

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-998**

**CHEMISTRY REVIEW(S)**

**NDA 21-998**

**Plan B One-Step**

**Gedeon Richter**

**Donna F. Christner, Ph.D.**

**Review Chemist**

**Office of New Drug Quality Assessment  
Division of Premarketing Assessment II  
Branch III**

**CMC REVIEW OF NDA 21-998  
For the Division of Reproductive and Urologic Products (HFD-580)**

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# Chemistry Review Data Sheet

1. NDA 21-998
2. REVIEW #: 2
3. REVIEW DATE: 01-Jun-2009
4. REVIEWER: Donna F. Christner, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original submission	24-Jan-2006
Amendment	20-Jun-2006
Amendment	16-Aug-2006
Amendment	13-Oct-2006
Amendment	19-Oct-2006

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Complete Response	09-Jan-2009
Amendment	19-May-2009
Amendment	06-Jun-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Gedeon Richter, Ltd
Address:	Gyomroi ut 19-21 H-1103 Budapest Hungary
Representative:	Michele G. Walsh One Belmont Ave, 11 <sup>th</sup> floor Bala Cynwyd, PA 19004
Telephone:	610-747-2600

**8. DRUG PRODUCT NAME/CODE/TYPE:**

- a) Proprietary Name: Plan B One-Step
- b) Non-Proprietary Name (USAN): Levonorgesterol
- c) Code Name/# (ONDC only): LNG
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 3
  - Submission Priority: S

**9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)**

**10. PHARMACOL. CATEGORY: Progestin/Emergency Contraception**

**11. DOSAGE FORM: Tablet**

**12. STRENGTH/POTENCY: 1.5 mg**

**13. ROUTE OF ADMINISTRATION: Oral**

**14. Rx/OTC DISPENSED:  Rx  OTC (Rx 17 and younger; OTC above 18)**

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

SPOTS product – Form Completed

Not a SPOTS product

## CHEMISTRY REVIEW

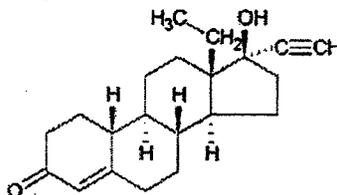
### Chemistry Review Data Sheet

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

**Chemical Names:**

- a. (-)-13-Ethyl-17-hydroxy-18,19-dinor-17 $\alpha$ -pregn-4-en-20-yn-3-one  
 b. 18,19-Dinorpregn-4-en-20-yn-3-one. 13-ethyl-17-hydroxy-(17 $\alpha$ )-(-)-

US Adopted Name (USAN): Levonorgestrel  
 International Non-Proprietary Name (INN): Levonorgestrel  
 Other Names: D-Norgestrel



Chemical Formula:  $C_{21}H_{28}O_2$   
 Molecular Weight: 312.45  
 CAS Registry Number: 797-63-7

#### 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
8806	II	Gedeon Richter, Ltd	Levonorgestrel	1	Adequate	02-Jun-2009	
					Adequate	11-Jul-1999	Reviewed by D. Lin. Information taken from CMC Review # 1
					Adequate	14-Dec-1995	Reviewed by R. Trimmer. Information taken from CMC Review # 1

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

**CHEMISTRY REVIEW**

**Chemistry Review Data Sheet**

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-045	Plan B (levonorgestrel) 0.75 tablets-formulation contains gelatin

**18. STATUS:**

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	ACCEPTABLE	02-Feb-2009	S. Adams
Pharm/Tox	N/A		
ClinPharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMEPA	ACCEPTABLE	01-May-2009	L. Toombs
EA	ACCEPTABLE	13-Nov-2006	M. Cooper, Ph.D.
Microbiology	N/A		

# The Chemistry Review for NDA 21-998

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This submission was a COMPLETE RESPONSE to an Approvable letter. All CMC issues were resolved in the first cycle, except for labeling issues that were deferred.

This NDA can be APPROVED from a CMC standpoint. The Office of Compliance has made an overall ACCEPTABLE recommendation for all manufacturing and testing sites. Labeling is adequate.

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

There are no Phase 4 commitments.

### II. Summary of Chemistry Assessments

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

The drug substance is Levonorgestrel. Full information is provided in DMF 8806. Information is adequate.

Information concerning the drug product is transferred from CMC Review # 1, by Monica Cooper, Ph.D, dated 13-Nov-2006.

##### Drug Product

Levonorgestrel 1.5 mg Tablets are round, \_\_\_\_\_, almost-white tablets, which contain levonorgestrel, colloidal silicon dioxide, potato starch, magnesium stearate, talc, corn starch, and lactose monohydrate. \_\_\_\_\_

b(4)

b(4)

Thus, the tablets are dose-proportional. The drug product is packaged in PVC/Aluminum blisters.



## CHEMISTRY REVIEW

### Executive Summary Section

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

Levonorgestrel 1.5 mg tablets will be supplied in one commercial configuration – a single PVC/Aluminum blister containing one tablet within a folded carton. The drug product will be dosed as one tablet taken once within 72 hours of unprotected sex.

#### **C. Basis for Approvability or Not-Approval Recommendation**

This NDA can be APPROVED from a CMC standpoint. The Office of Compliance has made an overall ACCEPTABLE recommendation for all manufacturing and testing sites. Labeling is adequate.

### **III. Administrative**

#### **A. Reviewer's Signature**

#### **B. Endorsement Block**

Donna F. Christner, Ph.D./08-Jun-2009  
Moo-Jhong Rhee, Ph.D./Date  
Jennifer Mercier/Date

#### **C. CC Block**

6 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

**CHEMISTRY REVIEW TEMPLATE**

Chemistry Assessment Section

13-MAR-2009

FDA CDER EES

Page 1 of 2

**ESTABLISHMENT EVALUATION REQUEST**

**SUMMARY REPORT**

Application : NDA 21998/000      Sponsor: GEDEON RICHTER  
Org Code : 580      ONE BELMONT AVE 11TH FLOOR  
Priority : 3S      BALA CYNWYD, PA 19004

Stamp Date : 24-JAN-2006      Brand Name : LEVONORGESTREL 1.5MG  
PDUFA Date : 12-JUL-2009      Estab. Name:  
Action Goal :      Generic Name: LEVONORGESTREAL 1.5MG TABLETS  
District Goal: 13-MAY-2009      Dosage Form: (TABLET)  
Strength : 1.5 MG

FDA Contacts: P. LUCARELLI      Project Manager (HFD-580)      301-796-2130  
D. CHRISTNER      Review Chemist      301-796-1341  
M. RHEE      Team Leader      301-796-1440

---

Overall Recommendation: ACCEPTABLE on 10-FEB-2009 by S. ADAMS (HFD-325)  
301-796-3193

ACCEPTABLE on 06-MAR-2006 by S. ADAMS (HFD-325) 301-796-  
3193

**CHEMISTRY REVIEW TEMPLATE**

Chemistry Assessment Section

Establishment : CFN : 9610154      FEI : 3002806761

GEDEON RICHTER LTD.

GYOMROI UT 19-21

BUDAPEST, , HU

DMF No:                              AADA:

Responsibilities:    DRUG SUBSTANCE MANUFACTURER

FINISHED DOSAGE LABELER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE OTHER TESTER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Profile    :    CSN                      OAI Status:    NONE

Last Milestone:    OC RECOMMENDATION

Milestone Date:    03-FEB-09

Decision    :    ACCEPTABLE

Reason     :    BASED ON PROFILE

Profile    :    TCM                      OAI Status:    NONE

**CHEMISTRY REVIEW TEMPLATE**

**Chemistry Assessment Section**

**Last Milestone: OC RECOMMENDATION**

**Milestone Date: 10-FEB-09**

**Decision : ACCEPTABLE**

**Reason : DISTRICT RECOMMENDATION**

---

**Establishment: CFN : 9611779 FEI : 3002806762**

**GEDEON RICHTER LTD.**

**ESZTERGOMI UT 27**

**DOROG, , HU**

**DMF No: AADA:**

**Responsibilities: DRUG SUBSTANCE MANUFACTURER**

**FINISHED DOSAGE OTHER TESTER**

**Chemistry Assessment Section**

13-MAR-2009

FDA CDER EES

Page 2 of 2

**ESTABLISHMENT EVALUATION REQUEST**

**SUMMARY REPORT**

**Profile : CSN OAI Status: NONE**

**Last Milestone: OC RECOMMENDATION**

**Milestone Date: 03-FEB-09**

**Decision : ACCEPTABLE**

**Reason : BASED ON PROFILE**

**Profile : CTX OAI Status: NONE**

**Last Milestone: OC RECOMMENDATION**

**Milestone Date: 03-FEB-09**

**Decision : ACCEPTABLE**

**Reason : BASED ON FILE REVIEW**

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

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/s/

-----  
Donna Christner  
6/16/2009 02:26:30 PM  
CHEMIST

Hard copy signed off on 03-Jun-2009. Minor changes made  
as per your review.

Moo-Jhong Rhee  
6/16/2009 02:29:04 PM  
CHEMIST  
Chief, Branch III

**NDA 21-998**

**TRADENAME  
(levonorgestrel) Tablets**

**Gedeon Richter, Ltd.  
Division of Reproductive and Urologic Products**

**Monica D. Cooper, Ph.D.  
ONDQA Pre-Marketing Assessment  
Division II/Branch III**

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# Chemistry Review Data Sheet

1. NDA 21-998

2. REVIEW #: 1

3. REVIEW DATE: 13-Nov-2006

4. REVIEWER: Monica D. Cooper, Ph.D.

5. PREVIOUS DOCUMENTS:

**Previous Documents**

None

**Document Date**

6. SUBMISSION(S) BEING REVIEWED:

**Submission(s) Reviewed**

NDA 21-998 (N000)

NDA 21-998 (N000 BZ)

NDA 21-998 (N000 BZ)

NDA 21-998 (N000 BC)

NDA 21-998 (N000 BC)

**Document Date**

24-Jan-2006

20-Jun-2006

16-Aug-2006

13-Oct-2006

19-Oct-2006

**CHEMISTRY REVIEW**

## Chemistry Review Data Sheet

**7. NAME & ADDRESS OF APPLICANT:**

**Name** Gedeon Richter, Ltd.  
Gyomroi ut 19-21  
**Address** H-1103 Budapest  
Hungary  
Joseph A. Carrado, VP of Clinical Reg. Affairs  
**Representative** Duramed Research, Inc.  
One Belmont Ave., 11<sup>th</sup> Floor  
Bala Cynwyd, PA 19004  
**Telephone** 610-747-2600

**8. DRUG PRODUCT NAME/CODE/TYPE:**

<b>Proprietary Name</b>	<b>TRADENAME*</b>
<b>Non-Proprietary Name (USAN)</b>	Levonorgestrel
<b>Code Name</b>	LNG
<b>Chemistry Type</b>	5 (New Formulation)
<b>Submission Priority</b>	S

\* The tradename for this drug product is currently pending. This issue will be addressed in the resubmission.

**9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)**

**10. PHARMACOL. CATEGORY:** Progestin/Emergency Contraceptive

**11. DOSAGE FORM:** Tablets

**12. STRENGTH/POTENCY:** 1.5 mg

**13. ROUTE OF ADMINISTRATION:** Oral

**14. Rx/OTC DISPENSED:**  Rx  OTC

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

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

\_\_\_\_\_ SPOTS product – Form Completed

X  Not a SPOTS product

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

#### Chemical Names:

- a. (-)-13-Ethyl-17-hydroxy-18,19-dinor-17 $\alpha$ -pregn-4-en-20-yn-3-one
- b. 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-(17 $\alpha$ )-(-)-

US Adopted Name (USAN):

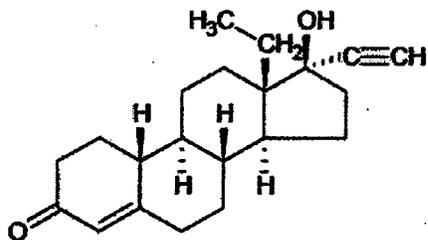
Levonorgestrel

International Non-Proprietary Name (INN):

Levonorgestrel

Other Names:

D-Norgestrel



Chemical Formula:

$C_{21}H_{28}O_2$

Molecular Weight:

312.45

CAS Registry Number:

797-63-7

**CHEMISTRY REVIEW**

## Chemistry Review Data Sheet

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
8806	II	Gedeon Richter Ltd	Levonorgestrel Drug Substance	3	Adequate	11-Oct-2006	Reviewed by M. Cooper
					Adequate	11-Jul-1999	Reviewed by D. Lin
					Adequate	14-Dec-1995	Reviewed by R. Trimmer

b(4)

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type I DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

## B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-045	Plan B® (levonorgestrel) 0.75 mg Tablets – formulation contains gelatin

**CHEMISTRY REVIEW**

## Chemistry Review Data Sheet

## 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	06-Mar-2006	S. Adams
LNC	N/A	----	----
Methods Validation	<i>To be initiated post-approval.</i>	----	----
ODS DMETS	Trade Names <i>Plan B</i> <del><i>Plan B</i></del> and _____ were Not Acceptable*	17-Aug-2006 and 20-Oct-2006	J. Jahng
EA	Categorical Exclusion Acceptable	See Review Date Above	M. Cooper
Microbiology	N/A	----	----

\* The tradename for this drug product is currently pending. This issue will be addressed in the resubmission.

b(4)

# The Chemistry Review for NDA 21-998

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This new drug application (21-998) is recommended for **APPROVAL** from the perspective of chemistry, manufacturing, and controls. All deficiencies identified during the NDA review cycle have been resolved.

The Office of Compliance has given an overall acceptable recommendation for the manufacturing and testing facilities.

Pending labeling issues will be addressed in the resubmission.

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

There are no Phase 4 commitments.

### II. Summary of Chemistry Assessments

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

Levonorgestrel is a well-characterized progestin that is the active component of numerous approved contraceptive drug products. This NDA has been submitted for the use of oral Levonorgestrel 1.5 mg tablets as an emergency contraceptive for use after a contraceptive accident or unprotected sex.

b(4)

#### Drug Substance

Levonorgestrel is the single enantiomer (D) of the racemic (D,L) norgestrel. It is a white to almost white crystalline powder that is practically insoluble in water, soluble in chloroform, and sparingly soluble in ethanol and methylene chloride. It has a melting range of 232 – 239°C and a specific optical rotation  $[\alpha_D^{20}]$  between -30° and -35° in c = 2% (m/V) chloroform solution. *Note:* These parameters distinguish

## CHEMISTRY REVIEW

### Executive Summary Section

levonorgestrel from racemic norgestrel. The literature and the manufacture's experiences have shown no evidence of polymorphism.

The current manufacturer (Gedeon Richter Ltd) has been manufacturing levonorgestrel since 1987 and the current reaction route was developed in 1990. The drug substance has a USP monograph and the proposed specifications are in accordance with the current levonorgestrel monograph. All proprietary information was referenced to DMF 8806, which was found adequate (See Review #13, M. Cooper). A retest has been established for the drug substance when stored at controlled room temperature, protected from light.

b(4)

#### Drug Product

Levonorgestrel 1.5 mg Tablets are round, almost-white tablets, which contain levonorgestrel, colloidal silicon dioxide, potato starch, magnesium stearate, talc, corn starch, and lactose monohydrate.

b(4)

Thus, the tablets are dose-proportional. The drug product is packaged in PVC/Aluminum blisters.

The applicant identified the critical manufacturing steps to be

b(4)

The sponsor includes a specification for in the drug product release specifications and levels are below ICH Q3C recommendations. The applicant validated their manufacturing process, showing that content uniformity, assay, and dissolution are equivalent to the approved Plan B® product. The applicant modified their dissolution specifications from that of the approved Plan B® 0.75 mg tablets [paddles at 75 rpm, NLT (Q) at 30 minutes] to

b(4)

The applicant was asked to provide dissolution profiles to justify this change in the 74-Day letter sent on 20-Mar-2006 and again in an Information Request letter dated 11-Jul-2006. The applicant provided the dissolution profiles in an Amendment dated 16-Aug-2006 (N000 BZ). However, the results did not support the time point. A fax was sent to the applicant on 08-Sep-2006 asking for any available dissolution data at the 30 minute time point during stability studies. In an Amendment dated 13-Oct-2006 (N000 BC), the applicant provided additional dissolution data at the 30-minute time point for the three primary drug product batches and for the three supportive drug product batches during stability studies. These data further supported that the 30-minute time point would be the appropriate time point for assessing dissolution of the drug product. In a teleconference on 17-Oct-2006 [and in the Amendment dated 19-Oct-2006 (N000 BC)] the applicant agreed to revise the acceptance criteria for dissolution to NLT (Q) in 30 minutes.

b(4)

Levonorgestrel 1.5 mg Tablets showed good stability in studies conducted out to 36 months, when stored in the primary packaging at controlled room temperature

## CHEMISTRY REVIEW

### Executive Summary Section

(25°C/60% RH). Hence, the applicant's request for a \_\_\_\_\_ expiration date for the drug product should be granted.

b(4)

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

Levonorgestrel 1.5 mg tablets will be supplied in one commercial configuration – a single PVC/Aluminum blister containing one tablet within a folded carton. The drug product will be dosed as one tablet taken once within 72 hours of unprotected sex.

#### C. Basis for Approvability or Not-Approval Recommendation

This new drug application (21-998) is recommended for **APPROVAL**. The manufacturing processes, specifications, and facilities (EES) are adequate to assure the quality of the drug product. There are no outstanding issues with regard to chemistry, manufacturing, and controls. Pending labeling issues will be addressed in the resubmission.

### III. Administrative

#### A. Reviewer's Signature

/s/ M.D. Cooper, Ph.D.

#### B. Endorsement Block

CMC Reviewer:	Monica D. Cooper, Ph.D.
Pharmaceutical Assessment Lead:	Donna Christner, Ph.D.
Branch Chief:	Moo-Jhong Rhee, Ph.D.

#### C. CC Block

Original NDA 21-998  
HFD-580 Division File

51 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)



# CHEMISTRY REVIEW TEMPLATE

## Chemistry Assessment Section

Profile : TCM OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 06-MAR-06  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

---

Establishment : CPN : 9611779 FEE : 3002806762  
GEDON RICHTER LTD  
ESZTERGOMI UT-17  
DOROG, HU

DMP No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER  
FINISHED DOSAGE OTHER TESTER

Profile : CSN OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 06-MAR-06  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION  
Profile : TCM OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 06-MAR-06  
Decision : ACCEPTABLE  
Reason : DISTRICT RECOMMENDATION

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### IV. List Of Deficiencies To Be Communicated

None.

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

/s/

-----  
Monica Cooper  
11/13/2006 05:52:59 PM  
CHEMIST

Moo-Jhong Rhee  
11/14/2006 08:41:53 AM  
CHEMIST  
Chief, Branch III

**NDA FILEABILITY CHECKLIST**

**NDA Number: 21-998      Applicant: Gedelon Richter      Stamp Date: 24-Jan-2006**  
**Drug Name: Levonorgestrel, 1.5 mg**

**IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) Yes**

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

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	x		
2	Is the section indexed and paginated adequately?	x		
3	On its face, is the section legible?	x		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	x		
5	Is a statement provided that all facilities are ready for GMP inspection?	x		
6	Has an environmental assessment report or categorical exclusion been provided?	x		
7	Does the section contain controls for the drug substance?	x		
8	Does the section contain controls for the drug product?	x		
9	Has stability data and analysis been provided to support the requested expiration date?	x		24 months of data is provided in support of 24 month expiry
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		No CMC information requested at preNDA meeting
11	Have draft container labels been provided?	x		
12	Has the draft package insert been provided?	x		
13	Has an investigational formulations section been provided?	x		
14	Is there a Methods Validation package?	x		
15	Is a separate microbiological section included?	x		

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.

Filing Review by: Donna Christner, Ph.D.

Date: 16-Feb-2006

Assigned Review Chemist: Monica Cooper, Ph.D.

Date: 16-Feb-2006

PAL: Donna F. Christner, Ph.D.

Date:

cc:

Original NDA 21-998  
HFD580/Division File  
HFD-580/MCooper/DChristner/MRhee  
HFD-580/NCrisostomo  
HFD-580/DShames

NDA Number: 21-998 Applicant: Gedeon Richter Drug Name: Levonorgestrel, 1.5 mg

Have all DMF References been identified?

DMF Number	Holder	Description	LOA Included	Status
8806	Gedeon Richter	Levonorgestrel	Yes	Adequate as of 12-Jul-2005 for ANDA 75-796 by Dr. U. Atwal
			Yes	Adequate as of 11-Jul-1999 for NDA 21-045 by Dr. D. Lin
			Yes	Adequate as of 14-Dec-1995 for <del>          </del> by Dr. R. Trimmer

b(4)

b(4)

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/  
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Donna Christner  
3/3/2006 05:01:31 PM  
CHEMIST

Fileability checklist

Moo-Jhong Rhee  
3/7/2006 09:52:26 AM  
CHEMIST  
Chief, Branch III

Initial Quality Assessment  
Branch III  
Pre-Marketing Assessment Division II

**OND Division:** Division of Reproductive and Urologic Products  
**NDA:** 21-998  
**Applicant:** Gedeon Richter Ltd  
**Stamp Date:** 24-Jan-2006  
**PDUFA Date:** 24-Nov-2006  
**Trademark:** None submitted  
**Established Name:** Levonorgestrel  
**Dosage Form:** Tablet, 1.5 mg  
**Route of Administration:** Oral  
**Indication:** Emergency Contraception

**PAL:** Donna F. Christner, Ph.D.

	YES	NO
<b>ONDQA Fileability:</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<b>Comments for 74-Day Letter</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

## Summary and Critical Issues:

### A. Summary

NDA 21-998 is for Levonorgestrel, 1.5 mg tablet, for Emergency Contraception. The approved product (Plan B, NDA 21-045) is a 0.75 mg tablet with a dosing regimen of 2 tablets taken 12 hours apart. The 1.5 mg tablet would be taken once. The formulation is dose proportional, but \_\_\_\_\_ which is already in the formulation. Stability up to 24 months is provided, and a 24 month expiry requested.

b(4)

The sponsor references DMF 8806 for Drug Substance information.

### B. Critical issues for review

The sponsor has based the development and specifications for this drug product on their approved drug product.

They have identified the critical drug product manufacturing steps to be \_\_\_\_\_ of the tablets, and other critical parameters to be the packaging of the dosage form.

b(4)

The sponsor has modified their dissolution specification from the approved product (Paddles at 75 RPM with release of NLT (Q) at 30 minutes) and has not provided adequate justification for this change. \_\_\_\_\_ Data will need to be provided to assure that dissolution specifications are set to assure drug product quality.

b(4)

### **C. Comments for 74-Day Letter**

*Please provide the dissolution profile data to support the dissolution release specification of NLT*

b(4)

### **D. Review, Comments and Recommendation:**

A pre-NDA meeting was held on 13-Dec-2005. There were no CMC issues. Monica Cooper was the assigned reviewer. Since she is up-to-date on the application, it is recommended that she be assigned as the primary reviewer.

#### **DRUG SUBSTANCE**

*The information provided in the application and the referenced DMF is adequate for review of the NDA. The Annual Report will need to be reviewed to determine if any changes were made since the last review of the DMF.*

*There are no comments to send to the sponsor or holder at this time. The primary reviewer will determine if additional information is required during the NDA review.*

#### **DRUG PRODUCT**

*The information provided in the application and the referenced DMFs is adequate for review of the NDA. The DMFs will need to be checked to see if any updates for these specific components have been submitted, and a review done if there have been changes.*

*The sponsor has not provided adequate justification for their dissolution specification. The sponsor should provide the dissolution profile data on which they based their dissolution release specification. This recommendation will be included in the 74-day letter.*

*The primary reviewer will determine if additional information is required during the NDA review.*

\_\_\_\_\_  
Donna F. Christner, Ph.D.  
Pharmaceutical Assessment Lead

\_\_\_\_\_  
Date

\_\_\_\_\_  
Moo-Jhong Rhee, Ph.D.  
Branch Chief

\_\_\_\_\_  
Date

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Draft Labeling (b5)

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/s/

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Donna Christner  
3/3/2006 04:59:39 PM  
CHEMIST

Initial Quality Assessment

Moo-Jhong Rhee  
3/6/2006 11:57:43 AM  
CHEMIST  
Chief, Branch III