

EXHIBIT 12



45 Horse Hill Road
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June 7, 2002

REVISED
Response to FDA Request for Information
Sent by Facsimile

Jane A. Dean, RN, MSN
Project Manager
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
FOOD and DRUG ADMINISTRATION
Attention: Document Control Room
9201 Corporate Boulevard, HFD-550
Rockville, MD 20857

Re: NDA #13-217/S-044
Skelaxin (metaxalone) Tablets

Dear Ms. Dean,

Reference is also made to our meeting yesterday via telephone conference. Also representing FDA were E. Dennis Bashaw, Pharm.D., Carmen DeBellis, R.Ph., and Jang-Ik Lee, Pharm.D., and also representing Elan was Michael C. Scaife, Ph.D., Vice President, Global Regulatory Affairs. The purpose of the meeting was to discuss the labeling text included in the May 31, 2002 approval letter to the above referenced supplement.

Elan expressed concern that the May 31, 2002 approval letter (which was published on June 3, 2002 on the FDA web site) was not reflective of the discussions that had occurred between the FDA and Elan. Although the letter states that the labeling text presented was agreed upon, it was not consistent with our understanding of the agreed text with respect to both inclusions and omissions.

We are very heartened that Dr. Bashaw has indicated that he wishes to rapidly conclude upon a mutually agreeable Pharmacokinetics section to be included in the labeling text for Skelaxin.

We understood from yesterday's discussion that the Agency was in broad agreement with the information contained within our submission dated April 25, 2002, with the caveat that the Agency would like Elan to propose some language to relate the PK findings to the possible clinical relevance, although it was mutually acknowledged that there no clinical data available that could provide specific guidance. To this end we have taken the labeling text from the approval letter that was sent to Elan by facsimile on May 31, 2002, and have proposed some minor modifications which have been highlighted by bold, italicized print.

Pharmacokinetics

In a single center, randomized, two-period crossover study with 42 healthy volunteers (31 males, 11 females), a single 400 mg SKELAXIN (metaxalone) tablet was administered under both fasted and fed conditions.

An analysis of variance (ANOVA) on the log transformed data demonstrated at the 5% level of significance that the co-administration of one SKELAXIN (metaxalone) 400 mg tablet with food statistically significantly increased the rate (C_{max}) and extent ($AUC_{(0-t)}$ and $AUC_{(0-inf)}$) of absorption of SKELAXIN (metaxalone) as compared with the same dose administered in the fasting state. Food also delayed the time to maximum plasma concentration (T_{max}) and decreased the mean terminal half-life ($t_{1/2}$). Although a higher C_{max} and AUC were observed after the administration of SKELAXIN (metaxalone) with a standardized high fat meal, the clinical relevance of these effects is unknown.

Under fasted conditions, mean peak plasma SKELAXIN (metaxalone) concentrations (C_{max}) of **865.3** ng/mL were achieved within 3.3 ± 1.2 hours after dosing (T_{max}). SKELAXIN (metaxalone) concentrations declined with mean terminal half-life ($t_{1/2}$) of 9.0 ± 4.8 hours. The mean apparent oral clearance (CL/F) of SKELAXIN (metaxalone) was **68 ± 34** L/h.

In the same study, the administration of a 400 mg SKELAXIN (metaxalone) tablet following a standardized high fat meal showed an increase in the mean C_{max} and the area under the curve ($AUC_{(0-t)}$ and $AUC_{(0-inf)}$) of metaxalone to 177.5%, 123.5% and 115.4%, respectively. The mean T_{max} was also increased to 4.3 ± 2.3 hr, whereas the mean $t_{1/2}$ was decreased to 2.4 ± 1.2 hr. ***The mean apparent oral clearance (CL/F) of SKELAXIN (metaxalone) was 59 ± 29 L/hr.***

The absolute bioavailability of SKELAXIN (metaxalone) tablets is not known. SKELAXIN (metaxalone) is metabolized by the liver and

excreted in urine as unidentified metabolites. The impact of age, gender, hepatic and renal disease on the pharmacokinetics of SKELAXIN (metaxalone) tablets has not been determined at this time.

Please note:

- 1.) the mean CL/F values quoted were derived using the individual $AUC_{(0-inf)}$ values for each subject. (In the May 31, 2002 approval letter the geometric mean of the $AUC_{(0-t)}$ had been used while we had previously employed the geometric mean of the $AUC_{(0-inf)}$. We acknowledge that both approaches were slightly incorrect, hence are modification).*
- 2.) the fasted C_{max} value that is quoted above is the back-transformed value for the geometric mean. In the May 31, 2002 approval letter, the arithmetic mean is quoted – this is inconsistent with the manner in which the other values have been reported.*

As we agreed, we would appreciate having the opportunity of discussing any further modifications that the FDA might care to propose prior to the issuance of the approval letter. We look forward to the speedy resolution of this issue. If you have any questions about this submission, please contact me at (973) 294-2329(T), (973) 294-5329 (F) or Linda.Fischer@elan.com.

Sincerely,



Linda Ballai Fischer
Director, Regulatory Affairs
Biopharmaceuticals
Elan Pharmaceuticals, Inc.

EXHIBIT 13

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC, OPIOID AND DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857



To: Linda Fischer

From: Ms. Nancy M. Halonen, BSN, C.D.E.

Fax: 973-294-5329

Fax: 301-827-2531

Phone: 973-294-2329

Phone: 301-827-2040

Pages: (2)

Date: June 11, 2002

Re: Bio-pharm response to June 7th fax from Elan regarding NDA 13-217/S044 Skelaxin 400 mg

Urgent For Review Please Comment Please Reply Please Recycle

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS
ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND
PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

Hello Linda,

Here is the response from Dennis Bashaw, Bio-Pharm Team Leader regarding your fax of June 7, 2002. Carmen Debellas is in class this morning, so I am sending this fax to you.

Regards,

Nancy Halonen

- 1.) Except where the dosage form/formulation itself is relevant, the drug is referred to by its generic name.
- 2.) The second paragraph in the 6/10/02 version is repetitive of the information in paragraphs three and four. For that reason it has been deleted although much of it has been incorporated into the text.
- 3.) An explanation regarding half-life has been included.

In a single center randomized, two-period crossover study in 42 healthy volunteers (31 males, 11 females), single 400mg SKELAXIN (metaxalone) tablet was administered under both fasted and fed conditions.

Under fasted conditions, mean peak plasma metaxalone concentrations (C_{max}) of 865.3 ng/ml were achieved within 3.3. +/- 1.2 hours after dosing (T_{max}). Metaxalone concentrations declined with a mean terminal half-life ($t_{1/2}$) of 9.2 +/- 4.8 hours. The mean apparent oral clearance (CL/F) of metaxalone was 68 +/- 34 L/h.

In the same study, following a standardized high fat meal, food statistically significantly increased the rate (C_{max}) and extent of absorption (AUC_{0-t} , AUC_{inf}) of metaxalone from SKELAXIN tablets. Relative to the fasted treatment the observed increases were 177.5%, 123.5%, and 115.4%, respectively. The mean T_{max} was also increased to 4.3 +/- 2.3 hours, whereas the mean $t_{1/2}$ was decreased to 2.4 +/- 1.2 hours. This decrease in half-life over that seen in the fasted subjects is felt to be due to the more complete absorption of metaxalone in the presence of a meal resulting in a better estimate of half-life. The mean apparent oral clearance (CL/F) of metaxalone was relatively unchanged relative to fasted administration (59 +/- 29L/hr). Although a higher C_{max} and AUC were observed after the administration of SKELAXIN (metaxalone) with a standardized high fat meal, the clinical relevance of these effects is unknown.

The absolute bioavailability of metaxalone from SKELAXIN tablets is not known. Metaxalone is metabolized by the liver and excreted in the urine as unidentified metabolites. The impact of age, gender, hepatic, and renal disease on the pharmacokinetics of SKELAXIN (metaxalone) has not been determined at this time.

EXHIBIT 14



45 Horse Hill Road
Cedar Knolls, NJ 07927-2003

T (973) 294-2329 F (973) 294-5329

FAX

To Carmen DeBellas, R.Ph.

Fax (301) 827-2531

From Linda Ballai Fischer

Date 6/11/02

Copy

Pages: 8 (including cover)

Subject NDA 13-217 Response to FDA fax dated June 11, 2002 Regarding S-044

Dear Carmen,

Thank you for the quick review of our proposed labeling. We are pleased to accept the text with Dr. Bashaw's comments that were faxed to us today. Attached is a copy of our formal letter to that effect.

Linda

Elan Pharmaceuticals, Inc.
a member of the Elan Group

Warning: This communication is intended only for the use of the individual or entity to which it is addressed and may contain information that is privileged, confidential, and exempt from disclosure under applicable law. If you are not the intended recipient, you are hereby notified that any use, dissemination, distribution, or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by telephone, and return this original message to us at the above address via the mail service. Thank you.



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June 11, 2002

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
FOOD and DRUG ADMINISTRATION
Attention: Document Control Room
9201 Corporate Boulevard, HFD-550
Rockville, MD 20857

Re: NDA #13-217
Skelaxin (metaxalone) Tablets

Dear Mr. DeBellas,

Reference is made to our meeting on June 6, 2002 via telephone conference. Also representing FDA were E. Dennis Bashaw, Pharm.D., Jane Dean, RN, MSN, and Jang-Ik Lee, Pharm.D., and also representing Elan was Michael C. Scaife, Ph.D., Vice President, Global Regulatory Affairs. The purpose of the meeting was to discuss the labeling text included in the May 31, 2002 approval letter to Supplement 044.

Elan expressed concern that the May 31, 2002 approval letter (which was published on June 3, 2002 on the FDA web site) was not reflective of the discussions that had occurred between the FDA and Elan. Although the letter states that the labeling text presented was agreed upon, it was not consistent with our understanding of the agreed text with respect to both inclusions and omissions.

On June 7, 2002, as agreed during the above referenced meeting, Elan provided (by facsimile) an alternate version of the new *Pharmacokinetics* section to be included in the labeling text for Skelaxin. Today we received by facsimile Dr. Bashaw's response to our proposal. We are pleased to accept this latest version (copy attached) that the Agency has proposed. Attached is a copy of our current

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Elan Pharmaceuticals, Inc.
a member of the Elan Group

labeling which has been revised to include this text as the new *Pharmacokinetics* section, and is presented in draft.

We appreciate having had the opportunity to discuss this issue with you and to comment prior to the issuance of the revised approval letter. We thank you for the Agency's commitment to the speedy resolution of this issue.

If you have any questions about this submission, please contact me at (973) 294-2329(T), (973) 294-5329 (F) or Linda.Fischer@elan.com.

Sincerely,

A handwritten signature in black ink, appearing to read 'L. Fischer', with a stylized initial 'L' and 'F'.

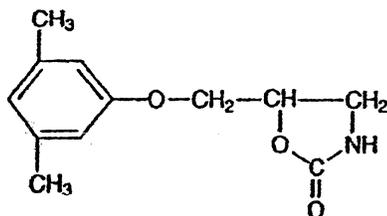
Linda Ballai Fischer
Director, Regulatory Affairs
Biopharmaceuticals
Elan Pharmaceuticals, Inc.

Attachments

SKELAXIN® (Metaxalone)

Description: Each pale rose, scored tablet contains: metaxalone, 400 mg.

Skelaxin® (Metaxalone) has the following chemical structure and name:



5-[(3,5-dimethylphenoxy)methyl]-2-oxazolidinone

Actions: The mechanism of action of metaxalone in humans has not been established, but may be due to general central nervous system depression. It has no direct action on the contractile mechanism of striated muscle, the motor end plate or the nerve fiber.

Indications: Skelaxin® (metaxalone) is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Metaxalone does not directly relax tense skeletal muscles in man.

Pharmacokinetics: In a single center randomized, two-period crossover study in 42 healthy volunteers (31 males, 11 females), a single 400 mg SKELAXIN (metaxalone) tablet was administered under both fasted and fed conditions.

Under fasted conditions, mean peak plasma concentrations (C_{max}) of 865.3 ng/mL were achieved within 3.3 +/- 1.2 hours after dosing (T_{max}). Metaxalone concentrations declined with a mean terminal half-life ($t_{1/2}$) of 9.2 +/- 4.8 hours. The mean apparent oral clearance (CL/F) of metaxalone was 68 +/- 34 L/h.

In the same study, following a standardized high fat meal, food statistically significantly increased the rate (C_{max}) and extent of absorption ($AUC_{(0-t)}$, AUC_{inf}) of metaxalone from SKELAXIN tablets. Relative to the fasted treatment the observed increases were 177.5%, 123.5%, and 115.4%, respectively. The mean T_{max} was also increased to 4.3 +/- 2.3 hours, whereas the mean $t_{1/2}$ was decreased to 2.4 +/- 1.2 hours. This decrease in half-life over that seen in the fasted subjects is felt to be due to the more complete absorption of metaxalone in the presence of a meal resulting in a better estimate of half-life. The mean apparent oral clearance (CL/F) of metaxalone was relatively unchanged relative to fasted administration (59 +/- 29 L/hr). Although a higher C_{max} and AUC were observed after the administration of SKELAXIN (metaxalone) with a standardized high fat meal, the clinical relevance of these effects is unknown.

The absolute bioavailability of metaxalone from SKELAXIN tablets is not known. Metaxalone is metabolized by the liver and excreted in the urine as unidentified metabolites. The impact of age, gender, hepatic, and renal disease on the pharmacokinetics of SKELAXIN (metaxalone) has not been determined at this time.

Contraindications: Metaxalone is contraindicated in individuals who have shown hypersensitivity to the drug. Metaxalone should not be administered to patients with a known tendency to drug induced, hemolytic, or other anemias. It is contraindicated in patients with significantly impaired renal or hepatic function.

Precautions: Elevation in cephalin flocculation tests without concurrent changes in other liver function parameters have been noted. Hence it is recommended that metaxalone be administered with great care to patients with pre-existing liver damage and that serial liver function studies be performed as required.

False-positive Benedict's tests, due to an unknown reducing substance, have been noted. A glucose-specific test will differentiate findings.

Pregnancy: Reproduction studies have been performed in rats and have revealed no evidence of impaired fertility or harm to the fetus due to metaxalone. Reactions reports from marketing experience have not revealed evidence of fetal injury, but such experience cannot exclude the possibility of infrequent or subtle damage to the human fetus. Safe use of metaxalone has not been established with regard to possible adverse effects upon fetal development. Therefore, metaxalone tablets should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgement of the physician the potential benefits outweigh the possible hazards.

Nursing Mothers: It is not known whether this drug is secreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Pediatric Use: Safety and effectiveness in children 12 years of age and below have not been established.

Adverse Reactions: The most frequent reactions to metaxalone include nausea, vomiting, gastrointestinal upset, drowsiness, dizziness, headache, and nervousness or "irritability." Other adverse reactions are: hypersensitivity reaction, characterized by a light rash with or without pruritus; leukopenia; hemolytic anemia; jaundice.

Dosage: The recommended dose for adults and children over 12 years of age is two tablets (800 mg) three to four times a day.

Management of Overdosage: Gastric lavage and supportive therapy as indicated. (When determining the LD₅₀ in rats and mice, progressive sedation, hypnosis and finally respiratory failure were noted as the dosage increased. In dogs, no LD₅₀ could be determined as the higher doses produced an emetic action in 15 to 30 minutes). No documented case of major toxicity has been reported.

How Supplied: Skelaxin® (metaxalone) is available as a 400 mg pale rose tablet, inscribed with 8662 on the scored side and “C” on the other. Available in bottles of 100 (NDC 0086-0062-10) and in bottles of 500 (NDC 0086-0062-50).

Store at Controlled Room Temperature, between 15° C and 30° C (59° F and 86° F).

Rx Only

The most recent revision of this labeling is June 2002.

EXHIBIT 15



DEPARTMENT OF HEALTH & HUMAN SERVICES

APR 6 2004

Food and Drug Administration
Rockville MD 20857

David M. Fox, Esq.
Hogan & Hartson, L.L.P.
Columbia Square
555 Thirteenth Street, NW
Washington, D.C. 20004-1109

Re: Docket No. 2003P-0321/CP1

Dear Mr. Fox:

This letter responds to your citizen petition (Petition) dated July 16, 2003, submitted on behalf of Valeant Pharmaceuticals International (Valeant).¹ You ask that the Food and Drug Administration (FDA) refrain from approving abbreviated new drug applications (ANDAs) under section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)) for generic² Rebetol® (ribavirin) products with labeling that omits information on the use of ribavirin with PEG-Intron® (peginterferon alfa-2b). Petition at 2. You state that a generic Rebetol product that omits information on the use of the product with PEG-Intron would be misbranded under section 502 of the Act (21 U.S.C. 352), and would lack the required approval under section 505 of the Act. Petition at 2. You also claim that "any general guidance the agency is providing to the class of sponsors who may be seeking to market generic ribavirin products, on the issue of labeling and cross labeling, must be provided under the agency's 'good guidance practice' regulations, with an opportunity for public participation." Petition at 2. You request, therefore, that FDA defer action on the labeling of generic ribavirin products until a public process has been initiated and completed on the issues raised in the petition. Petition at 2.

DECISION SUMMARY

Your request that we refrain from approving ANDAs for ribavirin products with labeling that omits information on the use of ribavirin in combination with PEG-Intron is denied. Under the Act, FDA regulations, and case law, the agency may approve ANDAs for ribavirin capsule drug products with labeling that omits protected information on the use of ribavirin in combination with PEG-Intron. We find your argument (*i.e.*, that generic ribavirin capsule drug products are

¹ By letter dated February 11, 2004, you notified the agency that the petition and subsequent filings previously submitted on behalf of ICN Pharmaceuticals, Inc., and Ribapharm Inc. should be regarded as pending under the corporate name Valeant Pharmaceuticals International (Valeant). Comments to your petition were submitted by, among others, Three Rivers Pharmaceuticals, LLC and Par Pharmaceutical, Inc. (3RP/Par), dated July 25, 2003; the Hepatitis C Action & Advocacy Coalition, dated July 29, 2003; and Geneva Pharmaceuticals, Inc. (Geneva), dated July 30, 2003. You submitted a supplement dated July 29, 2003 to your petition. Comments to your supplement were submitted by 3RP/Par, dated August 21, 2003, and by Geneva, dated August 26, 2003. You submitted a response dated October 3, 2003, to these comments. Comments to your October 3 response were submitted by Geneva, dated October 17, 2003, and by 3RP/Par, dated October 24, 2003. Teva Pharmaceuticals, USA, Inc (Teva), also submitted comments dated February 17, 2004, to your petition. You also submitted a supplement dated March 16, 2004, to your petition that primarily responds to Teva's comments. The agency's response to your petition is based on, among other things, a review of these submissions, comments submitted by others, and the administrative record of the relevant ANDAs.

² For brevity, we use the term "generic" in this response to refer to new drug products for which approval is sought in an ANDA submitted under section 505(j) of the Act.

nonetheless intended for use in combination with PEG-Intron) to be not only unpersuasive, but also contrary to law. Insofar as you request a public process in addition to that already accorded under 21 C.F.R. 10.30, we deny your request that FDA defer action on the labeling of generic ribavirin products.

OVERVIEW

In this petition response, we first explain that the agency may approve an ANDA for a ribavirin capsule drug product in accordance with the Act, FDA regulations, and case law. Then we explain why we find your arguments to be unpersuasive. Section I sets forth the background, including the relevant facts and statutory background. Section II sets forth the agency's analysis. Specifically, section IIA explains that the agency may approve an ANDA for a ribavirin capsule drug product with labeling that omits (patent- and exclusivity-) protected information on the use of ribavirin capsules in combination with PEG-Intron. Section IIB explains that FDA's approval of an ANDA for a ribavirin capsule drug product is consistent with other generic drug approval decisions. Section IIC explains why we are not persuaded by the arguments set forth in your petition. Section IID explains why the agency's interpretation is consistent with a fundamental canon of statutory interpretation and the underlying goals of the Hatch-Waxman Amendments. Section IIE explains why no additional public process is necessary. Finally, section III sets forth the agency's summary conclusion.

DISCUSSION

I. BACKGROUND

A. FACTUAL INFORMATION

Schering submitted a new drug application (NDA 20-903) under section 505(b) of the Act for Rebetron® Combination Therapy containing Rebetol (ribavirin, USP) Capsules and Intron® A (interferon alfa-2b, recombinant) Injection.^{3,4} FDA approved NDA 20-903 on June 3, 1998.⁵ By letter sent November 12, 1998, FDA clarified that Rebetol was approved under section 505 of the Act for use in combination with the previously licensed biological product, Intron A. The November 12, 1998, letter also noted that Intron A, as described in footnote 4, had already been licensed under the Public Health Service Act, and was not subject to the section 505 approval process. The "Indications and Usage" section of the Rebetron labeling read: "The combination

³ See "1.8 Description of Special Situations" in *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book), at xxii (stating that ribavirin 200 mg oral capsules are "indicated for use and comarketed with interferon alfa-2b, recombinant (Intron A), as Rebetron Combination Therapy").

⁴ Schering first submitted a biologic license application (BLA) (1013/0) for Intron A as a monotherapy for use in the treatment of hairy cell leukemia. FDA approved this BLA on June 4, 1986. Intron A is currently approved as a monotherapy for a number of other indications (e.g., chronic hepatitis C, malignant melanoma, chronic hepatitis B). Schering submitted a supplemental biologic license application (SBL) (103132/1130) for the use of Intron A in combination with ribavirin capsules in the treatment of chronic hepatitis C. FDA approved this SBL on November 16, 1999, to revise the Intron A package insert to include this use.

⁵ See Approval Letter for NDA 20-903 (June 3, 1998).

therapy of REBETOL (ribavirin, USP) Capsules with INTRON A (interferon alfa-2b, recombinant) Injection is indicated for the treatment of chronic hepatitis C in patients with compensated liver disease who have relapsed following alpha interferon therapy."^{6, 7}

Schering later submitted a supplemental new drug application (NDA 20-903/S-008) seeking approval for stand-alone Rebetol Capsules for use in combination with Intron A. FDA approved supplement S-008 on July 25, 2001.⁸ The "Indications and Usage" section of the original stand-alone Rebetol Capsule labeling read: "REBETOL (ribavirin, USP) Capsules are indicated only in combination with INTRON A (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients with compensated liver disease previously untreated with alpha interferon or who have relapsed following alpha interferon therapy."⁹

On March 6, 2002, approximately 8 months after the approval of stand-alone Rebetol Capsules for use in combination with Intron A, Schering received approval of a supplemental new drug application (NDA 20-903/S-20) for the use of Rebetol Capsules in combination with PEG-Intron.^{10, 11, 12} The "Indications and Usage" section of the Rebetol Capsule labeling read:

REBETOL (ribavirin, USP) Capsules are indicated in combination with INTRON A (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients with compensated liver disease previously untreated with alpha interferon or who have relapsed following alpha interferon therapy.

REBETOL Capsules are indicated in combination with PEG-INTRON

⁶ See Product Labeling for Rebetron Combination Therapy containing Rebetol (ribavirin, USP) Capsules and Intron A Injection (attached to Approval Letter dated June 3, 1998, for NDA 20-903).

⁷ A more current "Indications and Usage" section of the Rebetron labeling reads: "REBETOL (ribavirin, USP) Capsules is indicated in combination with INTRON A (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients with compensated liver disease previously untreated with alpha interferon or who have relapsed following alpha interferon therapy." See Product Labeling for Rebetron Combination Therapy containing Rebetol (ribavirin, USP) Capsules and Intron A (interferon alfa-2b, recombinant) Injection (attached to Approval Letter dated July 9, 2003, for NDA 20-903/S-30).

⁸ See Approval Letter for NDA 20-903/S-008, S-011, S-012, S-016 (July 25, 2001). We note that both the Rebetol Capsule component of Rebetron (Rebetol Capsules co-packaged with Intron A) and the stand-alone Rebetol Capsules are approved in NDA 20-903.

⁹ See Product Labeling for Rebetol (ribavirin, USP) Capsules (attached to Approval Letter dated July 25, 2001, for NDA 20-903/S-008, S-011, S-012 and S-016).

¹⁰ Schering submitted a BLA (103949/0) for PEG-Intron as a monotherapy for use in the treatment of chronic hepatitis C in patients not previously treated with interferon alfa who have compensated liver disease and are at least 18 years of age. FDA approved this BLA on January 19, 2001. Schering also submitted an SBL (103949/5002) for the use of PEG-Intron in combination with ribavirin capsules for use in the treatment of chronic hepatitis C. FDA approved this SBL on August 7, 2001.

¹¹ See Approval Letter for NDA 20-903/S-20 (March 6, 2002).

¹² We note that the approval of NDA 20-903/S-20 (incorporating information on the use of Rebetol Capsules in combination with PEG-Intron) occurred seven months after the approval of SBL (103949/5002), which incorporated information on the use of PEG-Intron in combination with ribavirin capsules into the PEG-Intron labeling. That is, FDA initially approved an SBL (103949/5002) on August 7, 2001. Schering did not receive approval for this change to the Rebetol Capsule labeling until March 6, 2002.

Docket No. 2003P-0321/CP1

(peginterferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age.

As a result of this March 6, 2002, approval, Schering received three years of marketing exclusivity (that expires on March 6, 2005) for conducting new clinical investigations essential to the approved use of ribavirin capsules with PEG-Intron.¹³ Schering has also listed method-of-use patents in the Orange Book for, among other things, the method of using Rebetol Capsules in combination with PEG-Intron powder for injection.¹⁴

Schering submitted an NDA for Rebetol (ribavirin, USP) Oral Solution (NDA 21-546), which FDA approved on July 29, 2003.¹⁵ Schering received not only three years of exclusivity (that expires on July 29, 2006) for the new dosage form, but also orphan drug exclusivity for the use of ribavirin in the treatment of chronic hepatitis C in pediatric patients.¹⁶ Schering then submitted a supplemental new drug application (NDA 20-903/S-032) for the inclusion of, among other things, certain pediatric information contained in the Rebetol Oral Solution labeling into the Rebetol Capsule labeling. FDA approved S-032 on October 10, 2003.¹⁷ As a result, Schering received orphan drug exclusivity for the use of ribavirin in the treatment of chronic hepatitis C in pediatric patients. The "Indications and Usage" section of the current Rebetol Capsule labeling reads:

REBETOL (ribavirin, USP) Capsules and Oral Solution are indicated in combination with INTRON A (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients 3 years of age and older with compensated liver disease previously untreated with alpha interferon or in patients 18 years of age and older who have relapsed following alpha interferon therapy.

REBETOL Capsules are indicated in combination with PEG-INTRON (peginterferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age.

¹³ See electronic Orange Book. Specifically, it indicates that three-year exclusivity was accorded for "INCORPORATION OF INFORMATION CONTAINED IN THE PEG-INTRON PACKAGE INSERT INTO THE REBETOL PACKAGE INSERT AND MEDGUIDE-PEG-INTRON WAS APPROVED FOR USE IN COMBINATION WITH REBETOL FOR TREATMENT OF CHRONIC HEPATITIS C VIRUS INFECTION ON 8/7/01."

¹⁴ See electronic Orange Book.

¹⁵ See Approval Letter for NDA 21-546 (July 29, 2003).

¹⁶ We note that FDA's Office of Orphan Products Development (OOPD) granted designation status to ribavirin for treatment of chronic hepatitis C in pediatric patients on April 4, 2003. See electronic Orange Book.

¹⁷ See Approval Letter for NDA 20-903/S-32 (October 10, 2003).

Three Rivers, Geneva, and Teva submitted ANDAs seeking approval to market generic ribavirin capsules.¹⁸ These applications contained paragraph IV certifications pursuant to section 505(j)(2)(A)(vii)(IV) of the Act, asserting that two patents (*i.e.*, '097 and '772) listed by Schering pursuant to section 505(b) of the Act will not be infringed by the manufacture, use, or sale of the generic products and that the patents are invalid and unenforceable. *Id.* ICN (now Valeant) initiated patent suits against Geneva, Three Rivers, and Teva on September 21, 2001, February 5, 2002, and May 24, 2002, respectively. *Id.* On July 14, 2003, the U.S. District Court for the Central District of California issued its decision (entered on July 15, 2003), concluding, among other things, that the manufacturers would not directly infringe certain patents and the manufacturers did not induce infringement of certain patents by physicians. *Id.* The next day you filed your petition asking that FDA refrain from approving ANDAs for ribavirin products.

B. RELEVANT STATUTORY BACKGROUND

1. Summary of Approval Process

Under the Act, sponsors seeking to market innovator drugs must first obtain FDA approval by filing a new drug application (NDA). NDAs contain, among other things, extensive scientific data demonstrating the safety and effectiveness of the drug. *See* sections 505(a), (b) of the Act. The NDA applicant is also required to submit to FDA patent information on any drug substance, drug product, or method of use patent that it claims will protect its exclusive marketing of the drug. Specifically, the sponsor is to submit information on any patent that "claims the drug . . . or a method of using such drug" and for which a claim of patent infringement could reasonably be asserted against an unauthorized party engaged in the manufacture, use, or sale of the drug. *See* sections 505(b)(1), (c)(2) of the Act. FDA is required to publish patent information for approved drugs, and does so, in the Orange Book. *See* sections 505(b)(1), (c)(2), (j)(7) of the Act; 21 C.F.R. 314.53(e). The Act permits the submission of ANDAs for approval of generic versions of approved drug products. *See* section 505(j) of the Act. The ANDA process shortens the time and effort needed for approval by, among other things, allowing the applicant to demonstrate that its drug product is bioequivalent to the innovator drug, rather than reproduce the safety and effectiveness data for the innovator drug. *See Eli Lilly and Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990). The timing of approval of an ANDA depends in part on statutory patent listing, patent certification, and exclusivity protections added to the Act by the 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments), Pub. L. No. 98-417, 98 Stat. 1585 (1984).

2. Summary of NDA Exclusivity

The Act provides different marketing exclusivity periods for drugs approved in NDAs, based on the level of innovation represented by the drug product. While these five- and three-year exclusivity periods are in effect, FDA may not (in some cases) accept or approve certain

¹⁸ *See ICN Pharmaceuticals, Inc., et al. v. Geneva Pharmaceuticals Technology Corp., et al.*, 272 F.Supp.2d 1028 (C.D. Cal. 2003) (noting publicly that Three Rivers, Geneva, and Teva submitted ANDAs for ribavirin capsules).

applications that rely on the protected product for approval. *See* sections 505(c)(3)(E)(ii)-(iv), (j)(5)(F)(ii)-(iv) of the Act.¹⁹

Five-year exclusivity is granted to a drug that contains no active ingredient (including any ester or salt of the active ingredient) previously approved under section 505(b) of the Act. *See* section 505(c)(3)(E)(ii), (j)(5)(F)(ii) of the Act; 21 C.F.R. 314.108. During this five-year period that begins with approval, FDA may not receive for review any ANDA referring to the listed drug with this protection. However, if the NDA holder for the listed drug with five-year exclusivity has submitted a patent for the drug pursuant to section 505(b)(1) or (c)(2) of the Act, an ANDA applicant wishing to challenge that patent may submit an application referencing the listed drug at the end of four years. *See* sections 505(c)(3)(E)(ii), (j)(5)(F)(ii) of the Act; 21 C.F.R. 314.108.

Three-year exclusivity is granted to a drug for which approval of an NDA or NDA supplement requires FDA to review new clinical studies conducted or sponsored by the applicant that are essential to the approval. This exclusivity bars FDA from approving for three years an ANDA referencing the listed drug (or a change to the listed drug) for which the new studies were submitted. *See* sections 505(c)(3)(E)(iii), (iv), (j)(5)(F)(iii), (iv) of the Act; 21 C.F.R. 314.108.

3. Summary of Patent Protection

The proposed drug described in an ANDA may not be finally approved until the patents and marketing exclusivity have expired or until the NDA holder and patent owners for patents on the listed drug²⁰ have had an opportunity to defend their patent rights in court. With respect to each patent submitted by the sponsor for the listed drug and listed in the Orange Book the ANDA applicant must submit to FDA one of four specified certifications. *See* section 505(j)(2)(A)(vii) - (viii) of the Act. The certification must state one of the following:

- (I) that the required patent information relating to such patent has not been filed;
- (II) that such patent has expired;
- (III) that the patent will expire on a particular date; or
- (IV) that such patent is invalid or will not be infringed by the drug for which approval is being sought.

These four certifications are not the only manner in which an ANDA applicant may address all relevant patents. An ANDA applicant may submit a section viii statement acknowledging that a

¹⁹ We note that sections of the Act have been renumbered because of recent amendments. In this response, the statutory cites correspond to the current version of the Act.

²⁰ Under 21 CFR 314.3(b) "[l]isted drug means a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification as a drug with an effective approval in the current edition of FDA's 'Approved Drug Products with Therapeutic Equivalence Evaluations' (the list) or any current supplement thereto, as a drug with an effective approval. A drug product is deemed to be a listed drug on the date of effective approval of the application or abbreviated application for that drug product."

given method of use patent has been listed, but stating that the patent at issue does not claim a use for which the applicant seeks approval. *See* section 505(j)(2)(A)(viii) of the Act. An ANDA applicant submitting a section viii statement is not required to provide notice to the patent owner and NDA holder; and does not face a 30-month stay if the patent owner brings a lawsuit.

If the ANDA applicant does not submit one or more section viii statements or challenge any of the listed patents, the application will not be approved until all the listed patents claiming the listed drug have expired. If an applicant wishes to challenge the validity of a patent or to claim that a patent would not be infringed by the product proposed in the ANDA, the applicant must submit a paragraph IV certification to FDA. The applicant must also provide a notice to the NDA holder and the patent owner stating that the application has been submitted and explaining the factual and legal bases for the applicant's opinion that the patent is invalid or not infringed. *See* sections 505(b)(2)(B), (j)(2)(B) of the Act. The filing of a paragraph IV certification "for a drug claimed in a patent or the use of which is claimed in a patent" is an act of infringement. 35 U.S.C. 271(e)(2)(A). If the patent holder or NDA holder brings a patent infringement suit against the ANDA applicant within 45 days of the date it received notice of the paragraph IV certification, the approval of the ANDA will be stayed for 30 months from the date of such receipt by the patent owner and NDA holder, unless a final court decision is reached earlier in the patent case or the patent court otherwise orders a longer or shorter period. *See* sections 505(c)(3)(C), (j)(5)(B)(iii) of the Act. Thus, under the procedures established in the Hatch-Waxman Amendments, an ANDA will not be approved until all applicable listed drug product exclusivity has expired and the listed patents have expired, have been successfully challenged or carved out by an applicant, or any applicable 30-month stay has expired. *See* 21 C.F.R. 314.107.

II. ANALYSIS

FDA may approve an ANDA for a ribavirin capsule drug product with proposed labeling that omits information on the use of ribavirin capsules in combination with PEG-Intron. It is clear under the Act, FDA regulations, and case law that an ANDA applicant could choose not to seek approval for, and "carve out" from the proposed labeling, the use of ribavirin capsules in combination with PEG-Intron. In fact, you concede in your petition one of the bases for our conclusion; that is, you agree that "[i]t is *settled* that certain specific differences in labeling between the innovator and generic are permitted." Petition at 7 (emphasis added). Accordingly, the first half of the analysis discusses the bases for our conclusion that the agency may lawfully approve an ANDA for a ribavirin capsule drug product with proposed labeling that omits information on the use of ribavirin capsules in combination with PEG-Intron.

Although you effectively concede that one of the bases for the agency's approval of an ANDA for a ribavirin capsule drug product is *settled*, you assert that a generic ribavirin product is subject to "competing statutory requirements," such that the agency may not lawfully approve an ANDA for a ribavirin capsule drug product with proposed labeling that omits information on the use of PEG-Intron. Specifically, you assert that: (1) a generic ribavirin capsule drug product with proposed labeling that omits information on the use of ribavirin capsules in combination with PEG-Intron is nonetheless intended for use in combination with PEG-Intron because the innovator's (*i.e.*, Schering's) PEG-Intron labeling contains information on the use of ribavirin

capsules in combination with PEG-Intron; and (2) because the proposed ribavirin capsule drug product would not be labeled for all the intended uses, it should not be approved because of the "competing statutory requirements that prohibit the marketing of misbranded and unapproved products." Petition at 1. As discussed below, we find your arguments to be unpersuasive.

A. FDA MAY APPROVE AN ANDA FOR A RIBAVIRIN CAPSULE DRUG PRODUCT WITH PROPOSED LABELING THAT OMITTS INFORMATION ON THE USE OF RIBAVIRIN CAPSULES IN COMBINATION WITH PEG-INTRON IN ACCORDANCE WITH THE ACT, FDA REGULATIONS, AND CASE LAW.

Under the Act, FDA regulations, and case law, the agency may approve ANDAs for ribavirin capsule drug products with proposed labeling that omits information protected either by patent or by exclusivity or by both (*i.e.*, information on the use of ribavirin capsules in combination with PEG-Intron) if the agency has determined that the differences in labeling would not render proposed ribavirin capsule drug products less safe or effective than Rebetol Capsules for the adult use of ribavirin capsules in combination with Intron A.²¹

1. *Under the Act, FDA regulations, and case law, FDA may approve an ANDA for a ribavirin capsule drug product with proposed labeling that omits information protected by patent (*i.e.*, information on the use of ribavirin capsules in combination with PEG-Intron).*
 - a. *The Act, FDA regulations, and case law on patent responsibilities for NDA and ANDA applicants authorize an ANDA applicant for ribavirin capsules to exclude from the proposed labeling a method of use protected by a listed patent (*i.e.*, information on the use of ribavirin capsules in combination with PEG-Intron).*

The Act provides that an innovator company must submit to FDA's Orange Book patents claiming a method of using a drug product and that an ANDA applicant may omit from proposed labeling methods of use covered by those patents. Sections 505(b)(1) and (c)(2) of the Act state that innovators must submit patents to FDA that claim the approved drug "or method of using such drug." Specifically, section 505(b)(1) of the Act requires NDA applicants to file as part of the NDA "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or *which claims a method of using such drug* and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." (Emphasis added). Section 505(c)(2) of the Act imposes a similar patent submission requirement on holders of approved NDAs that could not have submitted the patent information with the NDA.

²¹ As noted elsewhere, certain pediatric information is currently protected by orphan exclusivity, but ANDA applicants for generic ribavirin capsule drug products may still receive approval for the adult use of ribavirin capsules in combination with Intron A.

The Act also requires ANDA applicants to make certifications to each listed patent pertaining to the drug they intend to reference. *See* section 505(j)(2)(A)(vii) of the Act; *see also* relevant statutory background section of petition response. The purpose of these certifications is “to give notice, if necessary, to the patent holder so that any legal disputes regarding the scope of the patent and the possibility of infringement can be resolved as quickly as possible.” *See Torpharm, Inc. v. Thompson*, 260 F.Supp.2d 69, 71 (D.D.C. 2003).

However, the Act also allows an ANDA applicant to avoid certifying to a method of use patent by stating that the ANDA applicant is not seeking approval for the method of use claimed in that listed patent and is omitting from its proposed labeling the labeling that corresponds to that method of use. Specifically, section 505(j)(2)(A)(viii) of the Act provides that “if with respect to the listed drug referred to in clause [505(j)(2)(A)(i)] information was filed under subsection (b) or (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, [the ANDA shall contain] a statement that the method of use patent does not claim such a use.” The ANDA applicant seeking to omit a protected method of use from its proposed labeling need not certify to a patent that corresponds to that use, but instead must submit a statement to FDA that it is not seeking approval for a method of use claimed by a listed patent (commonly referred to as “section viii statement”). *See* section 505(j)(2)(A)(viii) of the Act. Accordingly, under the Act, a method of use claimed by a patent is also a method of use that an ANDA applicant may propose to carve out of the labeling.²²

FDA implementing regulations contain a parallel provision at 21 C.F.R. 314.94(a)(12)(iii). Section 314.94(a)(12)(iii) provides that “[i]f patent information is submitted under section 505 (b) or (c) of the [A]ct and § 314.53 for a patent claiming a method of using the listed drug, and the labeling of the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, [the ANDA applicant must submit] a statement explaining that the method of use patent does not claim any of the proposed indications.”²³

²² The agency's interpretation of the plain language of the Act is further supported by Congressional intent as evidenced by the passage below:

...The [ANDA] applicant need not seek approval for all of the indications for which the listed drug has been approved. For example, if the listed drug has been approved for hypertension and angina pectoris, and if the indication for hypertension is protected by patent, then the applicant could seek approval for only the angina pectoris indication.

H.R. Rep. No. 857 (Part I), 98th Cong. 2d sess. 21. Although the example above refers to omission of an indication protected by patent, the plain language of the Act is even more broad in that it refers to patents claiming a *method of use* -- a term which covers indications, dosing regimens, and other approved conditions of using the approved product.

²³ FDA regulations implementing this statutory provision use the term “indications” to refer to what information an ANDA applicant omits from its labeling in the context of submitting a statement that a protected use of a drug is not claimed in a listed patent. *See* 21 C.F.R. 314.94(a)(12)(iii) (subsection titled “Method of use patent”). However, the preambles for the proposed rule and final rule express no intent to distinguish between method of use and indication, and use the terms interchangeably. *See e.g.*, 59 *Fed. Reg.* 50338, 50347 (October 3, 1994). Moreover, the preamble to the final rule emphasizes that an ANDA applicant does not have the option of choosing between a paragraph IV certification and section viii statement; and where the labeling does not include the indication, only the section viii statement is appropriate. *Id.* The preamble to the proposed rule explains that where “the labeling for the applicant's

Accordingly, FDA regulations also expressly recognize that by submitting a section viii statement, an ANDA applicant may carve out from the proposed labeling a method of use protected by a listed patent, and therefore need not seek approval for that use.²⁴

Moreover, courts have explicitly recognized the right of an ANDA applicant to forgo seeking approval for a method of use protected by a listed patent. The D.C. Circuit clearly stated, "A section viii statement indicates that a patent poses no bar to approval of an ANDA because the applicant seeks to market the drug for a use other than the one encompassed by the patent." See *Purepac Pharmaceutical Company v. Thompson*, 354 F.3d 877, 880 (D.C. Cir. 2004). Similarly, another court stated, "A section viii statement avers that the patent in question has been listed, but does not claim a use for which the applicant seeks FDA approval." See *Torpharm, Inc. v. Thompson*, 260 F.Supp.2d 69, 73 (D.D.C. 2003). Both courts have confirmed the agency's interpretation of the statutory provisions discussed above. That is, an ANDA applicant may choose not to seek approval for a method of use protected by a listed patent, and to carve out that method of use from the proposed labeling.

Consistent with the Act, FDA regulations, and case law, it is clear that ANDA applicants for ribavirin capsules could choose not to seek approval for the use of ribavirin capsules in combination with PEG-Intron by submitting a section viii statement and by carving out this use from the proposed labeling. That is, Schering listed patents in the Orange Book covering, among other things, the method of using Rebetol Capsules in combination with PEG-Intron. On one hand, if an ANDA applicant for ribavirin capsules were to include in its proposed labeling a claim that its proposed ribavirin capsule could be used in combination with PEG-Intron, the ANDA applicant could properly file a paragraph IV certification for the patents. If, on the other hand, an ANDA applicant for ribavirin capsules excludes from the proposed labeling information on the use of ribavirin capsules in combination with PEG-Intron, and thereby eliminates the need to challenge those patents before obtaining approval, the ANDA applicant may not properly file a paragraph IV certification. Instead, the ANDA applicant must include in the ANDA a section viii statement explaining that fact. Accordingly, the Act, FDA regulations, and case law expressly allow ANDA applicants for ribavirin capsules to exclude from the proposed labeling the method of using ribavirin capsules in combination with PEG-Intron. As discussed elsewhere in this response, if the agency were to conclude that such information may be omitted from the proposed labeling in the ANDA without rendering the generic ribavirin capsule drug product less

proposed drug product does not include any indications that are covered by the use patent" the ANDA applicant would submit a section viii statement rather than a paragraph IV certification. See 54 Fed. Reg. 28872, 28886 (July 10, 1989). Accordingly, it is clear that an ANDA applicant need not seek approval for a method of use covered by a listed patent.

²⁴ Moreover, the agency recently reiterated this position in the preamble to the final rule titled, *Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug is Invalid or Will Not Be Infringed*. See 68 Fed. Reg. 36676 (June 18, 2003). In the preamble to this final rule, the agency stated that the section viii statement permits an ANDA applicant to "avoid certifying to a patent by stating that it is not seeking approval for the use claimed in the listed patent." *Id.* at 36682. The agency asserted, "our position has been that, for an ANDA applicant to file a section viii statement, it must 'carve-out' from the proposed ANDA labeling, the labeling protected by the listed patent." *Id.* The agency also stated that an ANDA applicant "does not have to seek approval for all uses approved for the reference listed drug." *Id.* at 36685.

safe or effective than Rebetol Capsules for all the remaining, non-protected conditions of use, it would be appropriate for ANDA applicants to carve this information out of the labeling.

- b. Under the Act, FDA regulations, and case law, FDA may approve an ANDA for a ribavirin capsule drug product with proposed labeling that omits information protected by patent (i.e., information on the use of ribavirin capsule in combination with PEG-Intron) because the generic ribavirin capsule drug product would be the same as Rebetol Capsules except for differences permitted by law.*

The conclusion that an ANDA applicant can carve out from the proposed labeling information protected by patent is reinforced by other sections of the statute that anticipate that patent-protected information can be carved out from the proposed labeling of a generic drug product.

- i. A generic ribavirin capsule drug product would have the same conditions of use as Rebetol Capsules except for conditions of use that may be omitted because of an existing patent (i.e., the use of ribavirin capsules in combination with PEG-Intron).*

The Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]." See section 505(j)(2)(A)(i) of the Act. This language reflects Congress' intent that the generic drug be safe and effective for each "condition of use" prescribed, recommended, or suggested in the generic drug labeling. The statute does not require that an ANDA be approved for each condition of use for which the reference listed drug is approved. By regulation, FDA has explicitly provided that a proposed generic drug product must have the same conditions of use as the listed drug, except that "conditions of use for which approval cannot be granted because of . . . an existing *patent* may be omitted." See 21 C.F.R. 314.92(a)(1) (emphasis added).

Accordingly, an ANDA for a ribavirin capsule drug product must contain information to show that it has the same conditions of use prescribed, recommended, or suggested in the proposed labeling as the Rebetol Capsule labeling for the adult use of ribavirin capsules in combination with Intron A. However, an ANDA applicant may omit from the proposed labeling the condition of using ribavirin capsules in combination with PEG-Intron because it is a condition of use for which Rebetol Capsules is approved, but for which there is also an existing patent.

- ii. A generic ribavirin capsule drug product would have the same labeling as Rebetol Capsules except for differences in labeling permitted by law (e.g., differences permitted because generic ribavirin capsules and Rebetol Capsules are produced or distributed by different manufacturers).*

The Act also requires that an ANDA contain "information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug. . . except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the Act] or because the new drug and the listed drug are produced or distributed by different manufacturers." See section 505(j)(2)(A)(v) of the Act. A parallel provision (*i.e.*, section 505(j)(4)(G) of the Act²⁵) appears in the section of the Act setting forth the grounds for not approving an ANDA (*i.e.*, section 505(j)(4) of the Act). Absent from section 505(j)(4) of the Act is a requirement that FDA approve a proposed generic drug unless the generic drug proposed labeling lists every indication or condition of use for which the listed drug has been approved.

Similarly, the regulations at 21 C.F.R. 314.94(a)(8)(iv) require that the "[l]abeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the [generic] drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers." Section 314.94(a)(8)(iv) sets forth examples of permissible differences in labeling that may result because the generic drug product and reference listed drug are produced or distributed by different manufacturers. By regulation the agency has interpreted these differences to include the following:

differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication **or other aspect of labeling protected by patent** or accorded exclusivity under section 505(j)(4)(D) of the Act.

21 C.F.R. 314.94(a)(8)(iv) (emphasis added).²⁶ FDA regulations, under 21 C.F.R. 314.127(a)(7) (on the "Refusal to approve an abbreviated new drug application"), further provide that to approve an ANDA containing proposed labeling that omits "aspects of the listed drug's labeling [because those aspects] are *protected by patent*," the agency must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining non-protected conditions of use" (emphasis added). Moreover, as you acknowledge, "FDA's regulation authorizing the agency to approve generic drug products that omit a protected indication or other *patent-* or *exclusivity-protected* information from the labeling has been upheld in *Bristol-Meyers Squibb Co. v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996)^[27] and in *Sigma-*

²⁵ Section 505(j)(4)(G) of the Act provides that FDA must approve an ANDA unless, among other things, "the information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for [the reference listed drug] except for changes required because of differences approved under [an ANDA suitability petition] or because the drug and the listed drug are produced or distributed by different manufacturers."

²⁶ We note that the reference in section 314.94(a)(8)(iv) to section 505(j)(4)(D) of the Act corresponds to current section 505(j)(5)(F) of the Act due to a series of amendments.

²⁷ In *Bristol-Meyers Squibb*, the innovator (Bristol-Meyers Squibb) marketed the reference listed drug Capoten (captopril), which was approved and labeled with four indications: hypertension, heart failure, left ventricular dysfunction (LVD) after myocardial infarction, and treatment of diabetic nephropathy in patients with type I diabetes mellitus and retinopathy. The ANDA applicant submitted an ANDA for a generic captopril drug product, and referenced Capoten as the listed drug. Accordingly, the generic captopril drug product was required to have the

Tau Pharmaceuticals, Inc. v. Schwetz, 288 F.3d 141 (4th Cir. 2002).^[28] Petition at 7, footnote 10 (emphasis added; and footnotes added).

Consistent with the Act, FDA regulations, and case law (upholding this scheme), a generic ribavirin capsule drug product with proposed labeling that omits information on the use of ribavirin capsules in combination with PEG-Intron would have the "same" labeling as Rebetol Capsules except for difference permitted by law. The Act expressly authorizes ANDA applicants to seek approval for fewer than all of the conditions of use, and permits labeling differences because the generic drug and the listed drug are produced or distributed by different manufacturers. By regulation, FDA has interpreted the Act to permit the omission of aspects of labeling protected by *patent*. Here, information contained in the Rebetol Capsule labeling on the use of ribavirin capsules in combination with PEG-Intron is currently protected by patent. Accordingly, an ANDA applicant for a ribavirin capsule drug product could omit from the proposed labeling information on the use of ribavirin capsules in combination with PEG-Intron; and the generic ribavirin capsule drug product would have the "same" labeling except for differences permitted by law. Further, as discussed elsewhere in this response, FDA may approve an ANDA for a ribavirin capsule drug product, provided that the resulting differences in labeling due to patent protection do not render the generic ribavirin capsule drug product less safe or effective than Rebetol Capsules for the adult use of ribavirin capsule in combination with Intron A.

2. ***Under the Act, FDA regulations, and case law, FDA may approve an ANDA for a ribavirin capsule drug product with proposed labeling that omits information protected by exclusivity.***

The law not only supports FDA approval of an ANDA for a ribavirin capsule drug product with proposed labeling that omits information protected by patent, but the law supports FDA approval of an ANDA for a ribavirin capsule drug product with proposed labeling that omits information

same labeling as Capoten except for certain differences permitted by law. In accordance with the "same labeling" provisions of the Act and FDA regulations, the ANDA applicant excluded from the generic drug labeling the latter two exclusivity-protected indications and corresponding indication-specific dosing information. The court specifically held that omission of an indication protected by exclusivity was a difference in labeling "required . . . because the drug and the listed drug are produced or distributed by different manufacturers" within the meaning of the Act. *Id.* at 1500.

²⁸ In *Sigma-Tau*, the innovator (*i.e.*, Sigma-Tau) challenged FDA approval of generic versions of Carnitor (levocarnitine) by arguing that the generic levocarnitine drugs were intended for use in the treatment of both the orphan-protected (end stage renal disease) and unprotected (inborn metabolic disorders) indications -- despite the fact that the generic levocarnitine drug labeling omitted the orphan-protected, end stage renal disease indication. The innovator argued that the court should consider "compelling, readily available, objective evidence of the generic's intended use, such as market data for Carnitor [levocarnitine], dosage forms, and federal drug reimbursement policies . . ." *Id.* at 145 (internal quotes omitted). The court stated that the innovator's "argument constitute[d] nothing more than another attempt to obtain market exclusivity for any and all uses of its drug, thereby preventing generic competitors from entering the market for any indication. Indeed, the D.C. Circuit rejected [the Carnitor innovator's] proposed interpretation of [section 505(j)(2)(A)(v) of the Act] for primarily this reason in the context of Hatch-Waxman pioneer-drug exclusivity under [section 505(j) of the Act]." *Id.* at 148, footnote 3 (citing *Bristol-Meyers Squibb*).

protected by exclusivity.

- a. *Three-year exclusivity is not a bar to FDA approval of an ANDA for a ribavirin capsule drug product for the existing non-protected conditions of use for which the listed drug is approved (i.e., the adult use of ribavirin capsules in combination with Intron A).*

The Act, FDA regulations, and case law support the approval of an ANDA for a ribavirin capsule drug product with proposed labeling that omits information protected by exclusivity (*i.e.*, information on the use of ribavirin capsules in combination with PEG-Intron). Three-year exclusivity is granted to a drug for which approval of an NDA or NDA supplement requires FDA to review new clinical studies conducted or sponsored by the applicant that are essential to the approval. This exclusivity bars FDA from approving for three years an ANDA referencing the listed drug (or a change to the listed drug) for which the new studies were submitted. *See* sections 505(c)(3)(E)(iii), (iv), (j)(5)(F)(iii), (iv) of the Act; 21 C.F.R. 314.108.

Specifically, the three-year exclusivity provision for NDA supplements (*i.e.*, section 505(j)(5)(F)(iv) of the Act)²⁹ provides three years of exclusivity *only* to "a change approved in the [NDA] supplement" to a previously approved drug, not to the drug as a whole. The plain language of section 505(j)(5)(F)(iv) does not extend any existing patent or exclusivity protection; nor does the plain language of this section prohibit the agency from approving an ANDA for the other remaining, but non-protected, conditions of use for which the listed drug is approved. It merely protects the particular change for which exclusivity was obtained. Thus, FDA will approve an ANDA for a listed drug with three years of exclusivity as long as omission of the labeling protected by exclusivity does not render the generic drug less safe or effective as the listed drug for the remaining, non-protected conditions of use. *See* 21 C.F.R. 314.127(a)(7).

Here, Schering received three years of exclusivity (that will expire on March 6, 2005), in accordance with section 505(j)(5)(F)(iv) of the Act, for the approval of supplement S-20 for the use of ribavirin capsules in combination with PEG-Intron.³⁰ However, this three-year exclusivity is not a bar to FDA approval of an ANDA for a ribavirin capsule drug product for the adult use

²⁹ Section 505(j)(5)(F)(iv) of the Act provides that:

if a supplement to an application approved under subsection (b) is approved after the date of the enactment of this subsection and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make approval of an application submitted under this subsection for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b).

³⁰ Specifically, the electronic Orange Book indicates that 3 year exclusivity was accorded for "INCORPORATION OF INFORMATION CONTAINED IN THE PEG-INTRON PACKAGE INSERT INTO THE REBETOL PACKAGE INSERT AND MEDGUIDE-PEG-INTRON WAS APPROVED FOR USE IN COMBINATION WITH REBETOL FOR TREATMENT OF CHRONIC HEPATITIS C VIRUS INFECTION ON 8/7/01."

of ribavirin capsules in combination with Intron A.

In fact, the D.C. Circuit in *Bristol-Meyers Squibb* has affirmed the agency's interpretation (*i.e.*, that section 505(j)(5)(F)(iv) (formerly section 505(j)(4)(D)(iv) or 505(j)(5)(D)(iv)) of the Act does not prohibit the agency from approving an ANDA for the remaining, but non-protected, conditions of use for which the listed drug is approved). The D.C. Circuit, in affirming the agency's interpretation, stated that section 505(j)(5)(F)(iv) "by its terms, appears to protect the manufacturer of a pioneer drug only against the manufacture of a generic substitute using the pioneer's proprietary research undertaken to obtain approval for a supplemental indication." *Id.* at 1500. That is, section 505(j)(5)(F)(iv) does not protect the innovator against any and all competition for the listed drug.

Not only did the D.C. Circuit affirm the agency's interpretation, but it also specifically rejected the innovator's interpretation of section 505(j)(5)(F)(iv) of the Act that would result in extensions of exclusivity not contemplated by the statute. That is, the court rejected a scenario where "every time a supplemental indication is added to the labeling of a pioneer drug, the manufacturer of the pioneer would get three more years of protection against the approval of any ANDA based upon that pioneer drug, including one that lists only the original indication(s) of the pioneer." *Id.*³¹

Consistent with the goals of the Hatch-Waxman Amendments and *Bristol-Meyers Squibb*, as well as the proper understanding of the notion of intended use, the agency's conclusion (*i.e.*, that it may approve an ANDA for a ribavirin capsule drug product with proposed labeling that omits protected information on the use of ribavirin capsules in combination with PEG-Intron) allows Schering to enjoy the benefits associated with its research in developing a new condition of use -- the use of ribavirin capsules in combination with PEG-Intron. At the same time, the agency's conclusion promotes generic competition for the remaining, non-protected condition of use for which the listed drug is approved -- the adult use of ribavirin capsules in combination with Intron A.

- b. Under the Act, FDA regulations, and case law, FDA may approve an ANDA for a ribavirin capsule drug product with proposed labeling that omits information protected by exclusivity (i.e., information on the use of ribavirin capsules in combination with PEG-Intron) because the generic ribavirin capsule drug product would be the same as Rebetol Capsules except for***

³¹ Similarly, we must reject the intended use theory advanced in your petition that would essentially produce the same result rejected in *Bristol-Meyers Squibb*. That is, assuming *arguendo*: (1) we adopted your intended use theory, and (2) Schering's PEG-Intron labeling misbrands a generic ribavirin capsule drug product because that generic ribavirin capsule drug product is not labeled for all the intended uses, and (3) therefore should not be approved in the first instance -- the result would be three more years of protection against the approval of any ANDA that references Rebetol Capsules, including an ANDA that seeks approval only for the adult use of ribavirin capsules in combination with Intron A. We, like the court in *Bristol-Meyers Squibb*, reject this result in favor of an interpretation that is not only consistent with the Act and FDA regulations, but also promotes the underlying goals of the Hatch-Waxman Amendments.

differences permitted by law.

As discussed above, the Act, FDA regulations, and case law permit certain labeling differences between the proposed generic drug product and the listed drug because of existing patent protection. The Act, FDA regulations, and case law not only allow for differences in labeling due to patent protection, but they also allow for differences in labeling because of exclusivity, as discussed below.

- i. A generic ribavirin capsule drug product would have the same conditions of use as Rebetol Capsules except for conditions of use that may be omitted because of existing exclusivity (i.e., the use of ribavirin capsules in combination with PEG-Intron).*

An ANDA for a ribavirin capsule drug product must contain information to show that it has the same conditions of use prescribed, recommended, or suggested in the proposed labeling as the Rebetol Capsule labeling for the adult use of ribavirin capsules in combination with Intron A. See section 505(j)(2)(A)(i) of the Act. FDA regulations explicitly provide that a proposed generic drug product must have the same conditions of use as the listed drug, except that "conditions of use for which approval cannot be granted because of *exclusivity* . . . may be omitted." See 21 C.F.R. 314.92(a)(1) (emphasis added).

Accordingly, an ANDA applicant may omit from the proposed labeling the condition of using ribavirin capsules in combination with PEG-Intron because it is a condition of use for which Rebetol Capsules is approved and for which Rebetol Capsules has exclusivity under section 505(j)(5)(F)(iv), as discussed above.

- ii. A generic ribavirin capsule drug product would have the same labeling as Rebetol Capsules except for differences in labeling permitted by law (e.g., differences permitted because generic ribavirin capsules and Rebetol Capsules are produced or distributed by different manufacturers).*

As mentioned elsewhere in this response, the Act requires that the proposed generic drug labeling be the same as the listed drug labeling except for differences in labeling because the proposed generic drug and the listed drug are produced or distributed by different manufacturers. See section 505(j)(2)(A)(v) of the Act, and section 505(j)(4)(G) of the Act.

The implementing regulations, under section 314.94(a)(8)(iv) set forth examples of permissible differences in labeling that may result because the generic drug product and reference listed drug are produced or distributed by different manufacturers. These permitted differences include, among other things, "omission of an indication or other aspect of labeling protected by patent or

accorded exclusivity under section 505(j)(4)(D) of the Act.³² See 21 C.F.R. 314.94(a)(8)(iv) (emphasis added).³³ Further, FDA regulations, under 21 C.F.R. 314.127(a)(7) (on the "Refusal to approve an abbreviated new drug application"), provide that to approve an ANDA containing proposed labeling that omits "aspects of the listed drug's labeling [because those aspects] are protected . . . by exclusivity," the agency must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use." (Emphasis added).

A generic ribavirin capsule drug product with labeling that omits information on the use of ribavirin capsules in combination with PEG-Intron would have the "same" labeling as Rebetol Capsules except for differences permitted by law (*i.e.*, differences due to the drugs being produced or distributed by different manufacturers). FDA has interpreted this provision of the Act by regulation to include differences in labeling because those aspects of the labeling are "accorded exclusivity" under section 505(j)(5)(F) of the Act. Rebetol Capsules and generic ribavirin capsules would be produced or distributed by different manufacturers. As explained above, information contained in Schering's Rebetol Capsule labeling on the use of ribavirin capsules in combination with PEG-Intron is currently protected by three-year exclusivity under section 505(j)(5)(F) of the Act. Accordingly, this information falls squarely under the permitted differences in labeling set forth in sections 505(j)(2)(A)(v), (j)(4)(G) of the Act, and 21 C.F.R. 314.94(a)(8)(iv). Further, FDA may approve an ANDA for a ribavirin capsule drug product provided the differences in labeling due to exclusivity protection do not render the proposed ribavirin capsule drug products less safe or effective than Rebetol Capsules for the adult use of ribavirin capsule in combination with Intron A.

As you concede in your petition, "FDA's regulation authorizing the agency to approve generic drug products that omit a protected indication or other patent- or exclusivity- protected information from the labeling has been upheld in *Bristol-Meyers Squibb Co. v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996) and in *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002)." Petition at 7, footnote 10. Specifically, in *Bristol Meyers Squibb*, the court upheld the agency's interpretation of section 505(j)(2)(A)(v) of the Act, and implementing regulations (*e.g.*, 21 C.F.R. 314.94(a)(8)(iv) and 21 C.F.R. 127(a)(7)), as permitting the agency to approve an ANDA for a generic drug with labeling that excluded exclusivity-protected indications and corresponding indication-specific dosing information for which the reference-listed drug was approved.

3. ***Generic ribavirin capsule drug products are no less safe or effective than Rebetol Capsules when information on the use of ribavirin capsules in combination with PEG-Intron is omitted from the generic drug labeling.***

³² As noted elsewhere in this response, the reference in section 314.94(a)(8)(iv) to section 505(j)(4)(D) of the Act corresponds to current section 505(j)(5)(F) of the Act due to a series of amendments.

³³ See generally *Zeneca, Inc. v. Shalala*, 213 F.3d 161 (4th Cir. 2000).

As discussed above, FDA may approve an ANDA for a proposed ribavirin capsule drug product, provided that the labeling differences (due to the fact that information is protected by patent or exclusivity) do not render the generic ribavirin capsule drug product less safe or effective than Rebetol Capsules for "all remaining, non-protected conditions of use." Accordingly, the relevant question is whether a generic ribavirin capsule drug product, when labeled to exclude protected information (*e.g.*, information on the use of ribavirin capsules in combination with PEG-Intron), will be rendered less safe or effective than Rebetol Capsules for the adult use of ribavirin capsules in combination with Intron A. *See* 21 C.F.R. 314.127(a)(7).³⁴

You assert in your petition that proposed generic ribavirin products that carve out from the Medication Guide information on PEG-Intron present a high risk of medication error. Petition Supplement dated October 3, 2003, at 8-9. You state that if an ANDA applicant for generic ribavirin capsule drug products is permitted to carve out information from the proposed Medication Guide on the use of ribavirin capsules in combination with PEG-Intron, then even "if only one patient who is prescribed the PEG-Intron/Rebetol combination receives generic Rebetol in place of the brand-name product, that patient will have been placed at risk for a serious medication error. The patient will be directed by the PEG-Intron Medication Guide to follow the instructions in the Rebetol or ribavirin Medication Guide. The patient will, in turn, be directed by the generic's Medication Guide to use a higher dose of ribavirin than is necessary." *Id.* at 8-9. You state that while the PEG-Intron labeling would instruct on the use of an 800 mg dosing schedule, the ribavirin product would instruct the patient to use a 1000 - 1200 mg dosing schedule. Petition at 12. You claim that the "potential for erroneous dosing and for confusion is manifest." *Id.* By making these statements, you claim, in effect, that the omission of PEG-Intron information from the generic Rebetol product labeling would render the generic ribavirin capsules product less safe than Rebetol.

After reviewing the relevant information, the agency has concluded that a generic ribavirin capsule drug product with labeling that excludes information on the use of ribavirin capsules in combination with PEG-Intron would not render the generic ribavirin capsule drug product less safe or effective than Rebetol Capsules for the adult use of ribavirin capsules in combination with Intron A (*i.e.*, the remaining, non-protected conditions of use). The generic ribavirin capsule drug product labeling would be the same as the Rebetol Capsule labeling for the adult use of ribavirin capsules in combination with Intron A. When FDA approved NDA 20-903, the agency determined that Rebetol Capsules are safe and effective for the adult use of Rebetol Capsules in combination with Intron A; and Rebetol Capsules are required to have adequate directions for the adult use of ribavirin capsules in combination with Intron A. Accordingly, a generic ribavirin capsule drug product (with labeling that excludes information on the use of

³⁴ We note that in *Zeneca v. Shalala*, 213 F.3d 161, at 169 (4th Cir. 2000), the court, in upholding both FDA's interpretation involving section 314.94(a)(8)(iv) and FDA's labeling decision, noted that "FDA's judgments as to what is required to ascertain the safety and efficacy of drugs falls squarely within the ambit of the FDA's expertise and merit deference from us" (internal citations omitted). Similarly, we note that FDA's determination – that labeling for a generic ribavirin capsule drug product that omits information on the use of ribavirin capsules with PEG-Intron renders the generic drug product no less safe or effective than Rebetol Capsules – is based on FDA's experience and expertise in reviewing labeling and making judgments with respect to the safety and effectiveness of drugs.

ribavirin capsules in combination with PEG-Intron) would still be as safe and effective as Rebetol Capsules for the adult use of ribavirin capsules in combination with Intron A.

Further, the Medication Guide for PEG-Intron clearly states that "**If you are taking PEG-Intron/ REBETOL combination therapy, also read the Medication Guide for Rebetol (ribavirin, USP) Capsules**" (emphasis added). The current Medication Guide for Rebetol Capsules expressly states, "Your health care provider has determined the correct dose of REBETOL Capsules or Oral Solution based on your weight. Your health care provider may lower your dose of REBETOL if you have side effects. It is important to follow your dosing schedule and your health care provider's instructions on how to take your medicines." A generic ribavirin capsule Medication Guide would include the same information. Thus, the Medication Guide would clearly instruct health care providers and patients to be mindful of proper dosing.

Assuming *arguendo* the health professional or patient mistakenly refers to the generic ribavirin capsule drug product labeling for dosing information on ribavirin capsules in combination with PEG-Intron, the dosing information on the use of ribavirin capsules in combination with PEG-Intron would be notably absent. That is, the labeling would not contain information on the use of an 800 mg dosing schedule corresponding to the use of ribavirin capsules in combination with PEG-Intron. The generic ribavirin capsule drug product labeling would only contain dosing information corresponding to the adult use of ribavirin capsules in combination with Intron A. The PEG-Intron package insert (as you acknowledge) includes the proper dosing information on the use of ribavirin capsules in combination with PEG-Intron. Petition at 3-4. We also note that the PEG-Intron labeling specifically refers to *Rebetol* or *Rebetol (ribavirin, USP)* by name in instances where the health professional or patient is instructed to refer to additional information on the use of PEG-Intron in combination with Rebetol Capsules.³⁵ The agency does not believe that the exclusion from the proposed generic ribavirin capsule drug labeling of information on the use of ribavirin capsules in combination with PEG-Intron would render a generic ribavirin capsule drug product less safe or effective than Rebetol Capsules for the remaining, non-protected conditions of use.

Further, as noted elsewhere in this response, the agency has approved other generic drug products (e.g., captopril) with labeling that omits protected indications and corresponding indication-specific dosing regimens (finding that omission of such information would not render the generic captopril products less safe or effective than Capoten (captopril) for the remaining, non-protected conditions of use). Although, here, you set forth some speculative and conclusory statements, you do not provide any evidence that a generic ribavirin capsule drug product with labeling that omits information on the use of ribavirin capsules in combination with PEG-Intron would be less safe or effective than Rebetol Capsules for the adult use of ribavirin capsules in combination with Intron A.

³⁵ We also note that Schering's Rebetol Capsule labeling also includes information on the use of Rebetol Oral Solution, which is *not* currently approved for use in combination with PEG-Intron. Although the PEG-Intron package insert specifically refers to *Rebetol* or *Rebetol (ribavirin, USP)* and is not specific with respect to dosage form (*i.e.*, capsules or oral solution), you do not claim that this reference would cause confusion.

B. FDA'S APPROVAL OF A GENERIC RIBAVIRIN CAPSULE DRUG PRODUCT WOULD BE CONSISTENT WITH OTHER GENERIC DRUG APPROVALS.

FDA's previous generic drug approval decisions provide support for the approval of a generic ribavirin capsule drug product with labeling that omits information on the use of ribavirin capsules in combination with PEG-Intron. For example:

- FDA has approved generic drug products with labeling that excludes protected conditions of use from the generic drug labeling. For example, FDA approved generic tramadol products with labeling that excluded a protected dosing schedule (*i.e.*, 25 mg, 16-day titration schedule). *See* FDA Docket Nos. 01P-0495, 02P-0191, and 02P-0252.

FDA has approved generic drug products with labeling that excludes indications with indication-specific dosing instructions. For example, FDA approved generic captopril with labeling that excluded two protected indications with corresponding protected, indication-specific dosing information.

FDA has approved generic versions of components of co-packaged products. For example, FDA has approved generic versions of ifosfamide, which had previously only been marketed by the innovator co-packaged with mesna. *See* FDA Docket No. 01P-0061; 67 Fed. Reg. 34457 (May 4, 2002).

FDA has approved generic drug products with Medication Guides. For example, FDA approved generic isotretinoin with a Medication Guide.³⁶

Accordingly, FDA's approval of a generic ribavirin capsule drug product (with labeling that omits information on the use of ribavirin capsules in combination with PEG-Intron) is consistent with previous generic drug approval decisions.³⁷

C. THE OTHER ARGUMENTS SET FORTH IN YOUR PETITION ARE NOT PERSUASIVE.

³⁶ While you do not claim that the existence of a Medication Guide presents a bar to generic approval, you do mention it as evidence that ribavirin does "pose a serious and significant public health concern," and that the Medication Guide is part of FDA-approved product labeling. Petition at 5-6. Accutane (isotretinoin) is an example of a reference listed drug with a Medication Guide for which FDA has approved generic products. We note that the Act imposes no "risk" criteria on the suitability of an approved drug to serve as a reference listed drug in an ANDA, nor does the Act establish grounds for refusing to approve an ANDA based on the degree of risk posed by the reference listed drug. *See* section 505(j)(4) of the Act. To the extent that a Medication Guide is approved labeling for the listed drug, an ANDA referencing that drug would be required to have the same Medication Guide except for differences permitted by law. *See generally* section 505(j)(2)(A)(v) of the Act and 21 C.F.R. 314.94(a)(8)(iv).

³⁷ FDA has also approved a number of generic drug products with labeling that omits information protected by orphan exclusivity.

You assert that you petitioned the agency "to ensure that the labeling for all generic ribavirin products will contain mutually conforming labeling for use with both Intron-A and PEG-Intron." Petition Supplement dated March 16, 2004 at 1; *see also* Petition at 8-9. You state that a generic Rebetol product that omits information on the use of the product with PEG-Intron would be misbranded under the Act, and also would lack the required approval under section 505 of the Act. Petition at 1. You also note that the introduction or delivery for introduction into interstate commerce of a misbranded or unapproved drug is a prohibited act. *Id.*; *see also* Petition at 12. You state in your petition that "Approval of labeling for one component of a combination product that is not reciprocal or mutually reinforcing of the labeling for the other component would, in this instance, render one or both components misbranded as false and misleading, as failing to disclose material facts, and as failing to provide adequate directions for use." Petition at 12.

Contrary to your argument: (1) The Act, FDA regulations, and case law authorize an ANDA applicant for a generic ribavirin capsule drug product to limit the intended use of a proposed generic drug product to the adult use of ribavirin capsules in combination with Intron A; (2) it is proper for the agency to look to the ANDA applicant's proposed labeling as evidence of the intended use of a generic ribavirin capsule drug product; (3) Schering's PEG-Intron labeling is not evidence of the intended use of an ANDA applicant's ribavirin capsule drug product; (4) evidence of Schering's purported agreements with ANDA applicants are not relevant, and certainly are not evidence of an ANDA applicant's intent to market its proposed generic drug product for use in combination with PEG-Intron given the facts; (5) it would not be reasonable for the agency to conclude that Schering's PEG-Intron labeling constitutes labeling for an ANDA applicant's ribavirin capsule drug product given the current facts; (6) the *Bristol-Meyers Squibb* court, in effect, rejected your misbranding theory; (7) "foreseeable use" is not a bar to the agency's decision to approve ANDAs for generic ribavirin capsule drug products; and (8) a proposed generic ribavirin capsule drug product with proposed labeling that omits information on the use of ribavirin capsules in combination with PEG-Intron would not, on that basis alone, be misbranded or lack the required approval under section 505 of the Act.

- 1. The Act, FDA regulations, and case law authorize an ANDA applicant for a generic ribavirin capsule drug product to limit the intended use of the proposed generic drug product to the adult use of ribavirin capsules in combination with Intron A.*

Schering's Rebetol Capsules are approved for use in combination with *either* Intron A or PEG-Intron.³⁸ As discussed at length, the Act, FDA regulations, and case law expressly authorize an ANDA applicant: (1) to submit a section viii statement and forgo seeking approval for, and carve out from the proposed labeling, the method of using ribavirin capsules in combination with PEG-Intron; (2) to omit the condition of using ribavirin capsules in combination with PEG-Intron because the condition of use is protected by patent and exclusivity; and (3) to exclude from the proposed ribavirin capsule drug labeling information on the use of ribavirin capsules in

³⁸ We note that Schering, by submitted NDA 20-903 under section 505(b) of the Act, is on notice that its listed drug Rebetol Capsules may be subject to generic competition under section 505(j) of the Act.

combination with PEG-Intron because of differences permitted because the generic ribavirin capsules and Rebetol Capsules are produced or distributed by different manufacturers (*e.g.*, labeling information protected by patent and exclusivity).³⁹

Therefore, it is clear under the Act, FDA regulations, and case law that an ANDA applicant for a ribavirin capsule drug product may seek approval for, and submit proposed labeling on, the adult use of ribavirin capsules in combination with Intron A. The very nature of this legal framework contemplates that an ANDA applicant for a ribavirin capsule drug product could limit the intended use of its product to this use alone, thereby promoting generic drug competition for the adult use of ribavirin capsules in combination with Intron A (*i.e.*, the remaining, non-protected condition of use).

2. *In the generic drug pre-approval context, an ANDA applicant's proposed labeling for a generic ribavirin capsule drug product is evidence of the intended use of that generic ribavirin capsule drug product.*

The *Sigma-Tau* court held that it is proper for the agency to look to the ANDA applicant's proposed generic drug labeling as evidence of the intended use for that generic drug product in the pre-approval context. *Id.* at 147-148. Accordingly, if an ANDA applicant for a ribavirin capsule drug product submits proposed labeling with information only on the adult use of ribavirin capsules in combination with Intron A, the proposed labeling would be evidence that the generic ribavirin capsule drug product is intended for that very use, not for some other use (*e.g.*, for use in combination with PEG-Intron).

This conclusion is consistent with 21 C.F.R. 201.128. Section 201.128 provides, in part, that "intended use" refers to the "objective intent of the person legally responsible for the labeling of drugs." Here, the proposed labeling would be the most relevant and compelling, if not exclusive, manifestation of the objective intent of the ANDA applicant legally responsible for that proposed generic ribavirin capsule drug product. Further, beyond the proposed labeling, you have provided no evidence as to the objective intent of a given ANDA applicant legally responsible for the labeling of a specific proposed generic ribavirin capsule drug product to market that proposed generic drug product for use in combination with PEG-Intron. An ANDA applicant's proposed labeling containing information only on the adult use of ribavirin capsules in combination with Intron A constitutes evidence that the generic ribavirin capsule drug product is intended for that use.

The *Sigma-Tau* court confirmed this conclusion by holding, "FDA did not commit plain error or act inconsistently with its regulations insofar as it declined to examine other evidence besides

³⁹ We note that you concede the latter two points by expressly stating that: (1) "[i]t is settled that certain specific differences in labeling between the innovator and generic are permitted" (emphasis added) (Petition at 7); and (2) "FDA's regulation authorizing the agency to approve generic drug products that omit a protected indication or other patent- or exclusivity- protected information from the labeling has been upheld in *Bristol-Meyers Squibb Co. v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996) and in *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002)" (Petition at 7, footnote 10).

proposed labeling [such as market data, dosage forms, and federal drug reimbursement policies] in approving the generic drugs at issue." *Id.* at 145, 148.

3. ***Schering's PEG-Intron labeling is not evidence of the intended use of an ANDA applicant's ribavirin capsule drug product.***

You assert that Schering's PEG-Intron labeling, including the Medication Guide, contains information on the use of ribavirin capsules and PEG-Intron. Petition at 4-6, 11. You also state that "[i]n no less than five instances, the labeling for PEG-Intron specifically refers the reader to the labeling for *Rebetol*." (emphasis added). Petition at 11. You assert that the labeling and intended use of Rebetol and PEG-Intron are "textually intertwined" and "inextricably linked" and that the labeling of PEG-Intron defines the intended use of Rebetol and any generic version thereof. Petition at 11. You state that even if ANDA applicants carve out from their labeling information regarding the use of ribavirin capsules with PEG-Intron, they "cannot escape the fact that PEG-Intron labeling continues to bear labeling on the use of PEG-Intron with ribavirin." Petition, at 10. You state that the PEG-Intron labeling "establishes beyond any doubt that *Rebetol* is intended for use in combination with PEG-Intron" (emphasis added). Petition Supplement dated October 3, 2003, at 3.

Under FDA regulations, "intended use" refers to the "objective intent of the person legally responsible for the labeling of drugs." *See* 21 C.F.R. 201.128. In asserting that Schering's PEG-Intron labeling defines an intended use for generic ribavirin capsules you ask that we infer intended use not from the objective intent of the manufacturers legally responsible for the labeling of the generic ribavirin capsule drug products, but rather from the objective intent of a *different manufacturer* (Schering). However, your focus is misplaced.

Here, the persons legally responsible for the labeling of generic ribavirin capsule drug products are the ANDA applicants. You provide no evidence of the objective intent of the ANDA applicant legally responsible for the labeling of the proposed generic ribavirin drug product to market that proposed generic drug product for use in combination with PEG-Intron.

Moreover, your intended use theory is inconsistent with the very cases you cite in support of your argument.⁴⁰ In those cases, the parties charged with misbranding (or other) violations were either themselves (or through their representatives) responsible for *both* the product(s) at issue and the labeling accompanying the product(s). Here, you provide no evidence that the ANDA applicants are legally responsible for Schering's PEG-Intron labeling (or that these ANDA applicants intend to market their proposed generic drug products in combination with PEG-Intron for that matter). What is clear, however, is that the ANDA applicants are legally responsible for the proposed labeling accompanying their proposed generic ribavirin capsule drug products (*i.e.*, proposed labeling that omits information on the use of ribavirin capsules in combination with PEG-Intron).

Indeed, just a few years ago the United States Court of Appeals for the Fourth Circuit found that "no court has ever found that a product is 'intended for use' or 'intended to affect' within the

⁴⁰ *See* Petition at 10; Petition Supplement dated March 16, 2004, at 4-5.

meaning of the [Act] absent manufacturer claims as to that product's use." *See Brown & Williamson Tobacco Corp. v. FDA*, 153 F.3d 155, 163 (4th Cir. 1998) (internal quotation marks omitted) (citing *Coyne Beahm, Inc. v. FDA*, 966 F. Supp. 1374, 1390 (M.D.N.C. 1997)), *aff'd*, 529 U.S. 120 (2000). *See also e.g., National Nutritional Foods Ass'n v. Mathews*, 557 F.2d 325 (2d Cir. 1977) ("The vendors' intent in selling the product to the public is the key element." "None of the promotions for therapeutic use in the record was attributed to the manufacturers or vendors."); *United States v. Undetermined Quantities . . . "Pets Smellfree"*, 22 F.3d 235, 240 (10th Cir. 1994) ("PSF's claims [in labeling and promotional materials] . . . bring Smellfree within the scope of [section 201(g)(1)(C) of the Act].").

In addition, none of the cases you cite in support of your intended use theory involve the generic drug pre-approval context. In this context (before approval), *Sigma-Tau* is precisely on point. The agency may properly look to the ANDA applicant's generic ribavirin capsule drug product proposed labeling as evidence of intended use.⁴¹

4. *The evidence of Schering's purported licensing agreements and contracts with ANDA applicants are not relevant and are not evidence of an ANDA applicant's intended use for a generic ribavirin capsule drug product given the facts here.*

In an attempt to create a relationship between an ANDA applicant's ribavirin capsule drug product and Schering's PEG-Intron labeling, you assert (based on certain press releases and an excerpt from Schering's SEC filings) that certain ANDA applicants and Schering have entered into licensing agreement/contracts, which you allege cover the use of PEG-Intron. Petition Supplement dated July 29, 2003. You assert that this information is evidence that a generic ribavirin capsule drug product is intended for use in combination with PEG-Intron. Petition Supplement dated March 16, 2004, at 4.⁴² In light of these apparent agreements (and Schering's PEG-Intron labeling), you assert that the "intended use" of a drug product is defined by labeling claims and by the circumstances surrounding the distribution of the product. Where a person knows that his product is being offered for a use for which the product lacks adequate labeling,

⁴¹ Should generic drug manufacturers engage in the unlawful promotion of approved generic ribavirin capsule drug products for use in combination with PEG-Intron, the agency could consider enforcement actions as individual circumstances warrant.

⁴² You claim that the ANDA applicants have entered into contracts with Schering and Schering will receive royalties from generic ribavirin capsule products. Petition Supplement dated October 3, 2003, at 4. You also claim that the ANDA applicants received permission to use the "inventions claimed in Schering's patents -- including patents on the use of ribavirin in combination with PEG-Intron." *Id.* You state that the "financial relationship" between Schering and ANDA applicants supports your argument that the "intended uses of ribavirin, as set forth in the labeling for PEG-Intron, also must be regarded as intended uses of the proposed generic products." *Id.* at 3. You also state that, as a result of these purported agreements, ANDA applicants have "integrated the marketing of their products with the marketing of PEG-Intron." *Id.* at 5.

he is required *as a matter of law* to label his product for that use" (emphasis in original). Petition Supplement dated October 3, 2003, at 2-3.⁴³

First, the information you submit in support of your position comes primarily from persons other than the ANDA applicants legally responsible for the labeling of the proposed generic ribavirin capsule drug products.⁴⁴ That is, among other things, you refer to two Schering press releases and one excerpt from Schering's SEC filing. Once again, this information does not represent the objective intent of the ANDA applicants legally responsible for the labeling of generic ribavirin capsule drug products to market their products for use in combination with PEG-Intron.

Further, assuming *arguendo* we should consider this information at all, it is merely speculative. The purported agreements apparently were reached to settle patent litigation. *See e.g.*, 3RP/Par comments dated August 21, 2003, and Geneva comments dated August 26, 2003. The press releases you cite include no explicit references to PEG-Intron. Assuming *arguendo* these agreements encompass PEG-Intron,⁴⁵ it is certainly plausible that ANDA applicants could negotiate agreements with the appropriate parties that would encompass the right to obtain approval in the future for generic ribavirin capsule drug products for use in combination with PEG-Intron. *See* 3RP/Par comments dated August 21, 2003, at 1, and Geneva comments. Moreover, based on the information you present and the comments submitted, these agreements apparently cover Schering's patents, not Hatch-Waxman exclusivity rights. *See* 3RP/Par comments dated August 21, 2003, at 1-2; Geneva comments dated August 26, 2003, at 2. You even acknowledge this point in your petition. Petition Supplement dated October 3, 2003, at 5-6.

Given the circumstances here, we cannot reasonably conclude that an ANDA applicant would "know," within the meaning of 21 C.F.R. 201.128, that its generic ribavirin capsule drug product would be offered for a use for which the product lacks adequate labeling (*e.g.*, for use in combination with PEG-Intron). Before approval, an ANDA applicant for a ribavirin capsule

⁴³ You cite the following part of 21 C.F.R. 201.128

if a manufacturer knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put.

⁴⁴ We note that you submit one press release from Par Pharmaceutical, Inc., which is described in 3RP/Par's comments as the marketing partner of Three Rivers. *See* 3RP/Par comments dated July 25, 2003, at 1. This press release (like the two Schering press releases) makes no express mention of PEG-Intron.

⁴⁵ Presumably you conclude that Three Rivers' agreement encompass PEG-Intron based on an excerpt from the SEC filing of a different manufacturer -- Schering. In response to a specific question, Schering states, "The licensing agreement includes all of Schering-Plough's U.S. patents relating to ribavirin and its use in treating hepatitis C, including its use in combination with interferon or peginterferon." Petition Supplement dated July 29, 2003, at 3. Although you acknowledge that the press releases make clear that the terms of Geneva and Teva's agreements have not been disclosed to the public, you nonetheless assume that they have reached similar agreements that purportedly encompass PEG-Intron. *Id.* We note that 3RP/Par states that Three Rivers' agreement includes peginterferon. *See* 3R/Par comments dated August 21, 2003. 3RP/Par and Geneva also note that their agreements were entered into before disposition of the patent cases. *See* 3RP/Par comments dated October 24, 2003, and Geneva comments dated August 26, 2003.

drug product would not even "know" if its generic ribavirin capsule drug product would be approved, let alone that (post-approval) it would be used in combination with PEG-Intron based on these facts.

5. *It would not be reasonable for the agency to conclude that Schering's PEG-Intron labeling constitutes "labeling" for an ANDA applicant's ribavirin capsule drug product given the current facts.*

In your latest submission, it appears that you argue that Schering's PEG-Intron labeling constitutes "labeling" for an ANDA applicant's generic ribavirin capsule drug product. Petition Supplement dated March 16, 2004, at 2-4. You state that the focus of your petition is on "labeling, within the meaning of the [Act], and on defining the universe of materials that represent 'labeling' of the proposed generic products." *Id.* at 2. This argument is misplaced, as discussed below.

Under the Act, "labeling" means "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." *See* section 201(m) of the Act. In *Kordel*, the Supreme Court stated that the phrase "accompanying such article" includes what supplements or explains an article "in the manner that a committee report of Congress accompanies a bill. No physical attachment one to the other is necessary. It is the textual relationship that is significant." *See Kordel v. United States*, 335 U.S. 345, at 349 (1948); *see also* Petition Supplement dated March 16, 2004, at 2-3 (citing *Kordel* in support of your argument).

Although you claim that, within the meaning of the Act and *Kordel*, Schering's PEG-Intron labeling constitutes "labeling" for an ANDA applicant's proposed ribavirin capsule drug product, this argument falls short for the same reason your intended use argument fails. That is, given the facts you present, there is no nexus between the ANDA applicants and Schering's PEG-Intron labeling. That is, the starting point in *Kordel* is "[i]t is undisputed that petitioner shipped or caused to be shipped in interstate commerce both the drugs and the literature." *Id.* at 346. The court emphasized that the "drugs and the literature had a common origin and a common destination. . . . [T]he products and the literature were interdependent." *Id.* at 348.

You provide no evidence of the objective intent of an ANDA applicant legally responsible for the labeling of the proposed generic ribavirin drug product to market that proposed generic drug product for use in combination with PEG-Intron. Here, Schering's PEG-Intron labeling does not manifest the necessary objective intent. As discussed above, the limited information you submit on agreements between Schering and ANDA applicants do not manifest that intent. Accordingly, Schering's PEG-Intron labeling does not constitute labeling for generic ribavirin capsule drug products within the meaning of the Act. On the other hand, an ANDA applicant's generic ribavirin capsule drug product labeling does constitute labeling for that product.

6. *The Bristol-Meyers Squibb court, in effect, rejected your misbranding theory.*

In *Bristol-Meyers Squibb*, the court rejected the misbranding theory in your petition. In that case, the generic drug labeling excluded exclusivity-protected intended uses and corresponding indication-specific dosing information. At the same time, the reference listed drug labeling continued to contain that information (on the exclusivity-protected intended uses and corresponding indication-specific dosing information). In expressly upholding the legal framework for carving out from the generic drug labeling protected information, the D.C. Circuit rejected the argument that the reference-listed drug labeling misbranded the generic drug by continuing to be labeled for those protected uses. In fact, you acknowledge as much by stating, "[f]or a single entity drug (*i.e.*, monotherapy), in which the generic sponsor controls all of the labeling that accompanies the product, the deletion of an indication is not likely to render the product misbranded." Petition Supplement dated October 3, 2003, at 7.

You nonetheless attempt to distinguish *Bristol-Meyers Squibb* from the facts here.⁴⁶ You maintain that "the fact that ribavirin is approved only as part of a combination product introduces issues of law and fact that were not present in *Bristol-Meyers [Squibb]*." Petition Supplement dated March 16, 2004, at 6. You assert that the *Bristol-Meyers Squibb* court "did not have to consider the legal impact of a labeling carve out in the context of a cross-labeled combination product." *Id.*

There is no language in *Bristol-Meyers Squibb* that even remotely suggests that the D.C. Circuit intended to limit its holding to monotherapies. The court, as mentioned above, rejected the possibility that a reference-listed drug's labeling renders an ANDA applicant's generic drug misbranded or lacking adequate directions for use.⁴⁷ It would be even more tenuous for the agency to take the position that another drug product's labeling (that is not the reference listed drug labeling) would render a generic ribavirin capsule drug product misbranded. That is, if the court rejected the possibility that Schering's Rebetol Capsules would render generic ribavirin capsules misbranded, it would certainly reject the possibility that Schering's PEG-Intron labeling would render the generic ribavirin capsules misbranded. Further, your misbranding theory is even more unreasonable given that Schering's PEG-Intron labeling specifically refers to "*Rebetol*" or "*Rebetol* (ribavirin, USP)" by name in instances where the health professional or patient is instructed to refer to additional information on the use of PEG-Intron in combination with Rebetol Capsules.

7. "Foreseeable use" is not a bar to the agency's decision to approve ANDAs for generic ribavirin capsule drug products.

⁴⁶ In response to Teva's comments stating that the "[l]egal authority for generic applicants to unilaterally limit the intended uses of their products through labeling carve-outs is well established beyond challenge, you state "We agree, but only to a point." See Teva Comments at 3; see also Petition Supplement dated March 16, 2004.

⁴⁷ That is, the court did *not* decide that the Capoten labeling (which the generic captopril drug product referenced) misbranded the generic captopril drug product because the Capoten labeling continued to contain information on use of Capoten (captopril) for left ventricular dysfunction (LVD) after myocardial infarction, and the use of Capoten (captopril) for treatment of diabetic nephropathy in patients with type I diabetes mellitus and retinopathy; *nor* did the court hold that the generic captopril drug product was an unapproved new drug. The court implicitly rejected these theories by specifically upholding the legal framework allowing an ANDA applicant to exclude from the labeling information protected by exclusivity.

You also state that generic manufacturers cannot "claim that substitution of generic Rebetol, for patients who are prescribed PEG-Intron/Rebetol combination therapy, is merely speculative." Petition Supplement dated October 3, 2003, at 9, footnote 5. Moreover, you state that at least 12 states have enacted laws mandating the substitution of generic products in place of innovator products. *Id.*

Both *Sigma-Tau* and *Bristol-Meyers Squibb* rejected your theory. In trying to distinguish those cases from the facts here, you state that "this is not a case in which FDA must speculate about hypothetical or foreseeable uses." Petition Supplement October 3, 2003, at 11. However, the facts here present precisely that type of case. In the ANDA pre-approval context, any assertions about the ANDA applicant's post-approval intended use of generic ribavirin capsules in combination with PEG-Intron would by their very nature constitute "foreseeable uses." The *Sigma-Tau* court rejected the foreseeable use theory as a bar to generic drug approvals. As the Fourth Circuit has recognized, applying a foreseeable-use test in the generic drug context would create "formidable problems" for the agency. *See Sigma-Tau Pharm.*, 288 F.3d 141, 146 (4th Cir. 2002).

Further, the agency considers drug products to be therapeutically equivalent and generally interchangeable only if they are "pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients *under the conditions specified in the labeling*" (emphasis added). *See* Orange Book, at viii. As discussed elsewhere in this response, when generic ribavirin capsule drug products are taken in conformance with the proposed labeling for the adult use of ribavirin capsules in combination with Intron A, the generic ribavirin capsule drug product would be as safe and effective as Rebetol Capsules for the adult use of ribavirin capsules in combination with Intron A.

Moreover, the *Bristol-Meyers Squibb* court explicitly recognized that there were "some state laws and health insurers that mandate[d] substitution of generic drugs." *Id.* at 1500. Yet the court still upheld the agency's interpretation of section 505(j)(2)(A)(v) of the Act, and implementing regulations (*e.g.*, 21 C.F.R. 314.94(a)(8)(iv) and 21 C.F.R. 127(a)(7)) as permitting the agency to approve an ANDA for a generic drug with labeling that omitted exclusivity-protected indications (and corresponding indication-specific dosing information) for which the innovator drug was approved. *Id.*

You also state that "if only one patient who is prescribed the PEG-Intron/Rebetol combination receives generic Rebetol in place of the brand-name product, that patient will have been placed at risk for a serious medication error." Petition Supplement dated October 3, 2003, at 8. You refer to an NIH Consensus Statement on Management of Hepatitis C (June 12, 2002); and Schering's statement that PEG-Intron and Rebetol combination therapy is the most prescribed treatment for chronic hepatitis C. *Id.* at 9, footnote 6.

To the extent you are implying that generic ribavirin capsules will be prescribed off-label for an unapproved use (*e.g.*, the use of ribavirin capsules in combination with PEG-Intron), and therefore the agency should not approve ANDAs for generic ribavirin capsule drug products, we

do not find your assertion to be an appropriate basis for refusing to approve an ANDA for a generic ribavirin capsule drug product.⁴⁸

The *Sigma-Tau* court, in rejecting a foreseeable use theory as a bar to generic drug approvals, stated that such a theory ". . . might frustrate the longstanding practice of Congress, the FDA, and the courts not to interfere with physicians' judgments and their prescription for off-label uses." *Id.* at 147. The court asserted that a "foreseeable off-label use [theory] to bar the approval of generic drugs, even for unprotected indications . . . [would add] a huge evidentiary hurdle to the generic drug approval process [and] would be profoundly anti-competitive." *Id.* at 147-148.⁴⁹ The *Bristol-Meyers Squibb* court specifically stated that FDA "does not regulate . . . possible substitution of a generic drug for the pioneer by doctors or pharmacists." *Id.* at 1496 (internal citations omitted).

8. *An ANDA for a generic ribavirin capsule drug product with proposed labeling that omits information on the use of ribavirin capsules in combination with PEG-Intron would not (on this basis alone) be misbranded or unapproved under section 505 of the Act.*

Because it is established that an ANDA applicant for ribavirin capsules is authorized to limit the intended use of its product to the adult use of ribavirin capsules in combination with Intron A, it follows that the generic ribavirin capsule drug product, if properly labeled for that intended use, would not on that basis alone lack the required approval under section 505 of the Act.

Further, a generic ribavirin capsule drug product with proposed labeling that excludes the use of ribavirin capsules in combination with PEG-Intron would not be misbranded on this basis. In approving NDA 20-903 (and relevant supplements), the agency has already determined that Rebetol Capsules have adequate directions for the adult use of ribavirin capsules in combination with Intron A. A generic ribavirin capsule drug product that has the "same labeling," as required

⁴⁸ Although the facts here do not involve off-label uses for the innovator drug, we note that the medical community's experience with an innovator drug frequently reveals clinically useful off-label uses, and by the time the generic version is approved it is likely to have known uses that are also not included in the labeling of the innovator drug. In the generic drug approval context, the Act requires FDA to approve generic versions of new drugs based on a showing that the generic drug is bioequivalent (biologically available to the same extent and at the same rate, within a range). See generally section 505(j) of the Act. With certain exceptions, the proposed generic drug must also have the same labeling as the listed drug and the same conditions of use for which the listed drug is approved. The purpose of the latter provision, as the D.C. Circuit noted in *Bristol-Meyers Squibb*, is to ensure that the generic drug is safe and effective for each condition of use prescribed, recommended, or suggested in the generic drug labeling. *Id.* at 1500. If FDA were to approve generic drug labeling based on these known but unlabeled uses of the innovator drug, then the generic drug would not have the same conditions of use for which the innovator drug is approved, and we could not be assured that the generic drug would be safe and effective for those conditions of use.

⁴⁹ In *Sigma-Tau*, the innovator argued that the court should consider as evidence of intended use its claim that "most of the need for the generics and most of the money to be made -- lies in treating patients with ESRD [i.e., the protected indication]." *Id.* at 147. Assuming arguendo most of the money to be made here is for the use of ribavirin capsules in combination with PEG-Intron, the agency, like the Fourth Circuit, finds this point to be "unavailing." *Id.* It is important to note that once generic ribavirin capsules are approved, generic drug manufacturers may lawfully promote them only for adult use in combination with Intron A for the approved indication.

by statute, would also have adequate directions for the adult use of ribavirin capsules in combination with Intron A.

D. THE AGENCY'S INTERPRETATION IS CONSISTENT WITH A FUNDAMENTAL CANON OF STATUTORY CONSTRUCTION AND THE UNDERLYING GOALS OF THE HATCH-WAXMAN AMENDMENTS.

1. *The agency's interpretation is consistent with a fundamental canon of statutory construction.*

It is axiomatic that the provisions of a statute should be construed as a whole. That is, statutory construction is a "holistic endeavor," in which the court examines not the "isolated context" of one subsection of a statute, but "the remainder of the statutory scheme." See *United Savings Ass'n v. Timbers of Inwood Forest Associates*, 484 U.S. 365, 371 (1988); see also *Gustafson v. Alloyd Co.*, 513 U.S. 561, 568 (1995) ("[O]ur duty [is] to construe statutes, not isolated provisions.").

Your interpretation runs afoul of this canon of statutory construction. On one hand, you acknowledge that it "is *settled* that certain specific differences in labeling between the innovator and generic are permitted." Petition at 7. You also concede that "FDA's regulation authorizing the agency to approve generic drug products that omit a protected indication or other patent- or exclusivity- protected information from the labeling has been upheld in *Bristol-Meyers Squibb Co. v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996) and in *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002)." Petition at 7, footnote 10. In fact, you set out much of the legal framework supporting the approval of an ANDA for a ribavirin capsule drug product. On the other hand, you argue that a generic ribavirin capsule drug product with labeling that omits information on the use of ribavirin capsules in combination with PEG-Intron does not bear adequate directions for use with PEG-Intron, and is misbranded under the Act and therefore should not be approved.⁵⁰

Although you use an intended use theory (rejected in *Bristol-Meyers Squibb* and *Sigma-Tau*) to create this apparent conflict, the agency's interpretation of these provisions creates no conflict at all. FDA's interpretation (set forth in this response) is consistent with the statute as a whole. As discussed at length, the agency may approve a generic ribavirin capsule drug product with proposed labeling that omits information on the use of ribavirin capsules in combination with PEG-Intron in accordance with certain provisions of the Act (*e.g.*, statutory provisions involving NDA and ANDA patent responsibilities, three-year exclusivity, same conditions of use, same

⁵⁰ You also state that section 21 C.F.R. 94(a)(8)(iv) (*i.e.*, the regulation permitting -- and setting forth examples of -- differences in labeling because the generic drug and the listed drug are produced or distributed by different manufacturers), "does not trump the unqualified statutory prohibition against the marketing of misbranded and unapproved new drugs." Petition Supplement dated October 3, 2003, at 6. However, as discussed at length, the agency's position here is not that the regulation trumps the statutory provisions. Rather, section 314.94(a)(8)(iv) implements the section of the *statute* (*i.e.*, section 505(j)(2)(A)(v)) that authorizes these differences in labeling. As discussed in the text, the agency's interpretation comports with the statutory scheme as a whole.

labeling requirements). Yet, the agency's interpretation still gives effect to other statutory provisions, such as those relating to misbranding and adequate directions for use. That is, among other things, a ribavirin capsule drug product: (1) must bear adequate directions for the adult use of ribavirin capsules in combination with Intron A, and (2) cannot have labeling that is false or misleading in any particular. *See* section 502 of the Act. Accordingly, only FDA's interpretation works with the statutory scheme as a whole.

We emphasize, however, that the agency would only approve a generic drug product with labeling that omits protected information if the differences do not render the generic drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use. *See* 21 C.F.R. 314.127.

2. *The agency's interpretation is consistent with underlying goals of the Hatch-Waxman Amendments, whereas your interpretation is inconsistent with those goals.*

The Hatch-Waxman Amendments provided sponsors of innovator drugs with marketing exclusivity and patent listing provisions as a quid pro quo for the abbreviated approval mechanism for sponsors of generic drugs whereby generic drugs could rely on the agency's finding of safety and effectiveness for the innovator drug. Accordingly, the Hatch-Waxman Amendments strike a balance between "(1) inducing pioneering research and development of new drugs and (2) enabling competitors to bring low-cost, generic copies of those drugs to market." *See ICN Pharmaceuticals v. Geneva Pharmaceuticals Technology*, 272 F.Supp.2d 1028, 1034 (C.D. Cal. 2003) (*citing Andrx Pharm., Inc. v. Biovail Corp.*, 276 F.3d 1368, at 1371 (Fed. Cir. 2002)).

Your interpretation -- that the PEG-Intron labeling defines the intended use for generic ribavirin capsules and therefore generic ribavirin capsules must be labeled for use with PEG-Intron -- would hinder the goal of bringing lower cost, generic ribavirin capsule drug products to market. If your theory were adopted, exclusivity and patent protection on ribavirin's use with PEG-Intron would block approval of any generic ribavirin capsule drug product even though adult use of ribavirin capsules in combination with Intron A lacks any remaining protection.

On the other hand, the agency's interpretation -- that FDA may approve an ANDA for a ribavirin capsule drug product with labeling that omits information on the use of ribavirin in combination with PEG-Intron -- allows the innovator and associated patent holders to enjoy the benefits associated with their research in developing a new condition of use (*i.e.*, the use of ribavirin capsules in combination with PEG-Intron). At the same time, the agency's conclusion promotes generic competition for the remaining, non-protected condition of use for which the listed drug is approved (*i.e.*, the adult use of ribavirin capsules in combination with Intron A). Accordingly, only the agency's interpretation strikes the balance contemplated by the Hatch-Waxman Amendments.

E. NO ADDITIONAL PUBLIC PROCESS IS NECESSARY.

You also claim that “any general guidance the agency is providing to the class of sponsors who may be seeking to market generic ribavirin products, on the issue of labeling and cross labeling, must be provided under the agency’s ‘good guidance practice’ regulations, with an opportunity for public participation.” Petition at 2. You also request, therefore, that FDA defer action on the labeling of generic ribavirin products until a public process is initiated and completed on the issues raised in the petition. Petition at 2, 12-13. You suggest that a particular letter that refers to “generic drug *applicants*” (Petition Supplement dated October 3, 2003, at 10 (emphasis in original)) “establishes agency policy concerning a class of products, not routine ANDA review.” *Id.*

First and foremost, FDA regulations, under 21 C.F.R. 314.102, titled “Communications between FDA and applicants” provide that “[d]uring the course of reviewing an . . . abbreviated application, FDA shall communicate with applicants about scientific, medical, and procedural issues that arise during the review process. Such communication may take the form of telephone conversations, *letters*, or meetings, whichever is the most appropriate to discuss the particular issue at hand” (emphasis added). Further, we note that guidance documents do not include “communications directed to individual persons or firms.” *See* 21 C.F.R. 10.115(b)(3).

The July 27, 2003, letter to which you refer was issued by the Office of Generic Drugs (OGD) to a single applicant in the context of the agency’s review of that applicant’s ANDA. The fact that the letter at one point refers in the plural to “generic drug applicants” does not convert that communication into a guidance document. The agency’s ANDA review process for proposed generic drug products includes a review of proposed labeling. Accordingly, it is entirely appropriate for the agency to communicate review issues by letter to specific ANDA applicants. Communicating with potential applicants for generic drugs is a routine part of FDA’s business that is generally conducted by letter responses to questioners, and not by the issuance of guidance documents. In 2002, the OGD received 744 requests for information. OGD received 971 requests for information in 2003. Because there are usually multiple generic applicants for the same reference listed drug, OGD often receives the same question from multiple sources. In 2002, FDA approved 321 generic drug products. Given these numbers, it would be infeasible and inconsistent with an underlying goal of the Hatch-Waxman Amendments (i.e., to promote generic competition) to issue guidance documents in response to all of these requests for information, and neither the statute nor FDA’s regulations requires us to do so.

We note that FDA had previously (as you now request) provided individual generic drug product labeling guidances. However, by *Federal Register* notice titled *Withdrawal of 53 Guidances on Individual Product Labeling*, the agency withdrew these guidances because they were “outdated and of little use to the generic drug industry.” *See* 67 Fed. Reg. 44857 (July 5, 2002). It would be inefficient for FDA to engage in the development of a guidance document whenever labeling is developed for a generic drug product for which there are multiple applicants. The fact that the conclusions reached about one applicant’s ANDA labeling have relevance to other applicants who submit ANDAs for the same drug seems rather self-evident when viewed in the context of

generic drugs, in which sameness of labeling is a fundamental concept. Further, the public nature of the good guidance practice procedures set forth in 21 C.F.R. 10.115, in many instances, would be inconsistent with the confidential nature of the ANDA approval processes. *See e.g.*, 21 C.F.R. 314.430(b)-(d). Finally, we note that the agency has developed general guidance and resources to assist industry in obtaining up-to-date labeling for reference listed drugs.⁵¹

III. CONCLUSION

FDA has reviewed your petition, the submitted comments, and other relevant data and information available to the agency. For the reasons discussed above, your request that we refrain from approving ANDAs for generic ribavirin products with labeling that omits information on the use of the product with PEG-Intron is denied. We also deny your request that FDA defer action on the labeling for generic ribavirin products until a public process has been initiated and completed on the issues raised in the petition, insofar as this constitutes a request for a public proceeding in addition to that already accorded under 21 C.F.R. 10.30 with respect to this petition.

Sincerely,



Steven K. Galson, M.D., M.P.H.
Acting Director
Center for Drug Evaluation and Research

⁵¹ *See e.g.*, guidance for industry titled, *Revising ANDA Labeling Following Revision of the RLD Labeling*; see also http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html for more resources and information.

EXHIBIT 16

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, 80 mg C

FOR USE IN OPIOID-TOLERANT PATIENTS ONLY

Rx only

WARNING: Oxycodone hydrochloride extended-release tablets are an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing oxycodone hydrochloride extended-release tablets in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Oxycodone hydrochloride extended-release tablets are an extended-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

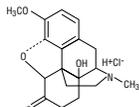
Oxycodone hydrochloride extended-release tablets are NOT intended for use as a prn analgesic.

Oxycodone Hydrochloride Extended-Release 80 mg Tablets ARE FOR USE IN OPIOID TOLERANT PATIENTS ONLY. This tablet strength may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

DESCRIPTION

Oxycodone Hydrochloride Extended-Release Tablets are an opioid analgesic supplied in 80 mg tablet strength for oral administration. The tablet strength describes the amount of oxycodone per tablet as the hydrochloride salt. The structural formula for oxycodone hydrochloride is as follows:



$\text{C}_{18}\text{H}_{21}\text{NO}_4\cdot\text{HCl}$ M.W. 351.82

The chemical formula is 4,5-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Oxycodone is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL). It is slightly soluble in alcohol (octanol water partition coefficient 0.7). Each tablet contains 80 mg of oxycodone hydrochloride. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, FD&C blue #2 indigo carmine lake, hypromellose (2208, 100M), iron oxide yellow, lactose anhydrous, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide and triacetin.

CLINICAL PHARMACOLOGY

Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, hydromorphone, fentanyl, codeine, and hydrocodone. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, as well as analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

Central Nervous System

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of oxycodone hydrochloride extended-release tablets overdose. (See OVERDOSAGE).

Gastrointestinal Tract and Other Smooth Muscle

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Concentration - Efficacy Relationships

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall "drug effect", analgesia and feelings of "relaxation."

As with all opioids, the minimum effective plasma concentration for analgesia will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients must be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.

Concentration - Adverse Experience Relationships

Oxycodone hydrochloride extended-release tablets are associated with typical opioid-related adverse experiences. There is a general relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation is altered by the development of tolerance to opioid-related side effects, and the relationship is not clinically relevant.

As with all opioids, the dose must be individualized (see DOSAGE AND ADMINISTRATION), because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

Pharmacokinetics and Metabolism

The activity of oxycodone hydrochloride extended-release tablets is primarily due to the parent drug oxycodone. Oxycodone hydrochloride extended-release tablets are designed to provide extended delivery of oxycodone over 12 hours. Breaking, chewing or crushing oxycodone hydrochloride extended-release tablets eliminates the extended delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone release from oxycodone hydrochloride extended-release tablets is pH independent. Oxycodone is well absorbed from oxycodone hydrochloride extended-release tablets with an oral bioavailability of 60% to 87%. The relative oral bioavailability of oxycodone hydrochloride extended-release tablets to immediate-release oral dosage forms is 100%. Upon repeated dosing in normal volunteers in pharmacokinetic studies, steady-state levels were achieved within 24 to 36 hours. Dose proportionally and/or bioavailability has been established for the 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC). Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life of oxycodone following the administration of oxycodone hydrochloride extended-release tablets was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism. In normal volunteers, the $t_{1/2}$ of absorption is 0.4 hours for immediate-release oral oxycodone. In contrast, oxycodone hydrochloride extended-release tablets exhibit a biphasic absorption pattern with two apparent absorption half-times of 0.6 and 6.9 hours, which describes the initial release of oxycodone from the tablet followed by a prolonged release.

Dose proportionality has been established for the 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 1 below). Given the short half-life of elimination of oxycodone from oxycodone hydrochloride extended-release tablets, steady-state plasma concentrations of oxycodone are achieved within 24 to 36 hours of initiation of dosing with oxycodone hydrochloride extended-release tablets. In a study comparing 10 mg of oxycodone hydrochloride extended-release tablets every 12 hours to 5 mg of immediate-release oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{max} , and similar for C_{min} (trough) concentrations. There was less fluctuation in plasma concentrations for the oxycodone hydrochloride extended-release tablets than for the immediate-release formulation.

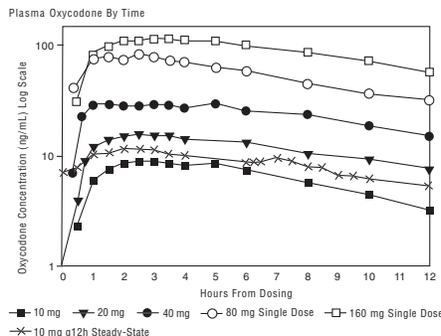


Table 1
Mean [% coefficient variation]

Regimen	Dosage Form	AUC (ng·hr/mL) [†]	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose	10 mg oxycodone hydrochloride extended-release tablets	100.7 [26.6]	10.6 [20.1]	2.7 [44.1]	n.a.
	20 mg oxycodone hydrochloride extended-release tablets	207.5 [35.9]	21.4 [36.6]	3.2 [57.9]	n.a.
	40 mg oxycodone hydrochloride extended-release tablets	423.1 [33.3]	39.3 [34.0]	3.1 [77.4]	n.a.
	80 mg oxycodone hydrochloride extended-release tablets*	1085.5 [32.3]	98.5 [32.1]	2.1 [52.3]	n.a.
Multiple Dose	10 mg oxycodone hydrochloride extended-release tablets q12h	103.6 [38.6]	15.1 [31.0]	3.2 [69.5]	7.2 [48.1]
	5 mg immediate-release q6h	99.0 [36.2]	15.5 [28.8]	1.6 [49.7]	7.4 [50.9]

[†] for single-dose $AUC=AUC_{0-12h}$; for multiple-dose $AUC=AUC_{0-12h}$
* data obtained while volunteers received naltrexone which can enhance absorption

Table 2
Mean [% coefficient variation]

Regimen	Dosage Form	AUC _∞ (ng·hr/mL) [†]	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose	4 x 40 mg oxycodone hydrochloride extended-release tablets*	1935.3 [34.7]	152.0 [28.9]	2.56 [42.3]	n.a.
	2 x 80 mg oxycodone hydrochloride extended-release tablets*	1859.3 [30.1]	153.4 [25.1]	2.78 [69.3]	n.a.
	1 x 160 mg oxycodone hydrochloride extended-release tablets*	1856.4 [30.5]	156.4 [24.8]	2.54 [36.4]	n.a.

[†] for single-dose $AUC=AUC_{0-12h}$; for multiple-dose $AUC=AUC_{0-12h}$
* data obtained while volunteers received naltrexone which can enhance absorption

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE NOT INDICATED FOR RECTAL ADMINISTRATION. Data from a study involving 21 normal volunteers show that oxycodone hydrochloride extended-release tablets administered per rectum resulted in an AUC 39% greater and a C_{max} 9% higher than tablets administered by mouth. Therefore, there is an increased risk of adverse events with rectal administration.

Food Effects

Food has no significant effect on the extent of absorption of oxycodone from oxycodone hydrochloride extended-release tablets.

Distribution

Following intravenous administration, the volume of distribution (V_{ss}) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk (see PRECAUTIONS).

Metabolism

Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known.

The formation of oxymorphone, but not noroxycodone, is mediated by cytochrome P450 2D6 and, as such, its formation can, in theory, be affected by other drugs (see DRUG-DRUG INTERACTIONS).

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone ≤14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults.

Special Populations

Elderly

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Renal Impairment

Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This is accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in $t_{1/2}$ of elimination for oxycodone of only 1 hour (see PRECAUTIONS).

Hepatic Impairment

Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than normal subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The $t_{1/2}$ elimination for oxycodone increased by 2.3 hours (see PRECAUTIONS).

Drug-Drug Interactions (see PRECAUTIONS)

Oxycodone is metabolized in part by cytochrome P450 2D6 to oxymorphone which represents less than 15% of the total administered dose. This route of elimination may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants). However, in a study involving 10 subjects using quinidine, a known inhibitor of cytochrome P450 2D6, the pharmacodynamic effects of oxycodone were unchanged.

INDICATIONS AND USAGE

Oxycodone hydrochloride extended-release tablets are an extended-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

Oxycodone hydrochloride extended-release tablets are NOT intended for use as a prn analgesic.

Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency for Health Research and Quality (formerly known as the Agency for Health Care Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society.

Oxycodone hydrochloride extended-release tablets are not indicated for pain in the immediate post-operative period (the first 12 to 24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. Oxycodone hydrochloride extended-release tablets are only indicated for post-operative use if the patient is already receiving the drug prior to surgery or if the post-operative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

CONTRAINDICATIONS

Oxycodone hydrochloride extended-release tablets are contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. Oxycodone hydrochloride extended-release tablets are contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

Oxycodone Hydrochloride Extended-Release 80 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. This tablet strength may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

Oxycodone Hydrochloride Extended-Release 80 mg Tablets are for use only in opioid tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more. Care should be taken in the prescribing of this tablet strength. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

Misuse, Abuse and Diversion of Opioids

Oxycodone is an opioid agonist of the morphine-type. Such drugs are sought

by drug abusers and people with addiction disorders and are subject to criminal diversion.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing oxycodone hydrochloride extended-release tablets in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Oxycodone hydrochloride extended-release tablets have been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS and DRUG ABUSE AND ADDICTION**).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse

Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

DRUG ABUSE AND ADDICTION

Oxycodone hydrochloride extended-release tablets are a mu-agonist opioid with an abuse liability similar to morphine and are a Schedule II controlled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

“Drug seeking” behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours; refusal to undergo appropriate examination, testing or referral, repeated “loss” of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Oxycodone hydrochloride extended-release tablets, like other opioids, have been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Oxycodone hydrochloride extended-release tablets are intended for oral use only. Abuse of the crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Respiratory Depression

Respiratory depression is the chief hazard from oxycodone, the active ingredient in oxycodone hydrochloride extended-release tablets, as with all opioid agonists. Respiratory depression is a particular problem in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Head Injury

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources of pre-existing increased intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Hypotensive Effect

Oxycodone hydrochloride extended-release tablets may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone may produce orthostatic hypotension in ambulatory patients. Oxycodone, like all opioid analgesics of the morphine-type, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

PRECAUTIONS

General

Opioid analgesics have a narrow therapeutic index in certain patient populations, especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.

Use of oxycodone hydrochloride extended-release tablets is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

The administration of oxycodone may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Interactions with other CNS Depressants

Oxycodone hydrochloride extended-release tablets should be used with caution and started in a reduced dosage (1/3 to 1/2 of the usual dosage) in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of oxycodone hydrochloride extended-release tablets.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

Ambulatory Surgery and Post-Operative Use

Oxycodone hydrochloride extended-release tablets are not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

Oxycodone hydrochloride extended-release tablets are not indicated for pain in the immediate post-operative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.

Oxycodone hydrochloride extended-release tablets are not indicated for pain in the post-operative period if the pain is mild or not expected to persist for an extended period of time.

Oxycodone hydrochloride extended-release tablets are only indicated for post-operative use if the patient is already receiving the drug prior to surgery or if the post-operative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate (see American Pain Society guidelines).

Patients who are already receiving oxycodone hydrochloride extended-release tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention (see **DOSE AND ADMINISTRATION**).

Oxycodone hydrochloride extended-release tablets and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

Use in Pancreatic/Biliary Tract Disease

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see **DOSE AND ADMINISTRATION: Cessation of Therapy**).

Information for Patients/Caregivers

If clinically advisable, patients receiving oxycodone hydrochloride extended-release tablets or their caregivers should be given the following information by the physician, nurse, pharmacist, or caregiver:

1. Patients should be aware that oxycodone hydrochloride extended-release tablets contain oxycodone, which is a morphine-like substance.
2. Patients should be advised that oxycodone hydrochloride extended-release tablets were designed to work properly only if swallowed whole. Oxycodone hydrochloride extended-release tablets will release all their contents at once if broken, chewed or crushed, resulting in a risk of fatal overdose.
3. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
4. Patients should be advised not to adjust the dose of oxycodone hydrochloride extended-release tablets without consulting the prescribing professional.
5. Patients should be advised that oxycodone hydrochloride extended-release tablets may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
6. Patients should not combine oxycodone hydrochloride extended-release tablets with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
7. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
8. Patients should be advised that oxycodone hydrochloride extended-release tablets are a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
9. Patients should be advised that if they have been receiving treatment with oxycodone hydrochloride extended-release tablets for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the oxycodone hydrochloride extended-release tablets dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.
10. Patients should be instructed to keep oxycodone hydrochloride extended-release tablets in a secure place out of the reach of children. When oxycodone hydrochloride extended-release tablets are no longer needed, the unused tablets should be destroyed by flushing down the toilet.

Use in Drug and Alcohol Addiction

Oxycodone hydrochloride extended-release tablets are an opioid with no approved use in the management of addictive disorders. Their proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug-Drug Interactions

Opioid analgesics, including oxycodone hydrochloride extended-release tablets, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Oxycodone is metabolized in part to oxymorphone via cytochrome P450 2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

Use with CNS Depressants

Oxycodone hydrochloride extended-release tablets, like all opioid analgesics, should be started at 1/3 to 1/2 of the usual dosage in patients who are concurrently receiving other central nervous system depressants including

sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies of oxycodone to evaluate its carcinogenic potential have not been conducted.

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. coli test with and without metabolic activation at doses of up to 5000 mcg, chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1500 mcg/mL and with activation 48 hours after exposure at doses of up to 5000 mcg/mL, and in the *in vivo* bone marrow micronucleus test in mice (at plasma levels of up to 48 mcg/mL). Oxycodone was clastogenic in the human lymphocyte chromosomal assay in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 mcg/mL) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 mcg/mL or greater with metabolic activation and at 400 mcg/mL or greater without metabolic activation.

Pregnancy

Teratogenic Effects—Category B: Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg and 125 mg/kg, respectively. These doses are 3 and 46 times a human dose of 160 mg/day, based on mg/kg basis. The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

Oxycodone hydrochloride extended-release tablets are not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn. Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

Nursing Mothers

Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving oxycodone hydrochloride extended-release tablets because of the possibility of sedation and/or respiratory depression in the infant.

Pediatric Use

Safety and effectiveness of oxycodone hydrochloride extended-release tablets have not been established in pediatric patients below the age of 18. **It must be remembered that oxycodone hydrochloride extended-release tablets cannot be crushed or divided for administration.**

Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% (see **PHARMACOKINETICS AND METABOLISM**). Of the total number of subjects (445) in clinical studies of oxycodone hydrochloride extended-release tablets, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected side effects were seen in the elderly patients who received oxycodone hydrochloride extended-release tablets. Thus, the usual doses and dosing intervals are appropriate for these patients. As with all opioids, the starting dose should be reduced to 1/3 to 1/2 of the usual dosage in debilitated, non-tolerant patients. Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Laboratory Monitoring

Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

Hepatic Impairment

A study of oxycodone hydrochloride extended-release tablets in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at 1/3 to 1/2 the usual doses and careful dose titration is warranted.

Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

Gender Differences

In pharmacokinetic studies, opioid-naïve females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic use at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

ADVERSE REACTIONS

The safety of oxycodone hydrochloride extended-release tablets was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received oxycodone hydrochloride extended-release tablets in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

Serious adverse reactions which may be associated with oxycodone hydrochloride extended-release tablet therapy in clinical use are those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension, or shock (see **OVERDOSAGE**).

The non-serious adverse events seen on initiation of therapy with oxycodone hydrochloride extended-release tablets are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (>5%) include: constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and asthenia.

In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as oxycodone hydrochloride extended-release tablets therapy is continued and some degree of tolerance is developed.

Clinical trials comparing oxycodone hydrochloride extended-release tablets with immediate-release oxycodone and placebo, revealed a similar adverse event profile between oxycodone hydrochloride extended-release tablets and immediate-release oxycodone. The most common adverse events (>5%) reported by patients at least once during therapy were:

	Oxycodone Hydrochloride Extended-Release Tablets (n=227)	Immediate-Release (n=225)	Placebo (n=45)
	(%)	(%)	(%)
Constipation	23	26	7
Nausea	23	27	11
Somnolence	23	24	4
Dizziness	13	16	9
Pruritus	13	12	2
Vomiting	12	14	7
Headache	7	8	7
Dry Mouth	6	7	2
Asthenia	6	7	—
Sweating	5	6	2

The following adverse experiences were reported in oxycodone hydrochloride extended-release tablets treated patients with an incidence between 1% and 5%. In descending order of frequency they were anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials or were reported in post marketing experience:

General: accidental injury, chest pain, facial edema, malaise, neck pain, pain

Cardiovascular: migraine, syncope, vasodilation, ST depression

Digestive: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, nausea and vomiting, stomatitis, ileus

Hemic and Lymphatic: lymphadenopathy

Metabolic and Nutritional: dehydration, edema, hyponatremia, peripheral edema, syndrome of inappropriate antidiuretic hormone secretion, thirst

Nervous: abnormal gait, agitation, amnesia, depersonalization, depression, emotional lability, hallucination, hyperkinesia, hyposthesia, hypotonia, malaise, paresthesia, seizures, speech disorder, stupor, tinnitus, tremor, vertigo, withdrawal syndrome with or without seizures

Respiratory: cough increased, pharyngitis, voice alteration

Skin: dry skin, exfoliative dermatitis, urticaria

Special Senses: abnormal vision, taste perversion

Urogenital: amenorrhea, decreased libido, dysuria, hematuria, impotence, polyuria, urinary retention, urination impaired

OVERDOSAGE

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

Deaths due to overdose have been reported with abuse and misuse of oxycodone hydrochloride extended-release tablets, by ingesting, inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when oxycodone hydrochloride extended-release tablets are abused concurrently with alcohol or other CNS depressants, including other opioids.

In the treatment of oxycodone overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. In patients who are physically dependent on any opioid agonist including oxycodone hydrochloride extended-release tablets, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

DOSAGE AND ADMINISTRATION

General Principles

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE WITH AN ABUSE LIABILITY SIMILAR TO MORPHINE.

OXYCODONE, LIKE MORPHINE AND OTHER OPIOIDS USED IN ANALGESIA, CAN BE ABUSED AND IS SUBJECT TO CRIMINAL DIVERSION.

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS LEADS TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

In treating pain it is vital to assess the patient regularly and systematically. Therapy should also be regularly reviewed and adjusted based upon the patient's own reports of pain and side effects and the health professional's clinical judgment.

Oxycodone hydrochloride extended-release tablets are indicated for the management of moderate to severe pain requiring treatment with a strong opioid for continuous, around-the-clock analgesia for an extended period of time. The extended-release nature of the formulation allows the oxycodone hydrochloride extended-release tablets to be effectively administered every 12 hours (see **CLINICAL PHARMACOLOGY: PHARMACOKINETICS AND METABOLISM**). While symmetric (same dose AM and PM), around-the-clock, q12h dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing, tailored to their pain pattern. It is usually appropriate to treat a patient with only one opioid for around-the-clock therapy.

Physicians should individualize treatment using a progressive plan of pain management such as outlined by the World Health Organization, the American Pain Society and the Federation of State Medical Boards Model Guidelines. Health care professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring [See **BOXED WARNINGS**].

Initiation of Therapy

It is critical to initiate the dosing regimen for each patient individually, taking into account the patient's prior opioid and non-opioid analgesic treatment. Attention should be given to:

1. the general condition and medical status of the patient;
2. the daily dose, potency and kind of the analgesic(s) the patient has been taking;
3. the reliability of the conversion estimate used to calculate the dose of oxycodone;
4. the patient's opioid exposure and opioid tolerance (if any);
5. special safety issues associated with conversion to oxycodone hydrochloride extended-release tablets doses at or exceeding 160 mg q12h (see **Special Instructions for Oxycodone Hydrochloride Extended-Release Tablets, 80 mg**); and
6. the balance between pain control and adverse experiences.

Care should be taken to use low initial doses of oxycodone hydrochloride extended-release tablets in patients who are not already opioid-tolerant, especially

those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications (see **PRECAUTIONS: Drug-Drug Interactions**).

For initiation of oxycodone hydrochloride extended-release tablets therapy for patients previously taking opioids, the conversion ratios from Foley, KM. [NEJM, 1985; 313:84-95], found below, are a reasonable starting point, although not verified in well-controlled, multiple-dose trials.

Oxycodone hydrochloride extended-release tablets should be individually titrated to a dose that provides adequate analgesia and minimizes side effects.

1. Using standard conversion ratio estimates (see Table 4 below), multiply the mg/day of the previous opioids by the appropriate multiplication factors to obtain the equivalent total daily dose of oral oxycodone.
2. When converting from oxycodone, divide this 24-hour oxycodone dose in half to obtain the twice a day (q12h) dose of oxycodone hydrochloride extended-release tablets.
3. Round down to a dose which is appropriate for the tablet strength available (80 mg tablets).
4. Discontinue all other around-the-clock opioid drugs when oxycodone hydrochloride extended-release tablets therapy is initiated.
5. No fixed conversion ratio is likely to be satisfactory in all patients, especially patients receiving large opioid doses. The recommended doses shown in Table 4 are only a starting point, and close observation and frequent titration are indicated until patients are stable on the new therapy.

	Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone* (Mg/Day Prior Opioid X Factor = Mg/Day Oral Oxycodone)	
	Oral Prior Opioid	Parenteral Prior Opioid
Oxycodone	1	—
Codeine	0.15	—
Hydrocodone	0.9	—
Hydromorphone	4	20
Levorphanol	7.5	15
Meperidine	0.1	0.4
Methadone	1.5	3
Morphine	0.5	3

*To be used only for conversion to oral oxycodone. For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

In all cases, supplemental analgesia (see below) should be made available in the form of a suitable short-acting analgesic.

Oxycodone hydrochloride extended-release tablets can be safely used concomitantly with usual doses of non-opioid analgesics and analgesic adjuvants, provided care is taken to select a proper initial dose (see **PRECAUTIONS**).

Conversion from Transdermal Fentanyl to Oxycodone Hydrochloride Extended-Release Tablets

Eighteen hours following the removal of the transdermal fentanyl patch, oxycodone hydrochloride extended-release tablets treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg q12h of oxycodone hydrochloride extended release tablets should be initially substituted for each 25 mcg/hr fentanyl transdermal patch. The patient should be followed closely for early titration, as there is very limited clinical experience with this conversion.

Managing Expected Opioid Adverse Experiences

Most patients receiving opioids, especially those who are opioid-naïve, will experience side effects. Frequently the side effects from oxycodone hydrochloride extended-release tablets are transient, but may require evaluation and management. Adverse events such as constipation should be anticipated and treated aggressively and prophylactically with a stimulant laxative and/or stool softener. Patients do not usually become tolerant to the constipating effects of opioids.

Other opioid-related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and is unacceptable to the patient, treatment with anti-emetics or other modalities may relieve these symptoms and should be considered.

Individualization of Dosage

Once therapy is initiated, pain relief and other opioid effects should be frequently assessed. Patients should be titrated to adequate effect (generally mild or no pain with the regular use of no more than two doses of supplemental analgesia per 24 hours). Patients who experience breakthrough pain may require dosage adjustment or rescue medication. Because steady-state plasma concentrations are approximated within 24 to 36 hours, dosage adjustment may be carried out every 1 to 2 days. It is most appropriate to increase the q12h dose, not the dosing frequency. There is no clinical information on dosing intervals shorter than q12h. As a guideline, except for the increase from 10 mg to 20 mg q12h, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose at each increase.

If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. If this adjustment leads to inadequate analgesia, a supplemental dose of immediate-release oxycodone may be given. Alternatively, non-opioid analgesic adjuvants may be employed. Dose adjustments should be made to obtain an appropriate balance between pain relief and opioid-related adverse experiences.

If significant adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated aggressively. Once adverse events are under control, upward titration should continue to an acceptable level of pain control.

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the health-care team, the patient and the caregiver/family.

Special Instructions for Oxycodone Hydrochloride Extended-Release Tablets, 80 mg

(For use in opioid-tolerant patients only)

Oxycodone Hydrochloride Extended-Release 80 mg Tablets are for use only in opioid-tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more. Care should be taken in the prescribing of this tablet strength. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

Supplemental Analgesia

Most patients given around-the-clock therapy with extended-release opioids may need to have immediate-release medication available for exacerbations of pain or to prevent pain that occurs predictably during certain patient activities (incident pain).

Maintenance of Therapy

The intent of the titration period is to establish a patient-specific q12h dose that will maintain adequate analgesia with acceptable side effects for as long as pain relief is necessary. Should pain recur then the dose can be incrementally increased to re-establish pain control. The method of therapy adjustment outlined above should be employed to re-establish pain control.

During chronic therapy, especially for non-cancer pain syndromes, the continued need for around-the-clock opioid therapy should be reassessed periodically (e.g., every 6 to 12 months) as appropriate.

Cessation of Therapy

When the patient no longer requires therapy with oxycodone hydrochloride

extended-release tablets, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

Conversion from Oxycodone Hydrochloride Extended-Release Tablets to Parenteral Opioids

To avoid overdose, conservative dose conversion ratios should be followed.

SAFETY AND HANDLING

Oxycodone hydrochloride extended-release tablets are solid dosage forms that contain oxycodone which is a controlled substance. Like morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act.

Oxycodone hydrochloride extended-release tablets have been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

HOW SUPPLIED

Oxycodone Hydrochloride Extended-Release Tablets, 80 mg are green, film-coated, oval, convex tablets debossed with "83" on one side and "33" on the other side. They are available in bottles of 100.

Store at controlled room temperature, between 20° and 25°C (68° and 77°F) (see USP).

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

CAUTION

DEA Order Form Required.

Manufactured By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18660



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