IND:ORIG.
[redacted]
HFD-120/P.Maturu
INIT:RCShultz
CSO: M Mille 9-5-89
DOC#3560e
CHEMISTRY DEFICIENCIES/INFORMATION REQUEST

This submission contains certificates of analysis in French language for the following lots used in the European clinical studies.

Capsules:

2.5 mg	LP12718
5 mg	LP12006; LP12068; LP12323: LP13122
7.5 mg	LP12719
10 mg	LP12005; LP12111; LP 12202: LP12298; LP12607; LP13123
12.5 mg	LP12766
15 mg	LP12319; LP12344; LP12428; LP12319; LP12428
20 mg	LPLP11948; LP12113; LP12209; LP12299; LP12608; LP12751; LP13125
25 mg	LP12320
30 mg	LP12174; LP12198; LP12277; LP12300; LP12357
35 mg	LP12321
40 mg	LP12301

Tablets:

10 mg	LP12465E; LP12558-E; LP13118E; TG1320-04A
20 mg	LP12565E; LP12572E; LP12599E; LP12649E; LP12666E

Injection:

5 mg/5 ml	LP12295
10 mg/10 ml	LP13042
20 mg/4 ml	LP13043

My own translation from French to English indicates that tests such as (1) Appearance; (2) Identity A (CCM); (3) Identity B (UV);(4) Disintegration;(5) Dissolution (900 ml/0.1 or 0.01 N HCl/37°C/Paddle/50 RPM/UV absorbance at 294 or 310 nm);(6) Content Uniformity;(7) Weight in mg; (8) Assay, were performed on the oral drug product.

I compiled the test results from the certificates of analysis upon translation. The batch size is not given for all the batches and where given the batch size is a laboratory batch size in many cases. Within lot variability and between lot variability seems very high for in vitro dissolution.

Capsules

2.5 mg	LP12718	Jan 85	2.4 mg potency/226.3 mg mass/2.5-3.3 min for % dissolution with a CV of % (0.01 N HCl/294 nm)
5 mg	LP12006 250 cap	Jan 83	4.85 mg potency/3.5% CV in potency (4.52 to 5.06)/222 mg weight/3.6-18.4 min for % dissolution (0.1 N HCl/294 nm)
5 mg	LP12068 2100 cap	Apr 83	5.06 mg potency/4.3% CV in potency (4.8 to 5.4 mg)/227 mg weight/3.4-5.2 min for % dissolution
		Mar 84	6.3-8.4 min for % dissolution (0.01 N HCl/294 nm)
5 mg	LP12323 4100 cap	Jan 84	5.1 mg potency/2.3% CV in potency (4.8 to 5.1)/227.7 mg weight
		Oct 83	2.7-4.2 min for % dissolution with a CV of % (0.01 N HCl/294 nm)
5 mg	LP13122	Feb 86	4.94 mg potency/3.0% CV in potency (4.9 to 5.4)/227 mg weight/3.3-4.5 min for % dissolution (0.01 N HCl/310 nm)
7.5 mg	LP12719	Jan 85	7.3 mg potency/1.6% CV in potency/226.2 mg mass/4.3-11.8 min for % dissolution
10 mg	LP12005 244 cap	Jan 83	10.3 mg potency/228 mg weight/4.4-28.3 min for % dissolution (0.01 N HCl/294 nm)
10 mg	LP12111 3000 cap	June 83	10 mg potency/224.9 mg weight/2.5-4.5 min for % dissolution (0.01 N HCl/294 nm)
10 mg	LP 12202 2950 cap	Sept 83	10 mg potency/227 mg weight/3.1-7.7 min for % dissolution with a CV of % (0.01 N HCl/310 nm)
10 mg	LP12298 15800 cap	Dec 83	10.1 mg potency/227.75 mg weight/4.3-7 min for % dissolution with a CV of % (0.01 N HCl/310 nm)

Lot 12478 is not 10 mg cap but it is a placebo (Study: Maillard/IFR27).

10 mg	LP12607	Sept 84	10 mg potency/229.4 mg weight/4.1-7.9 min for % dissolution with a CV of % (0.01 N HCl/310 nm)
10 mg	LP13123	Nov 86	9.96 mg potency/227 mg weight/3.2-4.5 min for % dissolution (0.01 N HCl/310 nm)
12.5 mg	LP12776	Feb 85	12.1 mg potency/226.5 mg weight/4.6-8.6 min for % dissolution (0.01 N HCl/310 nm)

15 mg	LP12319 1130 cap	Jan 84 Oct 83	14.8 mg potency/226.5 mg weight 4.6-13.9 min for % dissolution with a CV of % (0.01 N HCl/310 nm)
15 mg	LP12344 260 cap	Feb 84	14.3 mg potency/112.8 mg weight
15 mg	LP12428 27000 cap	Mar 84	15.2 mg potency/235.9 mg weight/3.7-11.1 min for % dissolution with a CV of % (0.01 N HCl/310 nm)
20 mg	LP11948 278 cap	Dec 82	20.7 mg potency/228 mg weight/4.9-7.7 min for % dissolution (0.01 N HCl/310 nm)
20 mg	LP12113 3000 cap	Jan 83	19.8 mg potency/225.8 mg weight
20 mg	LP12209 3250 cap	Sept 83	19.5 mg potency/224.5 mg weight/3.5-6.4 min for % dissolution with a CV of % (0.01 N HCl/310 nm)
20 mg	LP12299 16000 cap	Jan 84	20.2 mg potency/231 mg weight/12.5-13.2 min for % dissolution with a CV of (0.01 N HCl/310 nm)
20 mg	LP12608	Oct 84	19.9 mg potency/232.8 mg weight/6.3-11.2 min for % dissolution with a CV of % (0.01 N HCl/310 nm)
20 mg	LP12751	Feb 85	19.4 mg potency/227.7 mg weight/5.7-8.1 min for % dissolution (0.01 N HCl/310 nm)
20 mg	LP13125	Nov 86	20.4 mg potency/232 mg weight/3.4-5.7 min for % dissolution (0.01 N HCl/310 nm)
25 mg	LP12320 1200 cap	Jan 84	24.9 mg potency/226.8 mg weight/4.7-7.1 min for % dissolution with a CV of % (0.01 N HCl/310 nm)
30 mg	LP12174 400 cap	Aug 83	30.6 mg potency/228.6 mg weight/3.3-6.8 min for % dissolution (0.01 N HCl/310 nm)
30 mg	LP12198 400 cap	Sept 83	30.2 mg potency/229.7 mg weight/3.5-6.4 min for % dissolution (0.01 N HCl/310 nm)
30 mg	LP12277 477 cap	Dec 83	30.4 mg potency/225.7 mg weight
30 mg	LP12300	Jan 84	29.7 mg potency/229 mg weight/9.3-14 min for % dissolution with a CV of % (0.01 N HCl/310 nm)
30 mg	LP12357 260 cap	Feb 84	28.9 mg potency/113 mg weight

35 mg	LP12321 1050 cap	Jan 84	35.4 mg potency/229.4 mg weight/4.9-9 min for % dissolution with a CV of % (0.01 N HCl/310 nm)
40 mg	LP12301 2500 cap	Jan 84	39.2 mg potency/226.2 mg weight/10.3-15.6 min for % dissolution with a CV of % (0.01 N HCl/310 nm)

Tablets:

10 mg	LP12465E	July 84	10.1 mg potency/126.7 mg weight
10 mg	LP12558E	Aug 84	10.2 mg potency/126.6 mg weight/2.2-3.8 min for % dissolution (0.01 N HCL/310 nm)
10 mg	LP13118E		10 mg potency/identity for titanium dioxide is positive/complies for disintegration in 15 min
10 mg	TG1320-04A	Mar 87	10.1 mg potency/127 mg weight/identity for titanium dioxide is positive/complies for disintegration in 15 min
20 mg	LP12565E	Aug 84	20.3 mg potency/128 mg weight/identity for titanium dioxide is positive/complies for disintegration in 15 min Dissolution data is not readable because of the poor quality of the document.
20 mg	LP12572E	Sept 84	20.2 mg potency/125.6 mg weight/identity for titanium dioxide is positive/10.8 to 15.7 min for % dissolution with a CV of 11% (0.01 N HCl/310 nm)
20 mg	LP12599E	Sept 84	19.7 mg potency/126.9 mg weight/4.2 to 5.7 min for % dissolution with a CV of % (0.01 N HCl/310 nm)
20 mg	LP12649E	Dec 84	19.6 mg potency/124.8 mg weight/Dissolution data is not readable because of the poor quality of the document (0.01 N HCl/310 nm)
20 mg	LP12666E	Nov 84	19.6 mg potency/125.7 mg weight/Dissolution data is not readable because of the poor quality of the document (0.01 N HCl/310 nm)

Injection:

5 mg/5 ml	LP12295 3000 amp	Jan 84	Sterile/5 mg per 5 ml/pH 4.45
10 mg/10 ml	LP13042	Mar 86	Sterile/9.51 mg per 10 ml/pH 4.3
20 mg/4 ml	LP13043	Mar 86	Sterile/19.76 mg per 4 ml/pH 4.4

Chemists portion of letter to sponsor

Drug substance:

(a) Submit tests used to monitor the completion of reaction and purity at each step of synthesis. TLC purity profile at each step has to show the mass balance for the desired and undesired by products. Provide information on the number and identity of impurities at each step of the synthesis. Propose acceptance limits for the observed primary and secondary spots at each step of the synthesis based on lot to lot profile and production experience.

(b) Provide a side by side TLC comparison data for the drug substance produced by the 'current synthesis'and 'original synthesis' using different developing solvents and several lots from each synthesis scheme.

(c) Please provide the synthesis procedure for the key intermediate, manufactured under contract for by and synthesis for the starting materials through your suppliers.

(d) We suggest that you include the following additional specifications to assure purity.
M.P. specification
Mole fraction of tartaric acid.
Residual solvent methanol.

(e) We suggest that you replace the potentiometric titration method with a HPLC method as the primary quantitative assay method for the drug substance.

(f) Further characterize the reference standard batch P750.236.006 in terms of mole fraction of tartaric acid present in zolpidem tartrate. Provide purity and stability data for the reference standard batch.

(g) Submit a copy of the chromatogram for the reference standard to support that the method can separate drug from impurities carried over from one step to another step of the synthesis.

(h) Provide the titration curve for zolpidem base with tartaric acid to support the proposed pH specification for the drug substance.

(i) Provide oxygen content determination as a part of the elemental micro analysis under proof of chemical structure.

(j) Monitor the absence of polymorphism by using several standard techniques and not just limiting to IR technique.

(k) Submit IR scans for methanolate and nonmethanolate for the drug substance.

(l) Most recent CGMP inspection results for facilities.

Drug product:

(a) Please provide 'process validation data' for the oral capsule to support within lot uniformity and between lot uniformity. A review of the 'certificates of analysis in French language' for the different lots used in the European clinical studies (2.5, 5, 7.5, 10, 12.5, 15, 20, 25, 30, 35 and 40 mg capsule; 10 and 20 mg tablet; 5 mg/5 ml and 10 mg/10 ml injection) indicates that the batch size is not given for all the batches and where given the batch size is a laboratory batch size in many cases. Within lot variability and between lot variability seems very high for in vitro dissolution.

(b) Submit reasonable variations in the quantitative composition statement for the proposed film coated tablet. Please provide process validation and optimization data for the tableting and film coating operations.

(c) We suggest that zolpidem tartrate film coated tablets has to be assayed as directed in the assay by HPLC method and not by UV method to meet compendium standards for the content uniformity.

(d) The closure liners were not identified in the submission for the drug product lots used for stability testing. Provide test methods for identity of the liner and package that come in contact with the drug product.

(e) Light energy intensity was not specified.

(f) Please provide 3 year stability data to support a shelf life of 3 years. Provide a rational for 3 years dating given the commercially marketed product in France has only 2 year expiration dating.

(g) Please reconcile the disagreement in 'the mg of coat material specified in the quantitative composition section' with 'the computed coat material as per application procedure'.

(h) Please submit the release specifications and test procedures for the finished Opaspray M-1-7111-8 and for the raw materials since they were not filed in DMF but available to FDA only through the NDA applicant

(i) The proposed 'environmental assessment' should include the expected discharges into water and air based on expected demand and actual measurements of drug levels in water and air.

(j) Identify the drug substance lot used for each lot of the drug product used in the European clinical studies and submit purity and identity data.

3 pages

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Synthesis

FIGURE 4

Separation of a Mixture of Zolpidem Reference Standard (P750.236.006) and the Synthetic Impurities (Intermediates 1, 2 and 3)

(1) intermediate 2
(2) zolpidem (Acetamide)
(3) intermediate 3 (Hydroxyacetamide)
(4) intermediate 1

FIGURE 3

Zolpidem Tartrate - DTA Curve

ZOLPIDEM HEMITARTRATE

Batch : L.0236.005

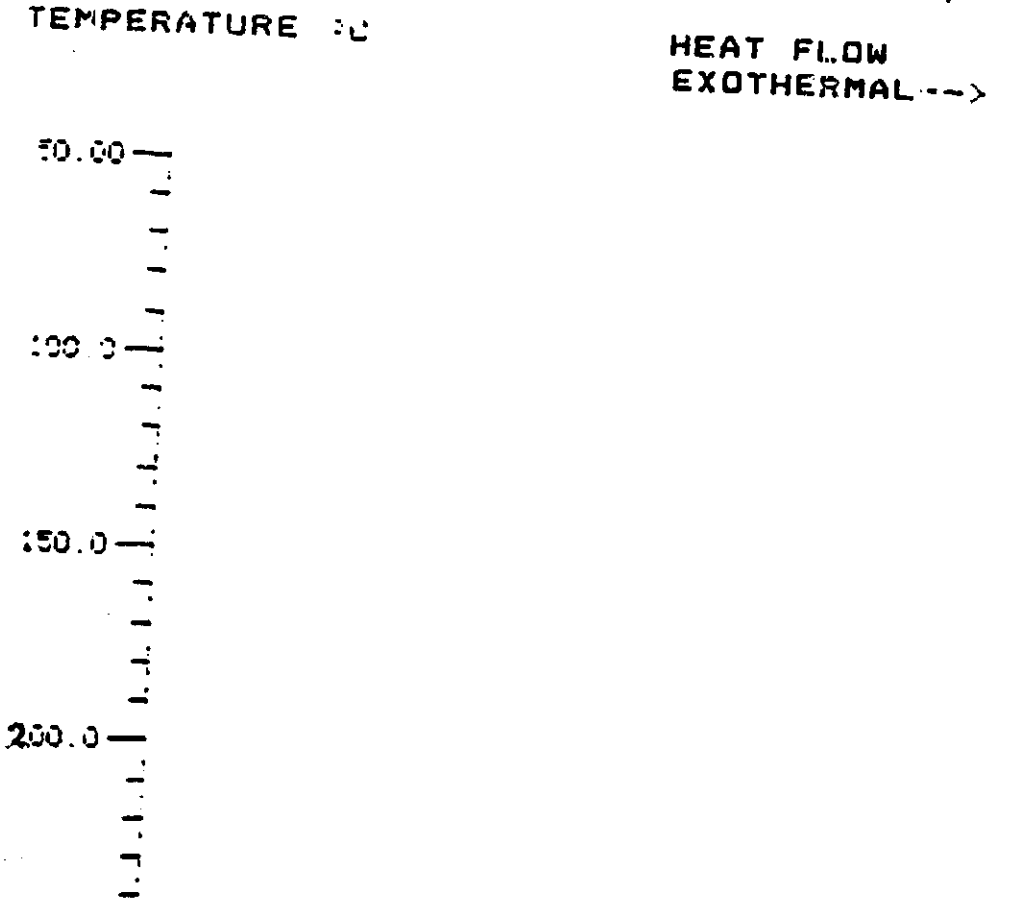
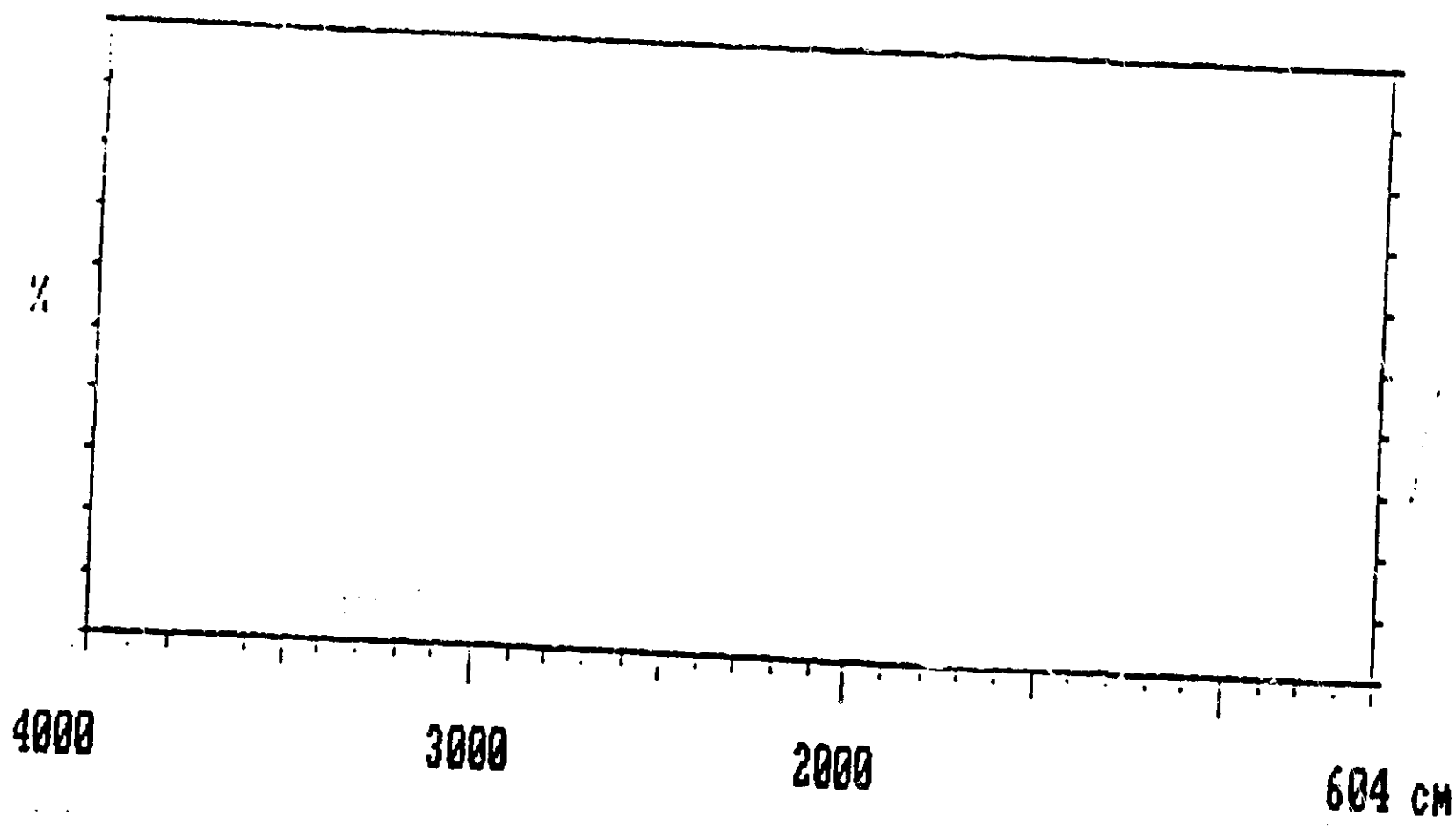


FIGURE 5

Titration Curve for Zolpidem
Base with Tartaric Acid

FIGURE 7

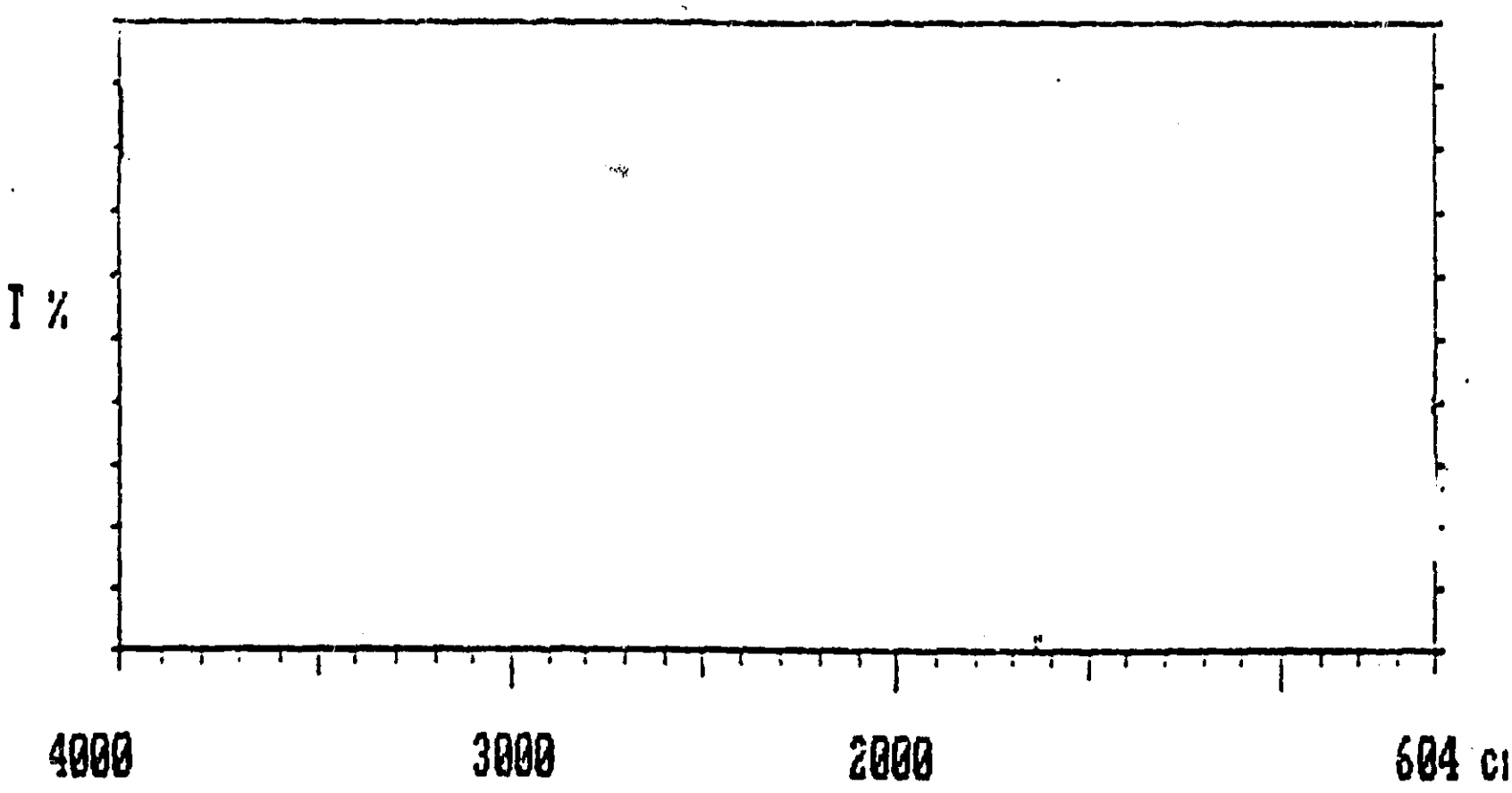
IR Spectrum of Zolpidem Methanolate



ZOLPIDEM HEMITARTRATE METHANOLATE

FIGURE 8

IR Spectrum of Zolpidem Non-Methanolate



ZOLPIDEM HEMITARTRATE batch L0236.005

TABLE 2

5 YEAR STABILITY SUMMARY FOR REFERENCE STANDARD LOT P750.236.006

Zolpidem Tartrate			Table No. 2			Start of Study		March 1983
Batch No. P750.236.006			STABILITY STUDY			Storage Conditions Temperature Rel. Humidity		Ambient Ambient
TESTS	Time	0	6 months	1 year	2 years	3 years	4 years	5 years
	Protocol	83.0282/1	83.0282/1	83.0282/2	83.0282/2	83.0282/3	83.0282/3	83.0282/3
Appearance		Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
TLC / IR Spectrum		Conforms	nt / Conforms	nt / Conforms	Conforms	Conforms	Conforms	Conforms
Appearance of solution / (pH)		Conforms (4.6)	Conforms (4.8)	Conforms (4.7)	Conforms (4.7)	Conforms (4.6)	Conforms (4.6)	Conforms (4.7)
Absorbance (A 1%/1cm)								
at 237 nm		667	672	nt	655	682	680	685
at 295 nm		382	nt	nt	370	375	280	382
Impurity Content (%)								
* Total		0.1	< 0.05	< 0.05	< 0.1	< 0.1		
* Imp I		nd	nd	nd	nd	nd	nd	nd
* Imp II					nd	nd	nd	nd
* Imp III					nd	nd	nd	nd
* Imp IV		nd	nd	nd	nd	nd	nd	nd
Water Content (%)		0.6	1.1	0.85	2.4	2.2	2.0	2.4
Assay (%)		99.8	nt	99.9	100.5	98.4	100.0	100.4

1 page

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manuf.

ZOLPIDEM TARTRATE - BATCH ANALYSES

Batch No.	Batch Size (Kg)	Appearance/ IR	A 1%,1cm		Identification Tests	pH	Imp. Cont. by HPLC (%)	Heavy Metals (ppm)	Water Content (%)	Res. on Ignition (%)	Assay (%)
			237nm	295nm							
P750.0236.001	4.7	Complies	669	405	Complies	4.6	0.17 0.05 - I	< 20	1.35	0	99.85
P750.0236.005	0.31	Complies	679	390	Complies	4.7	nd	< 20	1.2	0	99.8
P750.0236.006/993	26.8	Complies	667	382	Complies	4.6	< 0.1	<< 20	0.6	0	99.8
P750.0236.009	6.2	Complies	697	397	Complies	4.6	nd	< 20	0.3	0.02	99.5
P750.0236.010	9.2	Complies	682	385	Complies	4.6	nd	20	0.48	0.05	99.6
P0750.0236.12	1.8	Complies	682	381	Complies	4.95	nd	<< 20	0.39	0	100.0
P0750.0236.13	38.6	Complies	692	385	Complies	4.74	nd	<< 20	0.4	0.05	99.8
P0750.0236.15	58.0	Complies	689	386	Complies	4.5	< 0.1	< 20	0.18	0	100.1
P0750.0236.17	46.1	Complies	683	380	Complies	4.6	nd	<< 20	0.2	0	100.4
P0750.0236.23	9.1	Complies	682	381	Complies	4.9	nd	< 20	0.3	0	100.0
P0750.0236.25	3.9	Complies	680	378	Complies	4.8	nd	< 20	0.5	0.04	100.7
P0750.0236.26	7	Complies	700	388	Complies	4.7	nd	< 20	2.1	< 0.1	100.1
L0236.002	226.6	Complies	700	390	Complies	4.6	< 0.1	< 20	0.3	0	99.8
L0236.003	123.1	Complies	689	384	Complies	4.8	nd	< 20	0.8	< 0.1	100.4
L0236.004	127.6	Complies	696	388	Complies	4.8	0.02 - IV 0.02 - V	< 20	1.0	0	100.6

N.B. Batches before P0750.0236.12 were made by earlier synthesis.

REPORT N° : GUS2VS04 DATE : 25 10 89

REVISION DATE : Joselle ISSAOUI

REVISION NR. : PAGE :

STLATEC - TOURS

KJZZAT01/03

STABILITY STUDY

Product: TILNOX cp/pel 1 % of stearate	Assay: 10 mg	Batch N°6043	Storage conditions
Packaging: BLISTER	Type : PVC/Alu	Date of manufacture: 03/10/1986 Start of study: 09/02/1987	Temperature : 25°C Relative humidity :

	Charact color	Charact odour	Mean mass	Loss on drying	Hard-ness	Disagre gation	Ident ification Zolpidem	Assay HPLC Zolpidem	Proc Degra dation	Disso lution average	Disso lution mini	Disso lution maxi
Norms	cp white	none	128	/	/	less than 15	positive	9.5-10.5	/	/	/	/
Unit			mg	%	kp	min	//	mg/cp	%	% /15 min	% /15 min	% /15 min
0 months	white	none	125	/	10.5	7 min	Positive	10.2	nd	97.9	94.3	101.8
1 month	white	none	124.4	1.8	10.6	6min 45	Positive	10.1	nd	102.0	95.9	114.6
2 months	/	/	/	/	/	/	/	/	/	/	/	/
3 months	white	none	124.2	2.2	10.4	6min 35	Positive	9.8	nd	97.9	93.5	104.4
6 months	white	none	125	2.5	9.8	5min 56	positive	9.9	nd	100.6	93.2	111.1
12 months	white	none	124.7	2.7	10.2	6 min	Positive	10.1	nd	95.9	92.7	107.3
24 months	white	none	124.9	1.9	10.6	6 min	Positive	10.0	nd	100.1	96.3	108.0
36 months												
48 months												

nd - not detected

TABLE 1

ZOLPIDEM BATCH DISSOLUTION DATA BY DOSE
EUROPEAN CLINICAL STUDIES

Strength/Form		Batch	Batch Size	Dissolution %	%	%	%
2.5 mg	Cap	LP12718	7000				
5 mg	Cap	LP12006	249				
5 mg	Cap	LP12068	2100				
5 mg	Cap	LP12323	4100				
5 mg	Cap	LP13122	15000				
7.5 mg	Cap	LP12719	3000				
10 mg	Cap	LP12005	244				
10 mg	Cap	LP12111	3000				
10 mg	Cap	LP12202	2950				
10 mg	Cap	LP12298	15800				
10 mg	Cap	LP12607	30000				
10 mg	Cap	LP13123	15000				
12.5 mg	Cap	LP12766	4000				
15 mg	Cap	LP12319	1130				
15 mg	Cap	LP12406	300				
15 mg	Cap	LP12428	2700				
20 mg	Cap	LP11948	278				
20 mg	Cap	LP12113	3000				
20 mg	Cap	LP12209	3250				
20 mg	Cap	LP12299	16000				
20 mg	Cap	LP12608	30000				
20 mg	Cap	LP12751	25000				
20 mg	Cap	LP13125	15000				
25 mg	Cap	LP12320	1200				
30 mg	Cap	LP12174	400				
30 mg	Cap	LP12198	400				
30 mg	Cap	LP12277	477				
30 mg	Cap	LP12300	17500				
30 mg	Cap	LP12407	300				
35 mg	Cap	LP12321	1050				
40 mg	Cap	LP12301	2500				

* Number indicates minutes at which X% was dissolved.

REVIEW OF CHEMISTRY AND MANUFACTURING CON LS

NDA#. 19-908

Applicant:Lorex Pharmaceuticals
Sponsor:
Address: P.O.Box 163
4930 Oakton Street
Skokie, Illinois 60077
AF#: 65-898, Synthelabo Pharmacie

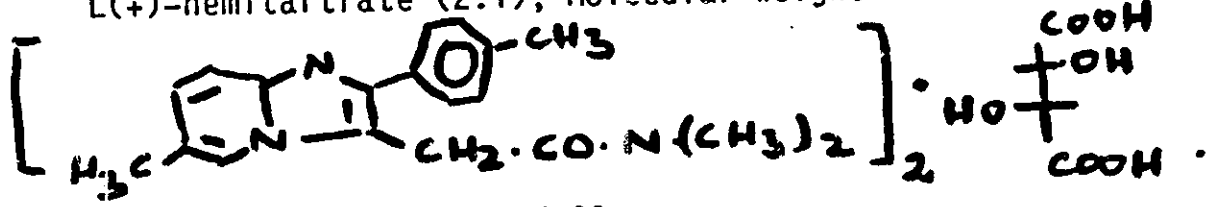
Division: HFD-120
Chemist Review: # 3
Reviewing Chemist: P.Maturu
Date Received: 4.7.89
Date Completed: 8.31.89
Received CDB: 4.4.89
Serial Number:

Product Name:
Proprietary: Stilnox
Non-proprietary: Zolpidem tartrate
Compendium:
USAN: Zolpidem tartrate
Code Name/Number: SL 80.0750-23N salt and CAS-99294-93-6
Drug Classification:Hypnotic; sedative
Patent Number: US Patent 4,382,938, May 10, 1983

Dosage Form(s) and Route(s) of Administration:
R_x. Film coated oral tablet

Pharmacological Category and/or Principal Indication:
Hypnotic; sedative

Structural Formula & Chemical Name:
N,N,6-Trimethyl-2-p-tolylimidazo(1,2a)pyridine-3-acetamide L(+)-hemitartrate (2:1); Molecular weight of 764.88.



Initial Submission: 1.26.89
Amendments(s): 3.31.89
Related Documents:
IND DMF# DMF#

Remarks:
The submission contains 'certificates of analysis in French language' for the different lots used in the European clinical studies (2.5, 5, 7.5, 10, 12.5, 15, 20, 25, 30, 35 and 40 mg capsule; 10 and 20 mg tablet; 5 mg/5 ml and 10 mg/10 ml injection. See next page for the continuation of chemists remarks.

Conclusions and Recommendations:
See enclosed updated chemists portion of letter to sponsor for chemistry deficiencies.

P Maturu
Reviewing Chemist, P.Maturu, Ph.D.

cc: IND:ORIG.
HFD-120
HFD-120/P.Maturu
INIT:RCShultz
CSO:M Mille 9-5-89
DOC#3660e
CHEMISTRY DEFICIENCIES/INFORMATION REQUEST

This submission contains certificates of analysis in French language for the following lot used in the European clinical studies.

Capsules:

2.5 mg	LP12018
5 mg	LP12006; LP12068; LP12323; LP13122
7.5 mg	LP12719
10 mg	LP12005; LP12111; LP 12202; LP12298; LP12607; LP13123
12.5 mg	LP12766
15 mg	LP12319; LP12344; LP12428; LP12319; LP12428
20 mg	LPLP11948; LP12113; LP12209; LP12299; LP12608; LP12751; LP13125
25 mg	LP12320
30 mg	LP12174; LP12198; LP12277; LP12300; LP12357
35 mg	LP12321
40 mg	LP12301

Tablets:

10 mg	LP12465E; LP12558-E; LP13118E; TG1320-04A
20 mg	LP12565E; LP12572E; LP12599E; LP12649E; LP12666E

Injection:

5 mg/5 ml	LP12295
10 mg/10 ml	LP13042
20 mg/4 ml	LP13043

My own translation from French to English indicates that tests such as (1) Appearance; (2) Identity A (CCM); (3) Identity B (UV);(4) Disintegration;(5) Dissolution (900 ml/0.1 or 0.01 N HCl/37^{o}C/Paddle/50 RPM/UV absorbance at 294 or 310 nm);(6) Content Uniformity;(7) Weight in mg; (8) Assay, were performed on the oral drug product.

I compiled the test results from the certificates of analysis upon translation. The batch size is not given for all the batches and where given the batch size is a laboratory batch size in many cases. Within lot variability and between lot variability seems very high for in vitro dissolution.

Capsules

2.5 mg	LP12718	Jan 85	2.4 mg potency/226.3 mg mass/2.5-3.3 min for % dissolution with a CV of % (0.01 N HCl/294 nm)
5 mg	LP12006 250 cap	Jan 83	4.85 mg potency/3.5% CV in potency (4.52 to 5.06)/222 mg weight/3.6-18.4 min for % dissolution (0.1 N HCl/294 nm)
5 mg	LP12068 2100 cap	Apr 83	5.06 mg potency/4.3% CV in potency (4.8 to 5.4 mg)/227 mg weight/3.4-5.2 min for % dissolution
		Mar 84	6.3-8.4 min for % dissolution (0.01 N HCl/294 nm)
5 mg	LP12323 4100 cap	Jan 84	5.1 mg potency/2.3% CV in potency (4.8 to 5.1)/227.7 mg weight
		Oct 83	2.7-4.2 min for % dissolution with a CV of % (0.01 N HCl/294 nm)
5 mg	LP13122	Feb 86	4.94 mg potency/3.0% CV in potency (4.9 to 5.4)/227 mg weight/3.3-4.5 min for % dissolution (0.01 N HCl/310 nm)
7.5 mg	LP12719	Jan 85	7.3 mg potency/1.6% CV in potency/226.2 mg mass/4.3-11.8 min for % dissolution
10 mg	LP12005 244 cap	Jan 83	10.3 mg potency/228 mg weight/4.4-28.3 min for % dissolution (0.01 N HCl/294 nm)
10 mg	LP12111 3000 cap	June 83	10 mg potency/224.9 mg weight/2.5-4.5 min for % dissolution (0.01 N HCl/294 nm)
10 mg	LP 12202 2950 cap	Sept 83	10 mg potency/227 mg weight/3.1-7.7 min for % dissolution with a CV of % (0.01 N HCl/310 nm)
10 mg	LP12298 15800 cap	Dec 83	10.1 mg potency/227.75 mg weight/4.3-7 min for % dissolution with a CV of % (0.01 N HCl/310 nm)

Lot 12478 is not 10 mg cap but it is a placebo (Study: Maillard/IFR27).

10 mg	LP12607	Sept 84	10 mg potency/229.4 mg weight/4.1-7.9 min for % dissolution with a CV of % (0.01 N HCl/310 nm)
10 mg	LP13123	Nov 86	9.96 mg potency/227 mg weight/3.2-4.5 min for % dissolution (0.01 N HCl/310 nm)
12.5 mg	LP12776	Feb 85	12.1 mg potency/226.5 mg weight/4.6-8.6 min for % dissolution (0.01 N HCl/310 nm)

15 mg	LP12319 1130 cap	Jan 84 Oct 83	14.8 mg potency/226.5 mg weight 4.6-13.9 min for % dissolution with a CV of % (0.01 N HCl/310 nm)
15 mg	LP12344 260 cap	Feb 84	14.3 mg potency/112.8 mg weight
15 mg	LP12428 27000 cap	Mar 84	15.2 mg potency/235.9 mg weight/3.7-11.1 min for % dissolution with a CV of % (0.01 N HCl/310 nm)
20 mg	LP11948 278 cap	Dec 82	20.7 mg potency/228 mg weight/4.9-7.7 min for % dissolution (0.01 N HCl/310 nm)
20 mg	LP12113 3000 cap	Jan 83	19.8 mg potency/225.8 mg weight
20 mg	LP12209 3250 cap	Sept 83	19.5 mg potency/224.5 mg weight/3.5-6.4 min for % dissolution with a CV of 20% (0.01 N HCl/310 nm)
20 mg	LP12299 16000 cap	Jan 84	20.2 mg potency/231 mg weight/12.5-13.2 min for % dissolution with a CV of % (0.01 N HCl/310 nm)
20 mg	LP12608	Oct 84	19.9 mg potency/232.8 mg weight/6.3-11.2 min for % dissolution with a CV of % (0.01 N HCl/310 nm)
20 mg	LP12751	Feb 85	19.4 mg potency/227.7 mg weight/5.7-8.1 min for % dissolution (0.01 N HCl/310 nm)
20 mg	LP13125	Nov 86	20.4 mg potency/232 mg weight/3.4-5.7 min for % dissolution (0.01 N HCl/310 nm)
25 mg	LP12320 1200 cap	Jan 84	24.9 mg potency/226.8 mg weight/4.7-7.1 min for % dissolution with a CV of % (0.01 N HCl/310 nm)
30 mg	LP12174 400 cap	Aug 83	30.6 mg potency/228.6 mg weight/3.3-6.8 min for % dissolution (0.01 N HCl/310 nm)
30 mg	LP12198 400 cap	Sept 83	30.2 mg potency/229.7 mg weight/3.5-6.4 min for % dissolution (0.01 N HCl/310 nm)
30 mg	LP12277 477 cap	Dec 83	30.4 mg potency/225.7 mg weight
30 mg	LP12300	Jan 84	29.7 mg potency/229 mg weight/9.3-14 min for % dissolution with a CV of % (0.01 N HCl/310 nm)
30 mg	LP12357 260 cap	Feb 84	28.9 mg potency/113 mg weight

35 mg	LP12321 1050 cap	Jan 84	35.4 mg potency/229.4 mg weight/4.9-9 min for dissolution with a CV of % (0.01 N HCl/310 nm)
40 mg	LP12301 2500 cap	Jan 84	39.2 mg potency/226.2 mg weight/10.3-15.6 min for dissolution with a CV of % (0.01 N HCl/310 nm)

Tablets:

10 mg	LP12465E	July 84	10.1 mg potency/126.7 mg weight
10 mg	LP12558E	Aug 84	10.2 mg potency/126.6 mg weight/2 ?-3.8 min for % dissolution (0.01 N HCL/310 nm)
10 mg	LP13118E		10 mg potency/identity for titanium dioxide is positive/complies for disintegration in 15 min
10 mg	TG1320-04A	Mar 87	10.1 mg potency/127 mg weight/identity for titanium dioxide is positive/complies for disintegration in 15 min
20 mg	LP12565E	Aug 84	20.3 mg potency/128 mg weight/identity for titanium dioxide is positive/complies for disintegration in 15 min Dissolution data is not readable because of the poor quality of the document.
20 mg	LP12572E	Sept 84	20.2 mg potency/125.6 mg weight/identity for titanium dioxide is positive/10.8 to 15.7 min for % dissolution with a CV of % (0.01 N HCl/310 nm)
20 mg	LP12599E	Sept 84	19.7 mg potency/126.9 mg weight/4.2 to 5.7 min for % dissolution with a CV of % (0.01 N HCl/310 nm)
20 mg	LP12649E	Dec 84	19.6 mg potency/124.8 mg weight/Dissolution data is not readable because of the poor quality of the document (0.01 N HCl/310 nm)
20 mg	LP12666E	Nov 84	19.6 mg potency/125.7 mg weight/Dissolution data is not readable because of the poor quality of the document (0.01 N HCl/310 nm)

Injection:

5 mg/5 ml	LP12295 3000 amp	Jan 84	Sterile/5 mg per 5 ml/pH 4.45
10 mg/10 ml	LP13042	Mar 86	Sterile/9.51 mg per 10 ml/pH 4.3
20 mg/4 ml	LP13043	Mar 86	Sterile/19.76 mg per 4 ml/pH 4.4

Chemists portion of letter to sponsor

Drug substance:

(a) Submit tests used to monitor the completion of reaction and purity at each step of synthesis. TLC purity profile at each step has to show the mass balance for the desired and undesired by products. Provide information on the number and identity of impurities at each step of the synthesis. Propose acceptance limits for the observed primary and secondary spots at each step of the synthesis based on lot to lot profile and production experience.

(b) Provide a side by side TLC comparison data for the drug substance produced by the 'current synthesis'and 'original synthesis' using different developing solvents and several lots from each synthesis scheme.

(c) Please provide the synthesis procedure for the key intermediate, manufactured under contract for by and synthesis for the starting materials through your suppliers.

(d) We suggest that you include the following additional specifications to assure purity.
M.P. specification
Mole fraction of tartaric acid.
Residual solvent methanol.

(e) We suggest that you replace the potentiometric titration method with a HPLC method as the primary quantitative assay method for the drug substance.

(f) Further characterize the reference standard batch P750.236.006 in terms of mole fraction of tartaric acid present in zolpidem tartrate. Provide purity and stability data for the reference standard batch.

(g) Submit a copy of the chromatogram for the reference standard to support that the method can separate drug from impurities carried over from one step to another step of the synthesis.

(h) Provide the titration curve for zolpidem base with tartaric acid to support the proposed pH specification 4 to 5.5 for the drug substance.

(i) Provide oxygen content determination as a part of the elemental micro analysis under proof of chemical structure.

(j) Monitor the absence of polymorphism by using several standard techniques and not just limiting to IR technique.

(k) Submit IR scans for methanolate and nonmethanolate for the drug substance.

(l) Most recent CGMP inspection results for facilities.

Drug product:

(a) Please provide 'process validation data' for the oral capsule to support within lot uniformity and between lot uniformity. A review of the 'certificates of analysis in French language' for the different lots used in the European clinical studies (2.5, 5, 7.5, 10, 12.5, 15, 20, 25, 30, 35 and 40 mg capsule; 10 and 20 mg tablet; 5 mg/5 ml and 10 mg/10 ml injection) indicates that the batch size is not given for all the batches and where given the batch size is a laboratory batch size in many cases. Within lot variability and between lot variability seems very high for in vitro dissolution.

(b) Submit reasonable variations in the quantitative composition statement for the proposed film coated tablet. Please provide process validation and optimization data for the tableting and film coating operations.

(c) We suggest that zolpidem tartrate film coated tablets has to be assayed as directed in the assay by HPLC method and not by UV method to meet compendium standards for the content uniformity.

(d) The closure liners were not identified in the submission for the drug product lots used for stability testing. Provide test methods for identity of the liner and package that come in contact with the drug product.

(e) Light energy intensity was not specified.

(f) Please provide 3 year stability data to support a shelf life of 3 years. Provide a rational for 3 years dating given the commercially marketed product in France has only 2 year expiration dating.

(g) Please reconcile the disagreement in 'the mg of coat material specified in the quantitative composition section' with 'the computed coat material as per application procedure'.

(h) Please submit the release specifications and test procedures for the finished Opaspray M-1-7111-8 and for the raw materials since they were not filed in DMF but available to FDA only through the NDA applicant

(i) The proposed 'environmental assessment' should include the expected discharges into water and air based on expected demand and actual measurements of drug levels in water and air.

(j) Identify the drug substance lot used for each lot of the drug product used in the European clinical studies and submit purity and identity data.

A D-120

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

MAR 24 1989

NDA#. 19-908

Applicant: Lorex Pharmaceuticals
Sponsor:
Address: P.O.Box 163
4930 Oakton Street
Skokie, Illinois 60077
AF#: 65-898, Synthelabo Pharmacie

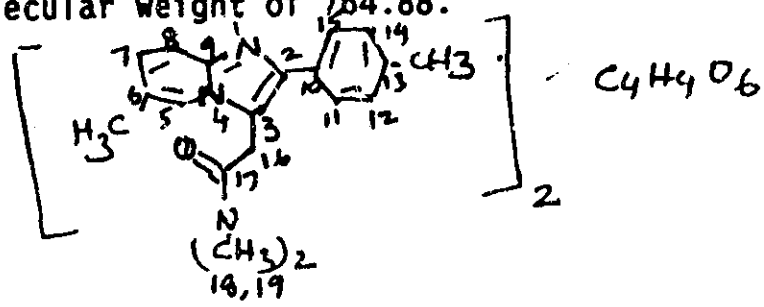
Division: HFD-120
Chemist Review: # 2
Reviewing Chemist: P.Maturu
Date Received: 3.23.89
Date Completed: 3.23.89
Received CDB: 3.17.89
Serial Number:

Product Name:
Proprietary: Stilnox
Non-proprietary: Zolpidem tartrate
Compendium:
USAN: Zolpidem tartrate
Code Name/Number: SL 80.0750-23N salt and CAS-99294-93-6
Drug Classification: Hypnotic; sedative
Patent Number: US Patent 4,382,938, May 10, 1983

Dosage Form(s) and Route(s) of Administration:
R_x. Film coated oral tablet

Pharmacological Category and/or Principal Indication:
Hypnctic; sedative

Structural Formula & Chemical Name:
N,N,6-Trimethyl-2-p-tolylimidazo(1,2a)pyridine-3-acetamide L(+)-hemitartrate (2:1); Molecular weight of 764.88.



Initial Submission: 1.26.89
Amendments(s): 3.16.89

Related Documents:
IND Lorex Pharmaceuticals, Zolpidem tartrate capsules.
DMF#

DMF#

Remarks:
This submission is in response to telecon request by the CSO, Merril; it contains certificates of analysis in French language for 2.5 mg capsules (LP12804), 5 mg capsules (lots DHV05-01A and 02A), 10 mg capsules (LP12705 and KLZ05-01C), and 20 mg capsules (LP12707 and XCV05-01C); it does not contain certificates of analysis for the zolpidem drug substance lots used in the preclinical and clinical investigation. See next page for the continuation of chemists remarks.

Conclusions and Recommendations:
Incomplete submission and recommends no action.

P Maturu
Reviewing Chemist, P.Maturu, Ph.D.

cc: IND:ORIG.
[redacted]
HFD-120/P.Maturu
INIT:RCShultz
CSO:
DOC#3408e
INCOMPLETE SUBMISSION/NAI 3-24-89

A telecon request was made by Merril for the certificates of analysis for the preclinical and clinical lots listed in the CMC summary section pages 001-0118 to 0125 by using methods indicative of identity, purity, and potency. Each lot of the clinical and preclinical drug product must identify the drug substance lot and include the certificates of analysis for the drug substance

This submission contains certificates of analysis in French language for 2.5 mg capsules (LP12804), 5 mg capsules (lots DHV05-01A and 02A), 10 mg capsules (LP12705 and KLZ05-01c), and 20 mg capsules (LP12707 and XCV05-01C). The tests include appearance, UV identity, fill weight in mg, content uniformity, potency, and dissolution in 30 min.

The response submission does not contain certificates of analysis for the zolpidem drug substance lots used in the preclinical and clinical investigation. This incomplete submission contains the certificates of analysis for zolpidem capsule product used in US clinical studies in French language.

Please note that NDA filing is not for the capsule drug product but for the film coated tablets with the following proposed specifications.

Specifications for the film coated zolpidem tartrate tablet:

Appearance.
Positive TLC identity.
Silica gel plate/ethyl acetate, heptane, and diethylamine mixture in ratio as eluant/UV detection at nm.
Positive UV identity.
Absorption maxima at nm.
Passes dissolution with Q NLT % at min.
ml N hydrochloride acid; USP paddle at RPM; UV absorbance at nm.
Passes USP Content uniformity.
UV absorbance at nm.
NLT % potency by HPLC.
Spherisorb ODS column; % methanol plus % acetonitrile in M potassium phosphate monobasic with pH adjusted to with ammonium hydroxide; ml per min flow rate; UV detection at nm.

To meet USP compendium standards for the content uniformity zolpidem tartrate film coated tablets has to be assayed as directed in the assay, by HPLC method and not by UV method.

Optical rotation specification was suggested for the zolpidem tartrate film coated tablet.

DOC#3408e/ft/PM/3.23.89.

HFD-120

MAR 8 1989

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA#. 19-908

Applicant: Lorex Pharmaceuticals
Sponsor:
Address: P.O.Box 163
4930 Oakton Street
Skokie, Illinois 60077
AF#: 65-898, Synthelabo Pharmacie

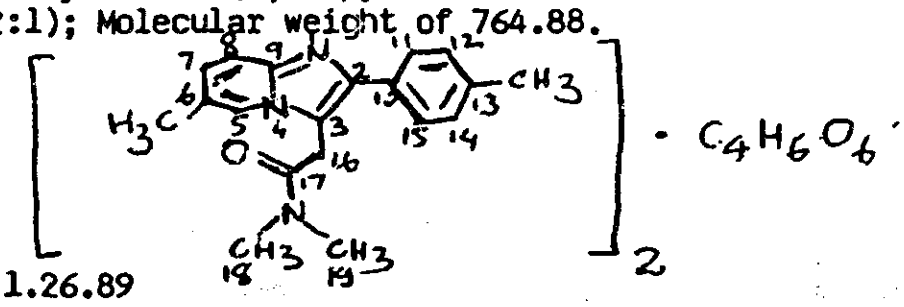
Division: HFD-120
Chemist Review: # 1
Reviewing Chemist: P.Maturu
Date Received: 2.2.89
Date Completed: 3.7.89
Received CDB: 2.1.89
Serial Number:

Product Name:
Proprietary: Stilnox
Non-proprietary: Zolpidem tartrate
Compendium:
USAN: Zolpidem tartrate
Code Name/Number: SL 80.0750-23N salt and CAS-99294-93-6
Drug Classification: Hypnotic; sedative
Patent Number: US Patent 4,382,938, May 10, 1983

Dosage Form(s) and Route(s) of Administration:
R_x. Film coated oral tablet

Pharmacological Category and/or Principal Indication:
Hypnotic; sedative

Structural Formula & Chemical Name:
N,N,6-Trimethyl-2-p-tolylimidazo(1,2a)pyridine-3-acetamide L(+)-hemitartrate (2:1); Molecular weight of 764.88.



Initial Submission: 1.26.89
Amendments(s):
Related Documents:
IND , Lorex Pharmaceuticals, Zolpidem tartrate capsules.
DMF#

DMF#

Remarks:
Please note that FDA may refuse to file an application under section CFR 314.101 (d) because the applicant had failed to submit complete data required under CFR 25.31, and failed to submit complete data to show compliance with CFR 58.105.
See next page for chemists remarks.

Conclusions and Recommendations:
Recommends a refusal to file a NDA application.
See chemists portion of letter to the sponsor.

P Maturu
Reviewing Chemist, P.Maturu, Ph.D.

cc: IND:ORIG.
HFD-102/CKumkumian
HFD-120
HFD-120/
INIT:RCShultz 3-8-89
CSO:
DOC#3346a
REFUSAL TO FILE A NDA

The submission does not contain information on test and control articles characterization (CFR 58.105 page 237) as a part of 'good laboratory practice for nonclinical laboratory studies'.

Did not submit the certificates of analysis for the preclinical and clinical lots listed in the CMC summary section pages 001-011^ to 0125.

The proposed 'environmental assessment' was compared to the required format given in CFR 25.31a on page 205. The proposed format does not contain information for item 14 - references, for items 15 (a) - appendices containing data summary charts, and for item 15(b)- test reports.

Dr. Richman reviewed the zolpidem tartrate capsules submission dated 11.15.84, and he recommended that it was safe to initiate the clinical study. The chemistry deficiencies were not communicated to Lorex Pharmaceuticals in the division letters dated 4.23.85 and 7.15.85.

The observed deficiencies were as follows. Replace the potentiometric titration method with a HPLC method for the drug substance; Assay of the drug substance and capsule dosage be performed by HPLC because the impurities present appear to interfere with the UV assay method; Absence of a M.P. specification for the drug substance; Requested a copy of the chromatogram for the reference standard; Requested comparison of assay values done by both UV and HPLC methods; Requested reasonable variations in the quantitative composition statement; Requested information regarding container/closure system.

The chemistry recommendations made at at the 'end-of-phase II' meeting on 10.9.87 were not addressed by the firm in the current submission.

Please provide 3 year stability data to support a shelf life of 3 years; Provide assurance that HPLC method will be used as the primary quantitative assay method.

Batch P750.236.006 was assigned as a reference standard. The analytical results for batch P750.236.006 includes an optical rotation. However, optical rotation was excluded from the proposed specifications. The proposed chemical name is,
N,N,6-Trimethyl-2-p-tolylimidazo(1,2a)pyridine-3-acetamide
L(+)-hemitartrate (2:1)

To prepare the drug substance, zolpidem in was reacted with in and the olpidem tartrate was washed with (DMF page 9). Please note the formation of 'methanolate' when zolpidem tartrate was formed in methanol (page 002-0044/X-ray studies).

Zolpidem base is insoluble in water, and zolpidem tartrate is sparingly soluble in water (23 mg per ml). Zolpidem tartrate is highly soluble in octanol with octanol to water partition of about 263 (page 002-0018 to 0020). Zolpidem has a pK_a of about 6.

IR spectral studies on zolpidem tartrate showed lack of polymorphism. In this submission, other analytical techniques, such as, X-ray, DSC, were not used to confirm the absence of polymorphism.

Zolpidem tartrate is a hygroscopic substance and it picks up moisture upto 3% moisture to from zolpidem tartrate hemihydrate (page 002-0022).

Zolpidem tartrate has no chiral center. However, the zolpidem tartrate shows a positive rotation due to (+) tartaric acid moiety. Zolpidem exhibits 'regio-isomerism'. I am still pursuing the definition of 'regio-isomerism' and the linkage between regio-isomerism and binding to omega receptor.

1 Components and 2 Composition: (002-0010)

5 mg round white film coated tablet and 10 mg oblong white scored film coated tablet.

Ingredients in core tablet	mg per tablet 5 mg tab	10 mg tab
Zolpidem tartrate	5	10
Lactose NF		
Microcrystalline cellulose NF		
Sodium starch glycolate NF		
Hydroxypropyl methyl cellulose USP		
Magnesium stearate NF		
Core tablet weight in mg		
Ingredients in tablet coating		
Hydroxypropyl methyl cellulose USP	2.8	5.76
Opaspray M-1-7111-B *		
(titanium dioxide suspension)		
Polyethylene Glycol NF		
Tablet coating weight in mg		

* As per my review of the 13 volumes filed for the DMF# Opaspray M-1-7111-B coating solution consists of % Hydroxypropyl methyl cellulose USP, % Titanium dioxide USP, and % SDA-3A alcohol; The release specifications and test procedures for the finished Opaspray were not filed but available through the NDA applicant.

3 Facilities and 4 Personnel:

A review of the administrative file 65-898 indicates that was found to be in compliance with CGMPs for the production of bulk Bethaxomol HCl for use in NDA 19-270 and NDA 19-507 based on the inspection conducted on dates 6/30/86 and 7/1/86.

Zolpidem tartrate drug substance is manufactured in France by Facilities, personnel, and general operating procedures are described in DMF#

A review of the DMF indicates the following. facilities are capable of producing 100 kg of the drug substance, and they are located in 11 buildings (about 3300 sqm surface area) on a site of hectars. The address is,

The establishment registration number is SIRET 786509737 00072.

The equipment at includes reactors liters), tanks liters), dryers liters), filters sqm filter area), autoclaves for hydrogenation liters), refrigeration unit (upto -20°C), etc..

facilities are located at The equipment include powder mixers liters), planetary mixers liters), granulators liters), grinders, micronizers, tableting machines, etc..

facilities are located at a different site The equipment includes UV spectrophotometer, IR spectrophotometer, hz NMR spectrophotometer, GC chromatograph with flame ionization detector, HPLC chromatography equipment, thermal analyzer, atomic absorption spectrophotometer, refractometer, polarimeter, melting point apparatus, TLC densitometer, etc..

5. Synthesis of zolpidem tartrate drug substance:

A review of the DMF# filed by indicates that a shorter synthesis was developed for zolpidem tartrate after the IND filing. The 'current synthesis' was as follows.

Step 1:

Step 2:

Step 3:

TLC:

HPLC:

Step 4:

Step 5:

TLC:

Step 6:

Material controls in the synthesis:

Supplier -
IR identity. Compound was dissolved in
TLC purity.
UV detection at nm; approximate R_f values was
NLT % potency. Potency was determined by titration with

Supplier -
IR identity of the liquid film.
TLC purity. Compound was diluted with
stationary phase;
at nm; approximate R_f values was
UV detection
Potency was determined by gas chromatography. % OV 17 plus ; Carbowax M on Chromosorb WHP as stationary phase; column temperature 150°C; helium at bars as carrier gas; flame ionization detector; detector temperature 250°C. Approximate retention times were 5 min for and 3 min for

L(+) Tartaric acid:

Supplier -
Specific rotation at D line/20°C for % solution in water. Rotation value was
Potency by titration with

Supplier - Manufactured under contract for

IR identity of the liquid film.
GLC purity was NLT %. Capillary column coated with OV1; column temperature 100°C; helium gas at bars; flame ionization detector; detector temperature 280°C. Approximate retention time was min.

6 Specifications for the zolpidem tartrate drug substance.

M.P. specification was not proposed to control the proposed 2:1 stochiometry for zolpidem tartrate.

Positive IR identity/KBr disc.
Positive TLC identity
in ratio as eluant/UV detection at nm.
Positive UV identity. Absorption maxima at nm.
Positive test for tartrate. A deep blue color was produced by mixing the drug substance with

Total HPLC impurities were NMT %, and a single HPLC impurity was NMT %.
Novapak C_{18} column; % methanol plus % acetonitrile in M phosphoric acid with pH adjusted to with triethylamine; ml per min flow rate; UV detection at nm.
% minimum potency by potentiometric titration with perchloric acid using calomel-glass electrode.
NMT ppm heavy metals.
NMT % water content.
NMT % residue on ignition.
Potential impurities I to VI were listed.

Proof of structure:

(1) Elemental microanalysis.

Oxygen content was not reported in the submission.

(2) IR spectrum was recorded with KBr pellet.

(3) ^{1}HNMR spectrum was run in DMSO solvent.

(4) Mass spectrum by electron impact ionization.

7 Other firms:

was manufactured under contract for

Opaspray M-1-7111-B tablet coating material was manufactured by DMF

will manufacture, package, and label zolpidem tartrate tablets.

will package, and label zolpidem tartrate tablets.

8 Manufacturing and processing of the film coated zolpidem tartrate tablets:

A simulated batch card was presented for a mg tablets batch.

	5 mg	15 kg
Zolpidem tartrate	mg	kg
Lactose NF	mg	kg
Microcrystalline cellulose NF	mg	kg
Sodium starch glycolate NF	mg	kg
Hydroxypropylmethyl cellulose USP	mg	kg
Magnesium stearate NF		

Base coating

Hydroxypropyl methylcellulose USP	mg	kg
Polyethylene Glycol NF	mg	kg
		lit

kg HPMC per kg base coating solution, or fraction weight.

(1) Stored at refrigerated temperature overnight after mixing for 1-2 hours .
(2) Screened the solution through mesh screen.
(3) Base coating solution can be stored for NMT 7 days at RT.

9 Container: (pages 002-0154 to 002-0172)

Zolpidem tartrate tablets will be supplied in a HDPE opaque bottles/pulpboard-paper-aluminiumfoil-vinyl coating-wax lined liner/glassine inner seal/tin plated steel cap or child resistant polypropylene cap as 100's and 500's.

Zolpidem tartrate tablets will be supplied in a blister package composed of 7.5 mil PVC film/aluminium foilpaper backing .

10 Packaging and Labelling:

11 Specifications for the film coated zolpidem tartrate tablet:
(page 002-0141 to 002-0153)

Appearance.
Positive TLC identity.

Positive UV identity.
Absorption maxima at nm.
Passes dissolution with Q NLT % at min.
ml N hydrochloride acid; USP paddle at RPM; UV absorbance at nm.
Passes USP Content uniformity.
UV absorbance at nm.
NLT % potency by HPLC.
Spherisorb ODS column; % methanol plus % acetonitrile in M potassium phosphate monobasic with pH adjusted to with ammonium hydroxide; ml per min flow rate; UV detection at nm.

13 Stability and stability testing:
(pages 002-0055, 002-0076, 002-0084 to 0092, 002-0177 to 0212)

The submission contains stability data for the reference drug substance lot P750.236.006 stored for 5 year at RT and 3 years at 40°C. Appearance, TLC spectrum, pH, UV absorbance, impurity content, water content, and assay values did not deviate in a significant way from the initial values. Stability protocol included monitoring repeat tests at yearly intervals.

Zolpidem tartrate drug substance stability was presented for 3 batches prepared by 'original synthesis' (Batch number P750.236.001/Batch size 1 kg; P750.236.006/26 kg; P750.236.009/8 kg) and for 3 batches prepared by 'current synthesis' (P750.236.12/4 kg; P750.236.17/46 kg; L236.002/226 kg).

No significant changes were reported during the 1 year storage of L236 002 /226 kg current synthesis batch, and no significant changes during the 5 years storage of P750.236.006/1 kg original synthesis batch.

Zolpidem tartrate tablets will be supplied in a HDPE opaque bottles/pulpboard-paper-aluminiumfoil-vinyl coating-wax lined liner/glassine inner seal/tin plated steel cap or child resistant polypropylene cap as 100's and 500's.

Zolpidem tartrate tablets will also be supplied in a blister package composed of 7.5 mil PVC film/aluminium foil.paper backing .

Light study: Light energy intensity was not specified. No significant changes in appearance, potency, dissolution, disintegration, were observed for the 5 mg and 20 mg zolpidem tartrate film coated tablet during the 1 month light sensitivity study (lots 8035, 8036, 8037).

100's: The closure liners were not identified in the submission for the drug product lots used for stability testing. No significant changes in appearance, potency, dissolution, disintegration, were observed for the 5 mg zolpidem tartrate film coated tablet packaged in HDPE with either C/R closure or metal cap during the 6 months storage at RT, 40°C, 40°C/85% RH, and 50°C and 1 month light sensitivity study (lots 8035, 8036, 8037).

500's: The closure liners were not identified in the submission for the drug product lots used for stability testing. No significant changes in appearance, potency, dissolution, disintegration, were observed for the 5 mg zolpidem tartrate film coated tablet packaged in HDPE with metal capsule as 100's during the 6 months storage at RT, 40°C, 40°C/85% RH, and 50°C (lot 8037).

Al. foil: No significant changes in appearance, potency, dissolution, disintegration, were observed for the 20 mg zolpidem tartrate film coated tablet during the 6 months storage at RT, 40°C, 40°C/85% RH, and 50°C (lots 8035, 8036, 8037).

Stability testing was done using 20 mg zolpidem tartrate film coated tablet with the following composition.

Zolpidem tartrate	20
Lactose NF	
Microcrystalline cellulose NF	
Sodium starch glycolate NF	
Hydroxypropylmethyl cellulose USP	
Magnesium stearate NF	
Hydroxypropylmethyl cellulose USP	
Opaspray M-1-7111-B (titanium dioxide suspension)	
Polyethylene Glycol NF	

14 Label copy: (page 003-0016 to 132).

Container labels contains the recommended storage condition (store below 30°C).
Proposed package insert contains the description section listing the inactive ingredients in an alphabetical order and how supplied section.

15 Environmental impact statement: (pages 003-0318)

The proposed 'environmental assessment' was compared to the required format given in CFR 25.31a on page 205. The proposed format does not contain information for item 14 - references, for items 15 (a) - appendices containing data summary charts, and for item 15(b)- test reports.

16 Form 356h:

Form 356h was signed by Frank J. Steinberg, President, Lorex Pharmaceuticals, telephone no. 312-982-8453.

Chemists portion of letter to sponsor

(1) The submission does not contain information on test and control articles characterization (CFR 58.105 page 237) as a part of 'good laboratory practice for nonclinical laboratory studies'.

Please submit the certificates of analysis for the preclinical and clinical lots listed in the CMC summary section pages 001-0118 to 0125 by using methods indicative of identity, purity, and potency. Each lot of the clinical and preclinical drug product must identify the drug substance lot and include the certificates of analysis for the drug substance.

(2) The proposed 'environmental assessment' does not contain information for item 14 - references, for items 15 (a) - appendices containing data summary charts, and for item 15(b)- test reports, as specified in CFR 25.31a.

Drug substance: N,N,6-Trimethyl-2-p-tolylimidazo(1,2a)pyridine-3-acetamide L(+)-hemitartrate (2:1)

(3) Please provide in process acceptance specifications for the following steps of the synthesis.

Step 1:
Step 2:

Step 3:

Step 4:

Step 5:

(4) Please provide the synthesis procedure for the key intermediate,

Provide the titration curve for zolpidem base with tartaric acid to support the proposed pH specification 4 to 5.5 for the drug substance.

(6) Include the following additional specifications to assure purity.
M.P. specification
Optical rotation specification.
Mole fraction of tartaric acid.
Residual solvent methanol.

(7) Replace the potentiometric titration method with a HPLC method for the drug substance.

(8) Further characterise the batch P750.236.006 assigned as a reference standard. in terms of mole fraction of tartaric acid present in zolpidem tartrate.

(9) Submit a copy of the chromatogram for the reference standard

(10)Oxygen content was not reported in the elemental microanalysis as a proof of chemical structure.

(11)Include X-ray, and DSC data to confirm the absence of polymorphism (page 002-0044/X-ray studies).

(12)IR scans for methanolate and nonmethanolate of the drug substance.

Drug product:

(13)Reasonable variations in the quantitative composition statement.

(14)To meet compendium standards for the content uniformity zolpidem tartrate film coated tablets have to be assayed as directed in the assay, by HPLC method and not by UV method.

(15)Include optical rotation as a specification for the zolpidem tartrate film coated tablet.

(16)The closure liners were not identified in the submission for the drug product lots used for stability testing.

(17)Light energy intensity was not specified.

(18)The closure liners were not identified in the submission for the drug product lots used for stability testing.

(19)Please provide 3 year stability data to support a shelf life of 3 years.

(20)The mg of coat material specified in the qunatitative composition section (page 002-0095) does not agree with the computed coat material as per application procedure (page 002-0126).

(21)Please submit the release specifications and test procedures for the finished Opaspray M-1-7111-8 and for the raw materials since they were not filed in DMF but available to FDA only through the NDA applicant

DOC#3346e/ft/pm/3.7.89.

quired under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.

(Collection of information requirements approved by the Office of Management and Budget under number 0910-0001)

[50 FR 7493, Feb. 22, 1985; 50 FR 14212, Apr. 11, 1985, as amended at 50 FR 21238, May 23, 1985]

§ 314.90 Waivers.

(a) An applicant may ask the Food and Drug Administration to waive under this section any requirement that applies to the applicant under §§ 314.50 through 314.81. An applicant may ask FDA to waive under § 314.126(c) any criteria of an adequate and well-controlled study described in § 314.126(b). A waiver request under this section is required to be submitted with supporting documentation in an application, or in an amendment or supplement to an application. The waiver request is required to contain one of the following:

(1) An explanation why the applicant's compliance with the requirement is unnecessary or cannot be achieved;

(2) A description of an alternative submission that satisfies the purpose of the requirement; or

(3) Other information justifying a waiver.

(b) FDA may grant a waiver if it finds one of the following:

(1) The applicant's compliance with the requirement is unnecessary for the agency to evaluate the application or compliance cannot be achieved;

(2) The applicant's alternative submission satisfies the requirement; or

(3) The applicant's submission otherwise justifies a waiver.

(Collection of information requirements approved by the Office of Management and Budget under number 0910-0001)

[50 FR 7493, Feb. 22, 1985, as amended at 50 FR 21238, May 23, 1985]

Subpart C—FDA Action on Applications

§ 314.100 Time frames for reviewing applications.

(a) Within 180 days of receipt of an application, the Food and Drug Administration will review it and send the applicant either an approval letter under § 314.105, an approvable letter under § 314.110, or a not approvable letter under § 314.120. This 180-day period is called the "review clock."

(b) During the review period an applicant may withdraw an application under § 314.65 and later resubmit it. FDA will then follow the same procedure as if a new application were submitted.

(c) The time period may be extended by mutual agreement between FDA and an applicant or, as provided in § 314.60, as the result of a major amendment.

§ 314.101 Filing an application.

(a) Within 60 days after the Food and Drug Administration receives an application, the agency will determine whether the application may be filed. The filing of an application means that FDA has made a threshold determination that the application is sufficiently complete to permit a substantive review.

(b) If FDA finds that none of the reasons in paragraphs (d) and (e) of this section for refusing to file the application apply, the agency will file the application and notify the applicant in writing. The date of filing will be the date 60 days after the date FDA received the application. The date of filing begins the 180-day period described in section 505(c) of the act. This 180-day period is called the "filing clock."

(c) If FDA refuses to file the application, the agency will notify the applicant in writing and state the reason under paragraph (d) or (e) of this section for the refusal. If FDA refuses to file the application under paragraph (d) of this section, the applicant may request in writing within 30 days of the date of the agency's notification an informal conference with the agency about whether the agency should file the application. If following the informal conference the applicant requests that FDA file the application (with or without amendments to correct the deficiencies), the agency will file the application over protest under paragraph (b) of this section, notify the applicant in writing, and review it as filed. If the application is filed over protest, the date of filing will be the date 60 days after the date the applicant requested the informal conference. The applicant need not resubmit a copy of an application that is filed over protest. If FDA refuses to file the application under paragraph (e) of this section, the applicant may amend the application and resubmit it and the agency will make a determination under this section whether it may be filed.

(d) FDA may refuse to file an application if any of the following applies.

(1) The application does not contain a completed application form.

(2) The application is not submitted in the form required under § 314.50 or § 314.55.

(3) The application is incomplete because it does not on its face contain information required under section 505(b) (1), (2), (3), (4), (5), and (6) or section 507 of the act and § 314.50 or § 314.55.

(4) The applicant fails to submit a complete environmental assessment which addresses each of the items specified in the applicable format under § 25.31 of this chapter or fails to provide sufficient information to establish that the requested action is subject to categorical exclusion under § 25.24 of this chapter.

(5) The application does not contain an accurate and complete English translation of each part of the application that is not in English.

(6) The application does not contain a statement for each nonclinical laboratory study that it was conducted in compliance with the requirements set forth in Part 58, or, for each study not conducted in compliance with Part 58, a brief statement of the reason for the noncompliance.

(7) The application does not contain a statement for each clinical study that it was conducted in compliance with the institutional review board regulations in Part 56, or was not subject to those regulations, and that it was conducted in compliance with the informed consent regulations in Part 50; or, if the study was subject to but was not conducted in compliance with those regulations, the application does not contain a brief statement of the reason for the noncompliance.

(e) The agency will refuse to file an application if any of the following applies:

(1) The drug product that is the subject of the submission is already covered by an approved application.

(2) The submission purports to be an abbreviated application under § 314.55, but the drug product is not one for which FDA has made a finding that an abbreviated application is acceptable under § 314.55(b). FDA will file a copy of the application as a citizen petition under § 10.30 seeking a finding under § 314.55 that an abbreviated application is acceptable for the drug product, and so notify the applicant in writing.

(3) The drug product is subject to licensing by FDA under the Public Health Service Act (58 Stat. 632 as amended (42 U.S.C. 201 et seq.)) and Subchapter F of Chapter I of Title 21 of the Code of Federal Regulations.

(f) (1) Within 180 days after the date of filing, plus the period of time the review period was extended (if any), FDA will either (i) approve the application or (ii) issue a notice of opportunity for hearing if the applicant asked FDA to provide it an opportunity for a hearing on an application in response to an approvable letter or a not approvable letter.

(2) This paragraph does not apply to applications that have been withdrawn from FDA review by the applicant.

[50 FR 7493, Feb. 22, 1985, as amended at 50 FR 16668, Apr. 26, 1985]

§ 314.102 Communication between FDA and applicants.

(a) *General principles.* During the course of reviewing an application, FDA shall communicate with applicants about scientific, medical, and procedural issues that arise during the review process. Such

ie written standard operating
res required under
)(1) shall set forth in suffi-
tail the methods, materials,
edules to be used in the rou-
)ection, cleaning, maintenance,
calibration, and/or standardi-
l equipment, and shall specify,
ppropriate, remedial action to
in the event of failure or mal-
n of equipment. The written
l operating procedures shall
e the person responsible for
ormance of each operation.
ritten records shall be main-
)f all inspection, maintenance,
calibrating and/or standardiz-
ations. These records, contain-
date of the operation, shall de-
whether the maintenance oper-
vere routine and followed the
standard operating proce-
Written records shall be kept of
ine repairs performed on
ent as a result of failure and
ction. Such records shall docu-
he nature of the defect, how
en the defect was discovered,
y remedial action taken in re-
to the defect.

ction collection requirements ap-
by the Office of Management and
nder control number 0910-0203)

60013, Dec. 22, 1978, as amended at
1780, Sept. 4, 1987]

bpart E—Testing Facilities
Operation

Standard operating procedures.

A testing facility shall have
d operating procedures in writ-
ing forth nonclinical laborato-
y methods that management is
l are adequate to insure the
and integrity of the data gen-
n the course of a study. All de-
in a study from standard oper-
rocedures shall be authorized
study director and shall be doc-
d in the raw data. Significant
in established standard oper-
ocedures shall be properly au-
l in writing by management.
tandard operating procedures
established for, but not limit-
e following:
imal room preparation.
imal care.

(3) Receipt, identification, storage, handling, mixing, and method of sampling of the test and control articles.

(4) Test system observations.

(5) Laboratory tests.

(6) Handling of animals found moribund or dead during study.

(7) Necropsy of animals or postmortem examination of animals.

(8) Collection and identification of specimens.

(9) Histopathology.

(10) Data handling, storage, and retrieval.

(11) Maintenance and calibration of equipment.

(12) Transfer, proper placement, and identification of animals.

(c) Each laboratory area shall have immediately available laboratory manuals and standard operating procedures relative to the laboratory procedures being performed. Published literature may be used as a supplement to standard operating procedures.

(d) A historical file of standard operating procedures, and all revisions thereof, including the dates of such revisions, shall be maintained.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987]

§ 58.83 Reagents and solutions.

All reagents and solutions in the laboratory areas shall be labeled to indicate identity, titer or concentration, storage requirements, and expiration date. Deteriorated or outdated reagents and solutions shall not be used.

§ 58.90 Animal care.

(a) There shall be standard operating procedures for the housing, feeding, handling, and care of animals.

(b) All newly received animals from outside sources shall be isolated and their health status shall be evaluated in accordance with acceptable veterinary medical practice.

(c) At the initiation of a nonclinical laboratory study, animals shall be free of any disease or condition that might interfere with the purpose or conduct of the study. If, during the course of the study, the animals contract such a disease or condition, the diseased animals shall be isolated, if necessary.

These animals may be treated for disease or signs of disease provided that such treatment does not interfere with the study. The diagnosis, authorizations of treatment, description of treatment, and each date of treatment shall be documented and shall be retained.

(d) Warm-blooded animals, excluding suckling rodents, used in laboratory procedures that require manipulations and observations over an extended period of time or in studies that require the animals to be removed from and returned to their home cages for any reason (e.g., cage cleaning, treatment, etc.), shall receive appropriate identification (e.g., tattoo, toe clip, color code, ear tag, ear punch, etc.). All information needed to specifically identify each animal within an animal-housing unit shall appear on the outside of that unit.

(e) Animals of different species shall be housed in separate rooms when necessary. Animals of the same species, but used in different studies, should not ordinarily be housed in the same room when inadvertent exposure to control or test articles or animal mixup could affect the outcome of either study. If such mixed housing is necessary, adequate differentiation by space and identification shall be made.

(f) Animal cages, racks and accessory equipment shall be cleaned and sanitized at appropriate intervals.

(g) Feed and water used for the animals shall be analyzed periodically to ensure that contaminants known to be capable of interfering with the study and reasonably expected to be present in such feed or water are not present at levels above those specified in the protocol. Documentation of such analyses shall be maintained as raw data.

(h) Bedding used in animal cages or pens shall not interfere with the purpose or conduct of the study and shall be changed as often as necessary to keep the animals dry and clean.

(i) If any pest control materials are used, the use shall be documented. Cleaning and pest control materials that interfere with the study shall not be used.

(Information collection requirements approved by the Office of Management and Budget under control number 0910-0203)

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987]

Subpart F—Test and Control Articles

§ 58.105 Test and control article characterization.

(a) The identity, strength, purity, and composition or other characteristics which will appropriately define the test or control article shall be determined for each batch and shall be documented. Methods of synthesis, fabrication, or derivation of the test and control articles shall be documented by the sponsor or the testing facility. In those cases where marketed products are used as control articles, such products will be characterized by their labeling.

(b) The stability of each test or control article shall be determined by the testing facility or by the sponsor either: (1) Before study initiation, or (2) concomitantly according to written standard operating procedures, which provide for periodic analysis of each batch.

(c) Each storage container for a test or control article shall be labeled by name, chemical abstract number or code number, batch number, expiration date, if any, and, where appropriate, storage conditions necessary to maintain the identity, strength, purity, and composition of the test or control article. Storage containers shall be assigned to a particular test article for the duration of the study.

(d) For studies of more than 4 weeks' duration, reserve samples from each batch of test and control articles shall be retained for the period of time provided by § 58.195.

(Information collection requirements approved by the Office of Management and Budget under control number 0910-0203)

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33781, Sept. 4, 1987]

§ 58.107 Test and control article handling.

Procedures shall be established for a system for the handling of the test and control articles to ensure that:

(a) There is proper storage.

(b) Distribution is made in a manner designed to preclude the possibility of

.25 Retroactive environmental consid-eration.

) FDA may consider the need for paring an EIS for an existing FDA ulation, approval, or other action, ether or not previously subject to ironmental analysis, when there is information before the agency t suggests that the action may sig-cantly affect the quality of the man environment.

) If FDA notifies an applicant or itioner who obtained an existing A approval that new information gests that the approval may have ificant environmental effects and t an EA is therefore required, the licant or petitioner shall submit an as described in § 25.31 for the ap-val. A notification under this para-ph will be in writing.

Subpart C—Preparation of Environmental Documents

.30 Content and format.

) Sections 25.31 through 25.34 de-ibe the environmental documents t may be required in the course of agency's consideration of the envi-nmental aspects of an action. These tions delineate the relationships of se documents to each other and ir purpose, contents, and format. ditional information concerning the are and scope of information that applicant or petitioner shall submit an environmental document may be ained on a case-by-case basis from e bureau, national center, or other ice of the agency having responsi-ity for the action that is the subject the environmental evaluation. Ap-cants and petitioners are encour-ed to submit proposed protocols for vironmental studies for technical view by agency staff. Applicants and titioners also are encouraged to con-lt applicable FDA environmental as-sment technical guides, which de-ribe protocols for environmental udies and discuss the interpretation sults.

(b) Data and information that are rotected from disclosure by 18 U.S.C. 1905 or 21 U.S.C. 331(j) or 360j(c) shall ot be included in environmental doc-ments prepared under this part. When such data and information are pertinent to the environmental review of a proposed action, an applicant or petitioner may submit such data and information separately as a confidential section of the application or petition, but shall summarize the confidential data and information in the environmental document to the extent possible.

§ 25.31 Environmental assessment formats.

(a) As defined by CEQ in 40 CFR 1508.9, the EA is the public document in which environmental and other pertinent information on a proposed action are presented, providing a basis for the agency's determination whether to prepare an EIS or a FONSI.

(b) An EA shall be prepared in the format presented in this section for each action not categorically excluded in § 25.24. The EA shall be a complete, objective, and well-balanced document that allows the public to understand the agency's decision.

(c) Consistent with 40 CFR 1500.4(j) and 1502.21, EA's may incorporate by reference information presented in other documents that are available to FDA and to the public.

§ 25.31a Environmental assessment for proposed approvals of FDA-regulated products—Format 1.

(a) For proposed actions to approve food or color additives, drugs, biological products, animal drugs, and class III medical devices, and to affirm food substances as generally recognized as safe (GRAS), the applicant or petitioner shall prepare an environmental assessment in the following format:

ENVIRONMENTAL ASSESSMENT

1. *Date:*

2. *Name of applicant/petitioner:*

3. *Address:*

4. *Description of the proposed action:* Briefly describe the requested approval; need for the action; the locations where the products will be produced; to the extent possible, the locations where the products will be used and disposed of; and the types of environments present at and adjacent to those locations.

5. *Identification of chemical substances that are the subject of the proposed action:* Provide complete nomenclature, CAS Reg. No. (if available), molecular weight, structural formulae, physical description, additives, and impurities. This information is required to be adequate to allow accurate location of data about chemicals in the scientific literature and to allow identification of closely related chemicals.

6. *Introduction of substances into the environment:* For the site(s) of production: list the substances expected to be emitted; state the controls exercised; include a citation of, and statement of compliance with, applicable emissions requirements (including occupational) at the Federal, State, and local level; and discuss the effect the approval of the proposed action will have upon compliance with current emissions requirements at the production site(s). Through use of calculations and/or direct measures, estimate to the extent possible the quantities and concentrations of substances expected to enter the environment as a result of use and/or disposal of products affected by the action.

7. *Fate of emitted substances in the environment:* Predict environmental concentrations of and exposures to substances entering the environment as a consequence (direct or indirect) of the use and/or disposal of the products affected by the action for the following environmental compartments, including consideration of the major environmental transport and transformation processes involved:

(a) Air—taking into account, to the extent possible, factors such as volatilization, photochemical and chemical degradation, rainout, and dispersion;

(b) Freshwater, estuarine, and marine ecosystems—taking into account, to the extent possible, factors such as chemical and biological degradation, exchange between the water column and sediments via sorption/desorption and biological processes, accumulation in animals, plants, and other organisms, introductions due to rainfall and losses due to volatilization;

(c) Terrestrial ecosystems—taking into account, to the extent possible, factors such as chemical and biological degradation, sorption/desorption and leaching in soils, accumulation in animals and plants, introductions due to rainfall, losses due to volatilization, and entry into groundwater.

8. *Environmental effects of released substances:* Given the information developed on the introduction (item 6) and fate (item 7) of substances which would be released as a consequence of the use and/or disposal of the products affected by the action, use any relevant toxicological data or other appropriate measures to predict, to the extent applicable, effects on animals, plants, humans, other organisms, and effects at the ecosystem-level in each of the environmental compartments listed in item 7.

9. *Use of resources and energy:* Specify the natural resources, including land use, minerals, and energy, required to produce, transport, use, and/or dispose of a given amount of any product which is the subject of the action, including the resources and energy required to dispose of wastes generated from production, use, and/or disposal. Effects, if any, upon endangered or threatened species and upon property listed in or eligible for listing in the National Register of Historic Places must be discussed.

10. *Mitigation measures:* Describe measures taken to avoid or mitigate potential adverse environmental impacts associated with the proposed action.

11. *Alternatives to the proposed action:* If potential adverse environmental impacts have been identified for the proposed action, describe in detail the environmental impact of all reasonable alternatives to the proposed action (including no action, and including measures that FDA or another government agency could undertake as well as those the applicant/petitioner would undertake). Describe particularly those alternatives that will enhance the quality of the environment and avoid some or all of the adverse environmental impacts of the proposed action. Discuss the environmental benefits and risks of the proposed action. Discuss the environmental benefits and risks of each alternative.

12. *List of preparers:* Those persons preparing the assessment together with their qualifications (expertise, experience, professional disciplines) shall be listed. Persons and agencies consulted shall also be listed.

13. *Certification:* The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm or agency responsible for preparation of the environmental assessment.

(Date) _____

_____

(Signature of responsible official)

(Title) _____

14. *References:* List complete citations for all referenced material. Copies of referenced articles not generally available should be attached.

15. *Appendices:* (a) Data summary sheets (e.g., structural formula, vapor pressure, water solubility, *n*-octanol/water partition coefficient, biodegradation half-life, LC_{50} for each species tested, etc.).

(b) Test reports (for each experiment: research objective, experimental design and procedure, all data relevant to interpretation of the test result given in item 15(a), sample calculations and statistical analyses).

(b) FDA has determined that, for the following actions, certain requirements of the environmental assess-

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[redacted]

ZOLPIDEM TARTRATE R.S.

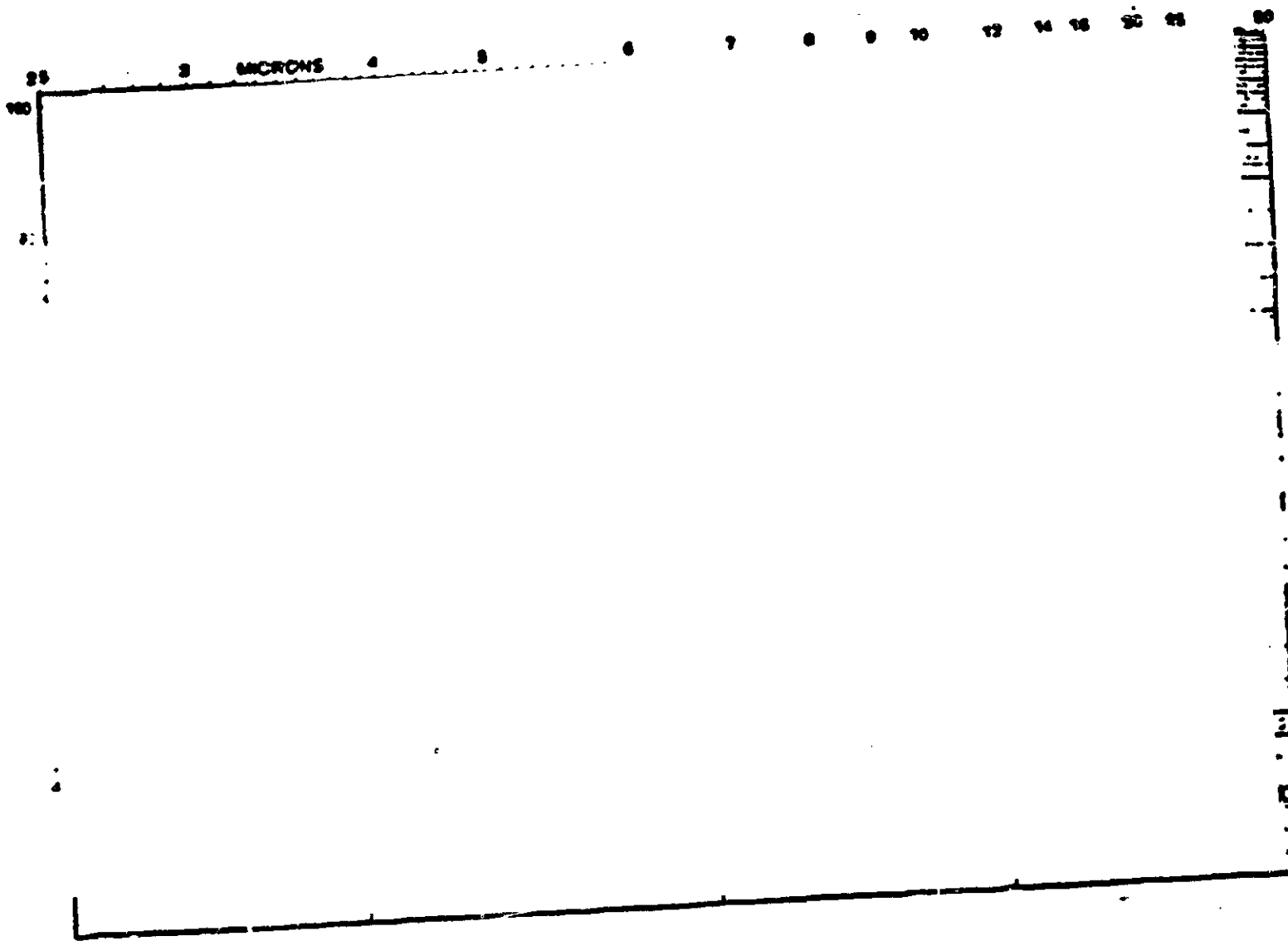
(SL 80.0750-23 N)

Batch : F0750.0236.06

Control : 4567

	RESULTS	SPECIFICATIONS
Description	complies	Off - white crystalline powder
Identification		
. A . IR spectrum	complies	R.S.
. B . UV spectrum	complies	R.S.
. Absorbance : A cm at nm		≃
nm		≃
. C . T.L.C.	complies	R.S.
. D .	complies	Tartrates
Tests		
. Clarity and colour of the solution	complies	A 1/ cm at nm nm
. Optical rotation	*	
. pH		
. Related substances (%)		
Major impurity	less than	Not more than
Other individually	less than	Not more than
. Heavy metals (ppm)	less than	Not more than
. Water content (%)		Not more than
. Residue on ignition (%)	null	Not more than
. Residual solvent : methanol (%)		
Assay (%)		

IR Spectrum of Zolpidem Tartrate (KBr)



Infrared spectrum (KBr)

3420 cm^{-1}:	• OH alcohol (tartrate anion)
2950-2800 cm^{-1}:	• CH_3, CH_2
2800-2000 cm^{-1}:	• NH
1640, 1630 cm^{-1}:	• C=O amide
820, 790 cm^{-1}:	• out of plane bending of adjacent hydrogens on the phenyl ring.

Potential Impurities of Zolpidem Tartrate

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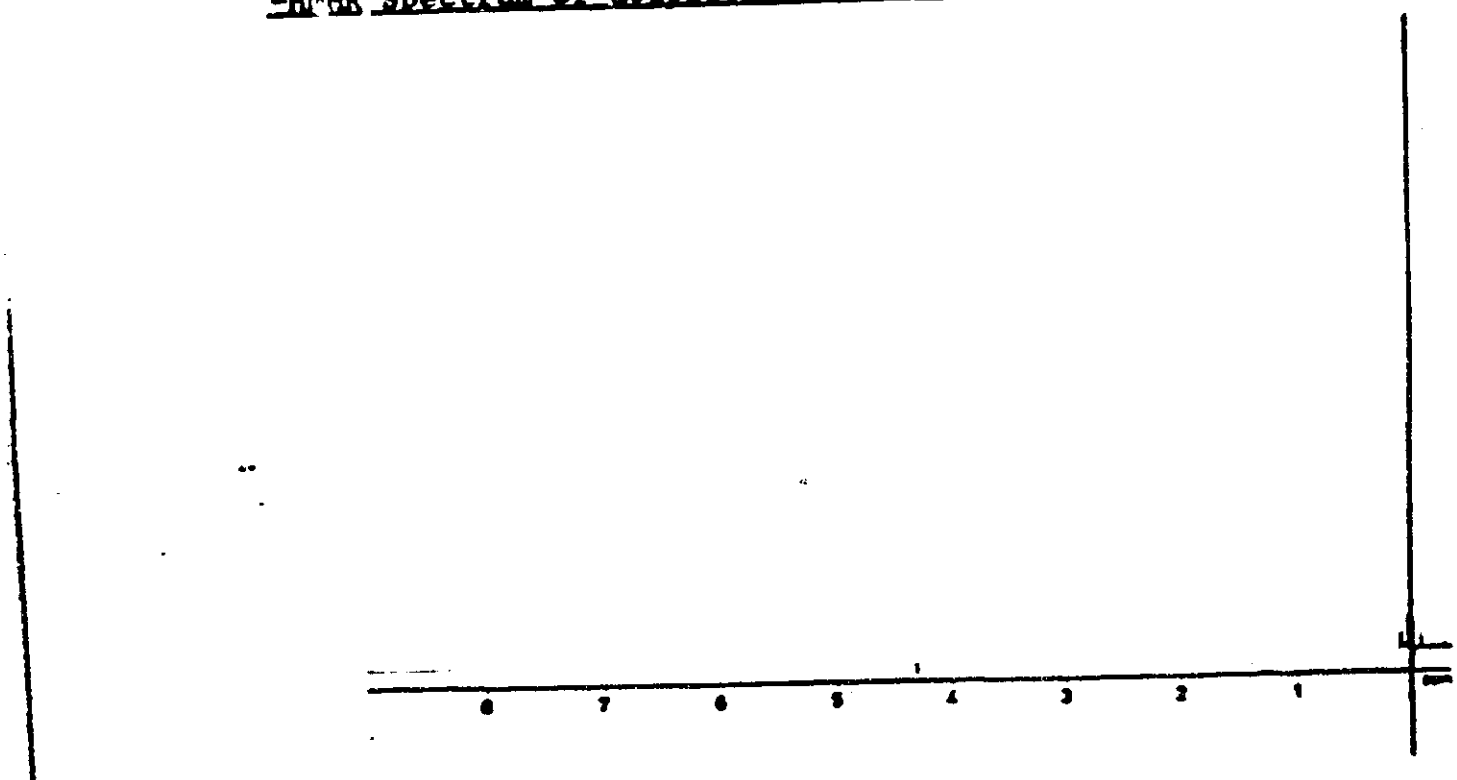
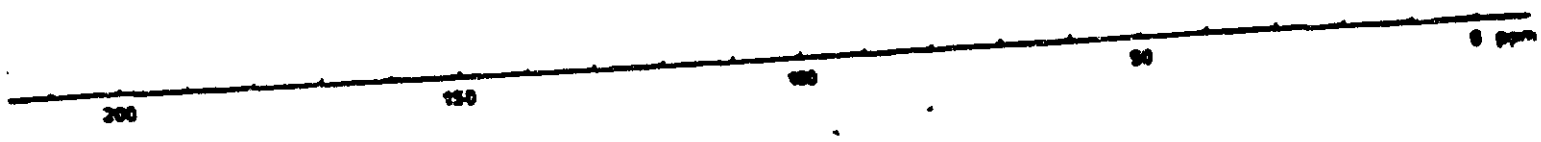
^{1}H NMR Spectrum of Zolpidem Tartrate (DMSO-d_6) (200 MHz)

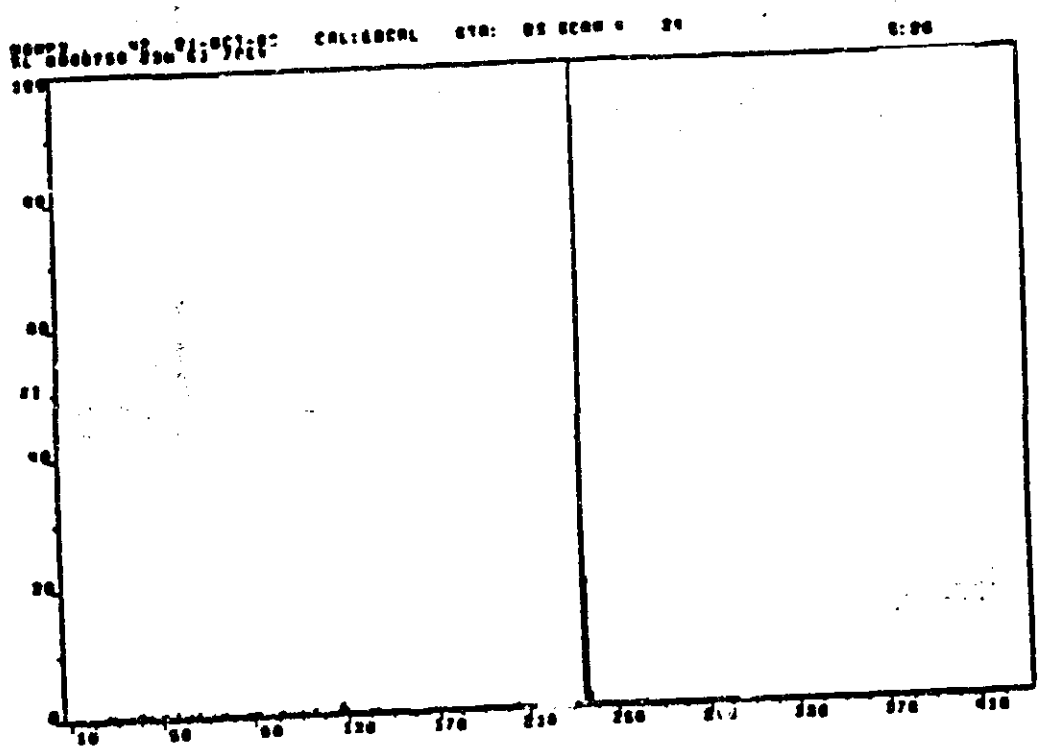


Chemical shift (ppm)	Multiplicity	Number of protons	Attribution
	Broad singlet	1	CH - 5
	AA' part of an AA'XX' system	2	CH - 11, CH - 15
	Doublet (J - 9 Hz)	1	CH - 8
	XX' part of an AA'XX' system	2	CH - 12, CH - 14
	Doublet of doublets (J = 9 Hz and - 1.6 Hz)	1	CH - 7
	Singlet	1	CH proton of one-half equivalent of tartrate anion
	Singlets	2	CH_2 - 16
	2 singlets	6	CH_3 - 18, CH_3 - 19
	2 singlets	6	CH_3 - 13 and CH_3 - 6

^{13}C NMR Spectrum of Zolpidem Tartrate (DMSO-d6)



Mass Spectrum of Zolpidem Tartrate



m/e	Intensity relative to base peak (%)	Presumed structure
307	11.8	Molecular ion ($M^{\cdot+}$)
235	100	$[M-[(CH_3)_2NCO]]^+$
219	8.2	$[M-[(CH_3)_2NCO]-CH_4]^+$
92	14.3	
72	13.6	$(CH_3)_2N-C\equiv O^+$
65	12.9	$C_4H_3N^+$

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INVESTIGATIONAL FORMULATIONS USED IN CLINICAL STUDIES WITH ZOLPIDEM

PG.1

Study	Dosage Form	Formulation**	Strength	Lot No.	NDA LOCATION+			
					PK	Phm	Ct	UCt
LSH01	Capsule	A	10 mg	LP12706				X
	Capsule	A	20 mg	LP12707				
LSH02	Capsule	A	2.5 mg	LP12804	X	X	X	
	Capsule	A	10 mg	LP12706				
	Capsule	A	20 mg	LP12707				
LSH03	Capsule	A	10 mg	LP12706		X		
	Capsule	A	20 mg	LP12707				
LSH04	Capsule	A	10 mg	LP12706		X		
	Capsule	A	20 mg	LP12707				
LSH05	Capsule	A	10 mg	LP12706		X		X
	Capsule	A	20 mg	LP12707				
LSH06	Capsule	A	20 mg	LP12707		X		
LSH07	Capsule	A	10 mg	LP12706				
	Capsule	A	20 mg	LP12707		X		X
LSH08	Capsule	A	2.5 mg	LP12804				
	Capsule	A	10 mg	LP12706 & KLZ05-01C*		X	X	
	Capsule	A	20 mg	LP127[illegible] & XCV05-01C*				
LSH09	Capsule	A	2.5 mg	LP12804		X	X	
	Capsule	A	10 mg	LP12706				
	Capsule	A	20 mg	LP12707				
LSH11	Capsule	A	2.5 mg	LP12706		X	X	
	Capsule	A	10 mg	LP12804				
	Capsule	A	20 mg	LP12707				

+Code: PK= Pharmacokinetics; Phm= Clinical pharmacology; Ct= Controlled trial; Uct= Uncontrolled trial

* -New synthetic process

** -Formulations can be found following tables

					NDA LOCATION*			
Study	Dosage Form	Formulation	Strength	Lot No.	PK	Phm	Ct	UCt
LSH12	Capsule	A	5 mg	DHV05-01A&T DHV05-02A				X
LSH13	Capsule	A	5 mg	DHV05-01A*	[Drug Abuse. Item 8]			
	Capsule	A	10 mg	KLZX5-01C*				
	Capsule	A	20 mg	XCV05-01C*				
LSH14	Capsule	A	5 mg	DHV05-02A	[Drug Abuse. Item 8]			
	Capsule	A	10 mg	KLZ05-01C*				
	Capsule	A	20 mg	XCV05-01C*				
LSH15	Capsule	A	5 mg	DHV05-02A	[Drug Abuse. Item 8]			
	Capsule	A	10 mg	KLZ05-01C*				
	Capsule	A	20 mg	XCV05-01C*				
LSH16	Capsule	A	5 mg	DHV05-02A	[Drug Abuse. Item 8]			
	Capsule	A	30 mg	XCV05-01C*				
LSH17	Capsule	A	5 mg	DHV05-01A&T DHV05-02A		X	X	
	Capsule	A	10 mg	KLZ05-01C*			-	
LSH19	Capsule	A	5 mg	DHV05-01A&T DHV05-02A		X	X	
	Capsule	A	10 mg	KLZ05-01C				

PG.3

Study	Protocol #	Dosage Form	Formulation	Strength	Lot No.	NDA LOCATION+ PK	Phm	Ct	UCt
Albin	IFR24	Tablet	C	20 mg	LP12565-E	X			
Apoil	IIFR09	Capsule	A	20 mg	LP12299			X	
Bercoff	IFR20	Capsule	A	20 mg	LP12209	X	X		
Blatrix	IFR13	Capsule Capsule Capsule	A A A	5 mg 10 mg 20 mg	LP12068 LP12202 LP12113		X		
Borbely	ICH03	Capsule Capsule	A A	10 mg 20 mg	LP13123 LP13125		X		
Bouchet	IFR12	Injectable Ampule	B	5 mg/5 ml	LP12295	X	X		
Cirignotta	IIIT06	Capsule	A	20 mg	LP12299		X		
Colle	IFR42	Tablet	C	10 mg	LP13118-E	X	X		
Colle	IFR44	Tablet	C	10 mg	LP13118-E	X	X		
Collignon	IIBE02	Tablet	C	10 mg	TGB 20-04A		X		
Coupez	IBE01	Capsule Capsule Capsule	A A A	5 mg 10 mg 20 mg	LP12006 LP12005 LP11948	X	X		
Coupez	IBE02	Capsule	A	20 mg	LP12113	X	X		
Coupez	IBE04	Capsule	A	20 mg	LP12299	X	X		
Coupez	IIBE01	Capsule	A	20 mg	LP12299		X	X	
Court	IFR05	Capsule	A	20 mg	LP12209		X		

						NDA LOCATION+			
Study	Protocol #	Dosage Form	Formulation	Strength	Lot No.	PK	Phm	Ct	UCt
Doyard	IIFR15	Capsule	A	2.5 mg	LP12718				X
		Capsule	A	5 mg	LP12323				
		Capsule	A	7.5 mg	LP12719				
		Capsule	A	10 mg	LP12298				
		Capsule	A	12.5 mg	LP12766				
		Capsule	A	15 mg	LP12428				
Dupuy	IIIFR07	Capsule	A	10 mg	LP12298			X	
		Capsule	A	20 mg	LP12299				
		Tablet	C	20 mg	LP12599-E				
Emeriau	IFR25	Capsule	A	20 mg	LP12209	X	X		
Emeriau	IIFR05	Capsule	A	5 mg	LP12323		X		X
		Capsule	A	10 mg	LP12298				
		Capsule	A	15 mg	LP12319				
		Capsule	A	20 mg	LP12299				
		Capsule	A	25 mg	LP12320				
		Capsule	A	30 mg	LP12300				
Emeriau	IIIFR10	Capsule	A	10 mg	LP12607		X	X	
		Capsule	A	20 mg	LP12299				
Ferreri	IIIFR01	Capsule	A	20 mg	LP12608			X	
Feuerstein	IFR04	Capsule	A	10 mg	LP12111		X		
		Capsule	A	20 mg	LP12113				
Forette	IFR34	Injectable Ampule	B	1 mg/ml	LP12295	X	X		
		Tablet	C	10 mg	LP12456-E				
Forster	ICH05	Injectable Ampule	B	5 mg/ml	LP13043	X	X		
Gaillard	ICH01	Capsule	A	10 mg	LP12111		X		
		Capsule	A	20 mg	LP12209				
Grilliat	IFR22	Capsule	A	20 mg	LP12299		X		
Hamdy	IIGB08	Capsule	A	10 mg	LP12111				X
		Capsule	A	20 mg	LP12209				

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PG.5

Study	Protocol #	Dosage Form	Formulation	Strength	[illegible] No:	NDA LOCATION+ PK	Phm	Ct	UCt
Harvengt	IBE03	Capsule	A	20 mg	LP12209	X	X		
Harvengt	IBE05	Tablet	C	20 mg	LP12599-E	X	X		
Herrmann	IIGE06	Capsule	A	20 mg	LP12299		X		X
Kumaer	IIGE02/03	Capsule	A	5 mg	LP12323		X		X
		Capsule	A	10 mg	LP12298				
		Capsule	A	15 mg	LP12319				
		Capsule	A	20 mg	LP12229				
		Capsule	A	25 mg	LP12320				
		Capsule	A	30 mg	LP12300				
		Capsule	A	35 mg	LP12321				
		Capsule	A	40 mg	LP12301				
Kunstler	IIIBE01	Capsule	A	20 mg	LP12299		X	X	
Kurtz	IFR38	Tablet	C	10 mg	LP12558-E	X	X		
Lambert	IFR08	Capsule	A	10 mg	LP12202	X			
Lambert	IFR21	Capsule	A	20 mg	LP12209	X	X		
Laxenaire	IIFR06	Capsule	A	15 mg	LP12319		X	X	
		Capsule	A	30 mg	LP12300				
Lemercier	IIFR17	Tablet	C	20 mg	LP12565-E		X		
Liebau	IIIGE02	Tablet	C	20 mg	LP12666-E		X		X
Linden	IIIGE01	Tablet	C	20 mg	LP12666-E				X
Lorizio	IIIT01/02	Capsule	A	10 mg	LP12202		X	X	
		Capsule	A	20 mg	LP12113				
Lorizio	IIIT04	Capsule	A	20 mg	LP12299		X		X

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PG.6

Study	Protocol #	Dosage Form	Formulation	Strength	Lot No.	NDA LOCATION* PK	Phm	Ct	UCt
Maarek	IIFR10	Capsule	A	20 mg	LP12299		X	X	
Maarek	IIIFR11	Tablet	C	20 mg	LP12649-E				X
Maggioni	IIIT03	Capsule	A	20 mg	LP12299		X	X	
Maillard	IFR27	Capsule Capsule	A A	10 mg 20 mg	LP12478 LP12209	X	X		
Meyer	IFR39	Tablet	C	10 mg	LP12558-E	X	X		
Monti	IIUR01	Tablet	C	10 mg	LP12558-E		X		X
Nicholson	IGB02/08	Capsule	A	10 mg	LP12202		X		
Olive	IFR31	Tablet	C	20 mg	LP12572-E	X			
Oswald	IIGB01	Capsule Capsule	A A	10 mg 20 mg	LP12111 LP12209		X	X	
Pacific	IIT01				[NAp - SEE REPORT]	X			
Pagot	IIIFR04	Capsule	A	20 mg	LP12608			X	
Perret	IIFR01	Capsule Capsule	A A	10 mg 30 mg	LP12111 LP12174& LP12198		X	X	
Pointel	IFR43	Tablet Injectable Ampule	C B	10 mg 10 mg	LP13118-E LP13042	X	X		
Ribeyre	IIFR11	Capsule	A	20 mg	LP12299			X	

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PG.7

						NDA LOCATION+			
Study	Protocol #	Dosage Form	Formulation	Strength	Lot No.	PK	Phm	Ct	UCt
Richens	IGB03	Capsule	A	5 mg	LP12323	X	X		
		Capsule	A	10 mg	LP12298				
		Capsule	A	20 mg	LP12299				
Rizzo	IIITOS	Capsule	A	10 mg	LP12298		X		
		Capsule	A	20 mg	LP12299				
Roger	IFR10	Capsule	A	5 mg	LP12068		X	X	
		Capsule	A	10 mg	LP12202				
		Capsule	A	20 mg	LP12113				
		Capsule	A	30 mg	LP12277				
Roger	IIIFR08	Tablet	C	20 mg	LP12599-E		X		X
Roger	IIIFR18	Capsule	A	5 mg	LP13122		X	X	
		Capsule	A	10 mg	LP13123				
Rulliere	IFR01	Capsule	A	20 mg	LP12299	X	X		
Ruther	IGE01	Capsule	A	10 mg	LP12202		X	X	
		Capsule	A	20 mg	LP12751				
Shaw	IIGB10	Capsule	A	10 mg	LP12298			X	
		Capsule	A	20 mg	LP12299				
Simon	IFR29/35	Capsule	A	20 mg	LP12299		X		
Terzaro	IITO2	Tablet	C	10 mg	LP12558-E		X	X	
Thebault	IFR02	Capsule	A	20 mg	LP12113		X		
Thebault	IFR03	Capsule	A	20 mg	LP11948		X		
Thebault	IFR06	Capsule	A	20 mg	LP12113		X		
Thebault	IFR09	Capsule	A	20 mg	LP12209	X			
Thebault	IFR11	Capsule	A	20 mg	LP12113	X			

						NDA LOCATION			
Study	Protocol #	Dosage Form	Formulation	Strength	Lot No.	PK	Phm	Ct	UCt
Thebault	IFR17	Capsule	A	20 mg	LP12113	X			
Thebault	IFR23	Capsule	A	20 mg	LP12299		X		
Thebault	IFR30	Tablet	C	20 mg	LP12666-E	X			
Torhorst	IIGE01	Capsule	A	15 mg	LP12344				
		Capsule	A	30 mg	LP12357				X
Valla	IIFR02	Capsule	A	10 mg	LP12111			X	
		Capsule	A	20 mg	LP12113				
Vandel	IFR26	Capsule	A	20 mg	LP12299		X		
Vandel	IFR28	Tablet	C	20 mg	LP12565-E	X	X		
Warrington	IGB01	Capsule	A	20 mg	LP12299	X			
Warrington	IGB05	Capsule	A	20 mg	LP12299		X		
Warrington	IGB09	Capsule/Tablet	A/C	10 mg	LP12607	X	X		
		Tablet	C	20 mg	LP12572-E& LP12465-E				
		Injectable Ampule	B	1 mg ml	LP12295				
Wheatley	IIIGB01	Capsule	A	10 mg	LP12111 & LP12202		X	X	
		Capsule	A	20 mg	LP12113 & LP12209				