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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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P-3651

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. **11.052.726A**
Solicitud de patente a nombre de **INTERMUNE INC**

Yo, DILIA RODRIGUEZ D'ALEMAN, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 No. 86-53, piso 6, obrando como obrando como apoderada de **INTERMUNE INC** solicitante de la patente de la referencia, en respuesta al oficio No. **5080** notificado por fijación en lista el 19 de marzo de 2013, me permito manifestar:

1. Con fundamento en la facultad que confiere el artículo 34 de la Decisión 486 al solicitante para modificar la solicitud de patente en cualquier momento del trámite, presento junto con este memorial un nuevo capítulo reivindicatorio, el cual consta de 10 reivindicaciones y reemplaza completamente el capítulo presentado anteriormente.

En cuanto a estas modificaciones, me permito decir que las mismas no amplían de ninguna manera la materia objeto de la presente solicitud y se realizaron con el ánimo de superar las objeciones planteadas por el examinador en su concepto técnico.

2. Materia no Patentable

Es deseo del solicitante poner de presente que se han realizado las siguientes modificaciones en el pliego reivindicatorio con el fin de superar las objeciones hechas por el Examinador:

Se ha modificado la reivindicación principal de tal forma que el preámbulo de la misma se dirige hacia un kit en lugar de hacia un método de tratamiento. Dicho "Kit que comprende pirfenidona"; está soportado en la descripción en la página 19 líneas 18-20. Las anteriores reivindicaciones 2 y 3 que hacían referencia a materia no patentable se han eliminado.

000001/86

El Examinador objeta a la patentabilidad de la presente invención respecto a D1-D3.

El Solicitante considera que **D1 (U.S. 2007/117841)** no destruye la novedad de las reivindicaciones actuales porque no da a conocer una población de pacientes con fibrosis pulmonar que haya mostrado una elevación de grado 2 en biomarcadores de lesión hepática. Los marcadores de la lesión hepática no tienen relación con la fibrosis pulmonar. En la medida en que D1 da a conocer una población de pacientes con fibrosis hepática, tales pacientes ya tenían una elevación en biomarcadores de la lesión hepática antes de la administración de pirfenidona. D1 no se refiere a la población de pacientes en los que la elevación de AST y/o ALT se produce después de la administración de pirfenidona, como en la presente invención. La población de pacientes de la invención no sólo es claramente diferente de los pacientes con enfermedad hepática, sino que además se trata de manera diferente. Una diversidad de pruebas respaldan esta postura.

Por ejemplo, la etiqueta de Pirespa® de Shionogi **(Anexo A)** da a conocer en la sección 3(1) en la página 2 que si se produce cualquier anomalía en las enzimas hepáticas (por ejemplo, AST, ALT) durante la administración de Pirespa®, debe interrumpirse la administración y deben tomarse medidas terapéuticas apropiadas. Merece la pena indicar que la sección de "Reacción adversa significativa" menciona que debe interrumpirse la administración. Sólo se menciona que la reducción de la dosis sea una opción en la sección 3(2) titulada "Otras reacciones adversas", es decir distintas de anomalías hepáticas. No hay ninguna descripción en la etiqueta de que deba reexponerse al paciente a pirfenidona. Si se recomendara la reexposición, la etiqueta lo habría mencionado claramente. Véase, por ejemplo, la etiqueta de Bosentan® **(Anexo D)** que recomienda los cambios en el tratamiento que se requieran si se elevan los niveles de aminotransferasa. Al contrario que la etiqueta de Parafon Forte® **(Anexo E)**, que menciona que debe interrumpirse la administración si un paciente desarrolla enzimas hepáticas anómalas.

Antes de la fecha de presentación de la presente solicitud se sabía de manera general que las anomalías de la función hepática que aparecen después de iniciar la administración de un fármaco pueden indicar la posibilidad de que dicho fármaco provoque lesión hepática inducida intensa, irreversible y posiblemente mortal. La "Draft Guidance: Drug-Induced Liver Injury: Premarketing Clinical Evaluation" (2007) de la Food and Drug Administration **(Anexo B),** menciona que: "la reexposición [a fármaco] puede iniciar una reacción más intensa y algunas veces fulminante, tal como se observó con halotano hace varias décadas". Por tanto, dada la directriz de borrador de la FDA, un experto habitual en la técnica evitaría la reexposición cuando se observan anomalías de la función hepática después de la administración.

Como prueba adicional de esto, se adjunta como **Anexo C** una presentación de la FDA, Positive Rechallenge Following Drug-induced Liver Injury: A review of 88 cases (2008) disponible en http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/ucm076835.pdf
que describe una elevación de AST o ALT de más de 2 veces respecto al límite superior de la normalidad (>2 X ULN) como uno de los criterios para determinar una posible lesión hepática intensa inducida por fármaco. También indica que los médicos deben evitar la reexposición después de lesión hepática inducida por un fármaco:

> *Se definió una reexposición a fármaco positiva usando los siguientes tres criterios. En primer lugar, el caso tenía que demostrar un acontecimiento hepático inicial que cumpliera con la definición de RUCAM publicada por Danan, et al., unos criterios internacionalmente reconocidos de AST, ALT o fosfatasa alcalina de más de dos veces respecto al límite superior de la normalidad.* (Página 3; énfasis añadido).

> *En conclusión, se necesita una mayor concienciación sobre la reexposición positiva después de lesión hepática inducida por fármaco, dada la posibilidad de acontecimientos adversos graves y desenlaces algunas veces mortales y en general, los médicos deben evitar tales reexposiciones.* (Página 37; énfasis añadido).

Por tanto, pruebas de fuentes diferentes muestran que en un paciente que ha mostrado una anomalía de grado 2 (aumento de más de 2,5 a 5 veces respecto al límite superior de la normalidad, ULN) en AST o ALT, debe interrumpirse la pirfenidona y debe evitarse la reexposición o nueva administración de pirfenidona. En cambio, la presente invención describe la pirfenidona para tratar a pacientes que normalmente habrían interrumpido la exposición al fármaco. Esta población de pacientes se caracteriza en las reivindicaciones actuales por haber mostrado una anomalía de función hepática de grado 2 después de iniciar la administración de pirfenidona. Los parámetros de una elevación de grado 2 se conocen bien en la técnica y se describen en la presente solicitud en la Tabla 1, párrafo [0043]. La técnica diverge por tanto de de la presente invención. El experto en la técnica no habría administrado pirfenidona a una población de pacientes que hubieran mostrado una anomalía de grado 2 en una o ambas de ALT y AST, después de la administración de pirfenidona.

D1 no da a conocer la población de pacientes mencionada en las reivindicaciones de la invención ni describe un envase que comprenda pirfenidona para su uso en dicha población de pacientes, y no debe afectar por tanto a la patentabilidad de la invención.

Respecto a **D2 (WO 2007/38315),** el Solicitante subscribe que no menciona nada con respecto a ningún marcador de la función hepática, mucho menos alanina transaminasa y aspartato transaminasa. Sólo por este motivo determinante, D2 no da a conocer la población de pacientes mencionada en las reivindicaciones, ni un envase que comprenda pirfenidona para su uso en tal población de pacientes, y no puede por tanto afectar la patentabilidad de la invención.

Respecto a **D3 (WO 2005/040758),** el solicitante subscribe que refiere a un contenido idéntico a D1, y por los mismos motivos no debe afectar a la presente invención.

En este orden de ideas, no queda duda de la evidencia de que la invención es nueva e inventiva y encaja dentro de la definición de patente de invención, se solicita respetuosamente a la Oficina de Patentes Colombiana retirar todas las objeciones y conceder la presente solicitud.

En consecuencia, solicitamos a ese despacho pronunciarse en relación con todos los argumentos presentados en este memorial dando estricta aplicación al principio del debido proceso consagrado en el artículo 29 de la Constitución Nacional. De igual forma, si el examinador considera que subsisten razones para objetar la presente invención ruego expedir otro examen de fondo con los debidos motivos y razones que sustenten su objeción con el fin de que mi mandante tenga la posibilidad de exponer sus argumentos con base en la interpretación de los artículos 45 de la Decisión 486 -el cual otorga la facultad al examinador para emitir los exámenes de fondo-, 35 y 59 del Código Contencioso Administrativo que señala que: *"habiéndose dado oportunidad a los interesados para expresar sus opiniones, y con base en las pruebas e informes disponibles, se tomará la decisión que será motivada al menos en forma sumaria si afecta a particulares"* y *"(..) deberá proferirse la decisión definitiva. Esta se motivará en sus aspectos de hecho y de derecho, y en los de conveniencia si es el caso"*, respectivamente (el subrayado es nuestro).

Señor Superintendente,

DILIA RODRIGUEZ D'ALEMAN
C.C. 41.654.882 de Bogotá
T.P. 20824 del C.S.J.
notificaciones@clarkemodet.com.co

REIVINDICACIONES

1. Un kit que comprende pirfenidona para uso en el tratamiento de un paciente quien se beneficiaria de la administración de la pirfenidona, dicho paciente debe haber mostrado una anomalía Grado 2 en una o ambas de la alanina transaminasa (ALT) y la aspartato transaminasa (AST), después de la administración de la pirfenidona, en el que (a) a dicho paciente se le administra pirfenidona en dosis de al menos 1600 mg/día.

2. El kit de acuerdo con la reivindicación 1, en donde (a) a dicho paciente se le administra pirfenidona en dosis de 2200 a 2600 mg/día, o a dicho paciente se le administra pirfenidona en una dosis de 2400 mg/día o 2403 mg/día.

3. El kit de acuerdo con cualquiera de las reivindicaciones 1-2, en donde, antes de la etapa (a), a dicho paciente se le administra pirfenidona en dosis menores de 1600 mg/día por un periodo de tiempo o a dicho paciente se le administra pirfenidona en dosis menores de 2400 mg/día por un periodo de tiempo.

4. El kit de acuerdo con cualquiera de las reivindicaciones 1-3, en donde, antes de la etapa (a), se descontinúa la administración de pirfenidona al paciente por un periodo de tiempo, opcionalmente por cerca de una semana, o hasta que los biomarcadores de la función hepática estén dentro de los límites normales.

5. El kit de acuerdo con cualquiera de las reivindicaciones 1-3, en donde, antes de la etapa (a), se descontinúa la administración de pirfenidona al paciente por un periodo de tiempo, opcionalmente por cerca de una semana, o hasta que los biomarcadores de la función hepática estén dentro de los límites normales, se administran al paciente 800 mg/día o 801 mg/día de pirfenidona durante un primer periodo de tiempo, opcionalmente por cerca de una semana, o hasta que los biomarcadores de la función hepática estén dentro de los límites normales, y opcionalmente se administran 1600 mg/día o 1602 mg/día de pirfenidona al paciente por un segundo periodo de tiempo que sigue al primer periodo, opcionalmente una semana, o hasta que los biomarcadores de la función hepática estén dentro de los límites normales.

6. El kit de acuerdo con cualquiera de las reivindicaciones 1-4, en donde, antes de la etapa previa (a), se administran al paciente 600-1000 mg/día de pirfenidona por un periodo de tiempo, opcionalmente por cerca de una semana, o hasta que los biomarcadores de la función hepática estén dentro de los límites normales.

7. El kit de acuerdo con cualquiera de las reivindicaciones 1-6, en donde la pirfenidona se administra tres veces por día con la comida.

8. El kit de acuerdo con cualquiera de las reivindicaciones 1 a 7, en donde el paciente quien se beneficiaría de la administración de la pirfenidona sufre de una condición de fibrosis.

9. El kit de acuerdo con cualquiera de las reivindicaciones 1-8, en donde el paciente quien se beneficiaría de la administración de la pirfenidona sufre de una condición seleccionada del grupo que consiste de fibrosis pulmonar, neumonía intersticial idiopática, enfermedades autoinmunes del pulmón, hipertrofia benigna de la próstata, infarto coronario o del miocardio, fibrilación auricular, infarto cerebral, fibrosis miocárdica, fibrosis del músculo esquelético, adhesiones post-quirúrgicas, cirrosis hepática, enfermedad fibrótica renal, enfermedad vascular fibrótica, esclerodermia, síndrome de Hermansky-Pudlak, neurofibromatosis, enfermedad de Alzheimer, retinopatía diabética, lesiones de la piel, fibrosis de nodo linfático asociada con el VIH, enfermedad pulmonar obstructiva crónica (EPOC), fibrosis pulmonar inflamatoria, la artritis reumatoide, espondilitis reumatoide, osteoartritis, gota, sepsis, choque séptico, choque endotóxico, sepsis por gramnegativos, síndrome de choque tóxico, síndrome de dolor miofacial (MPS), shigelosis, asma, síndrome de distrés respiratorio del adulto, enfermedad inflamatoria intestinal, enfermedad de Crohn, psoriasis, eccema, colitis ulcerosa, nefritis glomerular, tiroiditis crónica, enfermedad de Grave, enfermedad de Ormond, gastritis autoinmune, miastenia grave, anemia hemolítica autoinmune, neutropenia autoinmune, trombocitopenia, fibrosis pancreática, hepatitis activa crónica, enfermedad renal aguda y crónica, fibrosis renal, síndrome del intestino irritable, piresis, restenosis, malaria cerebral, lesión y apoplejía isquémica, trauma neural, enfermedad de Huntington, enfermedad de Parkinson, dolor agudo y crónico, alergias, hipertrofia cardiaca, insuficiencia cardiaca crónica, síndrome coronario agudo, caquexia, malaria, lepra, leishmaniasis, enfermedad de Lyme, síndrome de Reiter, sinovitis aguda, degeneración muscular, bursitis, tendinitis, tenosinovitis, hernia, rotura, o síndrome del disco intervertebral prolapsado, osteopetrosis , trombosis, silicosis, sarcosis pulmonar, enfermedades de resorción ósea, cáncer, reacción del injerto contra huésped, enfermedades autoinmunes, SIDA, herpes zoster, herpes simple I o II, el virus de la influenza, el síndrome respiratorio agudo severo (SARS), el citomegalovirus, y la diabetes mellitus.

10. El kit de acuerdo con cualquiera de las reivindicaciones precedentes, en donde el paciente ha mostrado un nivel anormal de alanina transaminasa y/o aspartato transaminasa, después de la administración de la pirfenidona, y en el que el nivel anormal es mayor 2.5-veces y menor que o igual a 5-veces el límite superior de lo normal.

ANEXO A

Prepared: October 2008 (1st version)

Standard Commodity Classification No. of Japan
873999

- Antifibrosis agent -

Pirespa® Tablets 200 mg

<Pirfenidone tablets>

Powerful drug, designated drug and prescription drug [1)]

Storage
Store at room temperature.

Expiration date
Indicated on the package etc. (Expiration period: Four years)

Approval No.	22000AMX02373
Date of listing in the NHI reimbursement price	Not listed in the NHI reimbursement price
Date of initial marketing in Japan	
International birth date	October 2008

1) Caution – Use only as directed by a physician

WARNINGS

1. **Before this drug is used, it should be adequately explained to the patient that chromosome structure abnormality was shown in light genotoxicity test, indicating the possibility of carcinogenesis of the skin accompanied by light exposure. After the patient's understanding is confirmed, administration should be initiated. [Refer to the items of "Important Precautions" and "Other Precautions."]**
2. **This drug should be used under the supervision of a physician familiar with treatment of idiopathic pulmonary fibrosis.**

CONTRAINDICATIONS (Pirespa® is contraindicated in the following patients.)

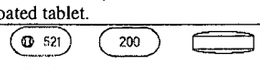
Patients with a history of hypersensitivity to any of the ingredients of this drug.

COMPOSITION AND DESCRIPTION

1. Composition

Brand name	Pirespa® Tablets 200 mg
Ingredient/content (Content per tablet)	Pirfenidone 200 mg
Inactive ingredients	Lactose hydrate, carmellose calcium, hydroxypropylcellulose, magnesium stearate, hypromellose, triethyl citrate, titanium oxide, talc, and yellow iron sesquioxide

2. Description

Brand name	Pirespa® Tablets 200 mg
Description/dosage form	A pale yellow to pale yellowish brown oval film-coated tablet.
Appearance	 Surface Back Side
Size	Major axis: Approx 12.2 mm Minor axis: Approx 6.4 mm Thickness: Approx 4.5 mm

Weight	Approx 0.30 g
Identification code	521:200

INDICATIONS

Idiopathic pulmonary fibrosis

DOSAGE AND ADMINISTRATION

Usually, an initial dose of 200 mg/time of pirfenidone is orally administered to adults three times a day (600 mg/day) after meals. The dose is gradually increased by 200 mg up to 600 mg/time (1800 mg/day) while observing the patient's state. The dose is appropriately adjusted according to symptoms.

<Precautions Relating to Dosage and Administration>

1. It is preferred that administration of this drug be initiated from 200 mg/time (600 mg/day) as the initial dose and that the dose be gradually increased by 200 mg/time over a standard of 2 weeks and maintained at 600 mg/time (1800 mg/day).
2. When gastrointestinal distress, etc. occurs, consider dose reduction or drug withdrawal as necessary. When the symptom is relieved, it is preferred that the dose be gradually increased according to 1. and the standard maintenance dose be set as 400 mg/time (1200 mg/day) or more.
3. Since fasting administration may result in a higher plasma concentration in comparison to administration after eating and adverse drug reactions may occur, this drug should be administered after meals. [Refer to the item "PHARMACOKINETICS."]

PRECAUTIONS

1. **Careful Administration (Pirespa® should be administered with care in the following patients.)**
   (1) Patients with hepatic impairment [may worsen hepatic impairment.]
   (2) Patients with renal impairment [There is little experience with such use.]
   (3) Elderly patients [see "Use in the Elderly."]
2. **Important Precautions**
   (1) **Photosensitivity may occur** and **there is the possibility of carcinogenesis of the skin accompanied by light exposure.** Patients should be carefully instructed on the following points before administration.
      1) **When going outdoors,** take protective measures against light exposure, such as avoiding UV rays by wearing long-sleeved clothes and a hat, using a parasol, or applying a sunscreen with a high sun protection factor (SPF50+, PA+++). [Refer to the item "Other Precautions."]
      2) If skin abnormalities such as rash or itching are observed, contact a physician immediately.
   (2) Since Pirespa may induce sleepiness, dizziness or unsteadiness, patients should be cautioned against engaging in **potentially hazardous operation of equipment, such as driving a car.**
   (3) **Jaundice and hepatic dysfunction** accompanied by elevated AST (GOT), ALT (GPT), etc. may occur. Periodic tests should be performed during administration of this drug and the patient's status should be carefully monitored. [Refer to the item "Serious adverse reactions."]
3. **Adverse Reactions**
   Out of 265 cases evaluated for safety before NDA approval, adverse reactions were observed in 233 cases (87.9%). The primary adverse reactions were photosensitivity (137 cases, 51.7%), anorexia (61 cases, 23.0%), stomach discomfort (37 cases, 14.0%), and nausea (32 cases, 12.1%). Abnormal changes in clinical laboratory test values were observed in 120 cases (45.3%) among 265 cases evaluated for safety. The primary change was elevated γ-GTP (53 cases, 20.0%).
   (1) **Serious adverse reactions**
   Hepatic dysfunction and jaundice (0.1 to less than 1%): Since jaundice and hepatic dysfunction accompanied by elevated AST (GOT), ALT (GPT), etc. may occur and result in hepatic failure, the patient's status should be carefully monitored by periodic testing, etc. If any abnormalities are observed, administration should be discontinued and appropriate therapeutic measures should be taken.
   (2) **Other adverse reactions**
   If the following adverse reactions occur, appropriate therapeutic measures such as dose reduction or discontinuation of administration should be performed as necessary.

Incidence	≥ 5%	1% to less than 5%	< 1%
Dermatologic	photosensitivity (51.7%), rash	itching, erythema, eczema, lichen planus	
Gastrointestinal	anorexia (23.0%), stomach discomfort (14.0%), nausea (12.1%), diarrhea, heartburn	abdominal fullness, vomiting, constipation, gastric reflux, stomatitis, abdominal discomfort, abdominal pain, cheilitis	labial erosion
Cardiovascular		palpitations	
Psychoneurologic	sleepiness, dizziness, unsteadiness (sensation)	headache, headache dull	
Hepatic	Elevated γ-GTP (20.0%), elevated AST (GOT), elevated ALT (GPT), elevated Al-P, elevated LDH	Elevated bilirubin	
Hematologic		leukocytosis, eosinophilia, leukopenia	thrombocytopenia
Others	malaise	weight loss, fever, dysgeusia, musculoskeletal pain, hot flashes	

4. **Use in the Elderly**
   Since the elderly has decreased physiological function in general, this drug should be carefully administered.
5. **Use During Pregnancy, Delivery or Nursing**
   (1) The drug should not be given to pregnant women or women who may be pregnant. [A prolonged gestational period, a decreased birth rate, and drug transfer to the fetus have been observed in studies in rats. Abortion or premature birth has been observed in studies in rabbits. Teratogenicity was not observed in studies in either laboratory animal[1),2)].]
   (2) Women who are nursing should avoid doing so while taking this drug. [Drug transfer to milk and inhibition of weight gain in offspring after the midpoint of the nursing period have been observed in rats[2),3)].]
6. **Pediatric Use**
   The safety of this drug in low birth weight infants, neonates, nursing infants, infants and children has not yet been established. [There is no experience with such use.]
7. **Precautions For Use**
   When dispensing the drug: For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the drug from the package prior to use. (There are reports that when the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, resulting in severe complications such as mediastinitis.)
8. **Other Precautions**
   (1) Light chromosomal abnormality test using cultured cells derived from Chinese hamster lung has revealed light exposure-induced chromosome structure abnormality. Since there is no difference between the plasma concentration that induces phototoxicity (photosensitivity) and the drug concentration that produces

photogenotoxicity,there is the risk of light exposure being accompanied by skin cancer[4].

(2) Skin phototoxicity tests using guinea pigs revealed that the drug is a skin phototoxin. It has been confirmed that sunscreen of SPF50+ and PA+++ can prevent the manifestation of phototoxicity[5].

(3) Long-term carcinogenicity tests using mice and rats (104 weeks) revealed the increased occurrence of hepatocytic tumor (800 mg/kg/day or more in mice, 750 mg/kg/day or more in rats) and uterine tumor (1500 mg/kg/day in rats), but both were considered to be due to a rodent-specific mechanism[6]. The results of genotoxicity tests were negative[7].

(4) Cardiovascular tests using rats and dogs revealed hypotension (300 mg/kg in rats) and increased heart rate (100 mg/kg or more in both rats and dogs). Electrocardiograms revealed atrioventricular block (100 mg/kg or more in rats), rapid ventricular extrasystole (300 mg/kg in rats), and an effect on the QTc interval (100 mg/kg or more in dogs). *In vitro* cardiac electrophysiological tests confirmed that the effect on myocardial action potential and hERG current is small[8].

PHARMACOKINETICS

1. Plasma concentration

(1) Fasting administration of a single dose

Figure 1 and Table 1 show the plasma concentration and pharmacokinetic parameters with fasting administration of a single dose of 200, 400 or 600 mg of this drug to 6 healthy men each.

Both the Cmax and AUC increased almost in proportion to a dose[9].

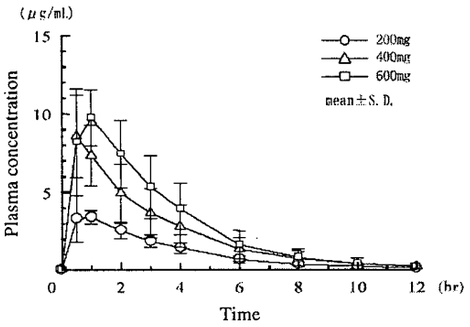


Fig. 1. Plasma concentration with fasting oral administration of a single dose

Table 1. Pharmacokinetic parameters

Dose (mg)	*n*	Cmax (μg/mL)	Tmax (hr)	AUC_{0-48} (μg·hr/mL)	$T_{1/2}$ (hr)
200	6	3.88 ± 0.82	0.75 ± 0.27	13.97 ± 2.71	2.10 ± 0.45
400	6	9.24 ± 1.74	0.58 ± 0.20	29.10 ± 11.77	1.96 ± 0.55
600	6	10.57 ± 1.78	0.83 ± 0.26	37.03 ± 11.97	1.76 ± 0.40

(Measurement method: HPLC) (mean ± S.D.)

(2) Repeated administration

Table 2 shows the pharmacokinetic parameters with oral administration for 18 consecutive days to 12 healthy men by the gradual increase method whereby 200 mg, 400 mg, and 600 mg were each administered 3 times/day after breakfast, lunch, and dinner, for a 6-day period (administered twice/day after breakfast and lunch on days 1 and 6 of administration).

The plasma concentration on days 1 and 6 of administration showed virtually the same change over time with each dose, with the Cmax and AUC on day 1 of administration both increasing proportional to dose[9].

Table 2. Pharmacokinetic parameters

Dose/ time (mg)	*n*	Administration day (Overall)	$Cmax_{0-4}$ [a] (μg/mL)	$Tmax_{0-4}$ [a] (hr)	$Cmax_{4-24}$ [b] (μg/mL)	$Tmax_{4-24}$ [b] (hr)
200	12	1	2.71 ± 0.91	1.08 ± 0.47	2.83 ± 1.12	6.04 ± 1.05
		6	3.06 ± 1.28	1.08 ± 0.82	2.70 ± 0.51	6.29 ± 0.96
400		1 (7)	4.94 ± 1.29	1.79 ± 0.89	6.22 ± 1.59	5.79 ± 1.36
		6 (12)	6.19 ± 1.89	1.17 ± 0.54	5.91 ± 2.09	6.38 ± 1.15
600		1 (13)	8.20 ± 1.29	1.25 ± 0.45	9.21 ± 1.97	6.33 ± 1.15
		6 (18)	8.19 ± 1.54	1.71 ± 0.54	10.00 ± 1.70	6.13 ± 1.00

Dose/ time (mg)	*n*	Administration day (Overall)	AUC_{0-24} [c] (μg·hr/mL)	$T_{1/2}$ (hr)
200	12	1	19.17 ± 6.46	2.17 ± 0.30
		6	22.03 ± 5.47	2.25 ± 0.29
400		1 (7)	46.13 ± 10.01	2.42 ± 0.48
		6 (12)	48.69 ± 11.21	2.36 ± 0.38
600		1 (13)	77.22 ± 15.44	2.53 ± 0.42
		6 (18)	82.31 ± 16.50	2.55 ± 0.45

a) Value with administration after breakfast

b) Value with administration after lunch

c) Value with administration twice/day

(Measurement method: HPLC) (mean ± S.D.)

2. Effects of meals

Figures 2 and Table 3 show the plasma concentration and pharmacokinetic parameters with administration of a single dose of 400 mg after eating and while fasting to 6 healthy men. Meals significantly decreased Cmax and AUC and significantly delayed Tmax[9].

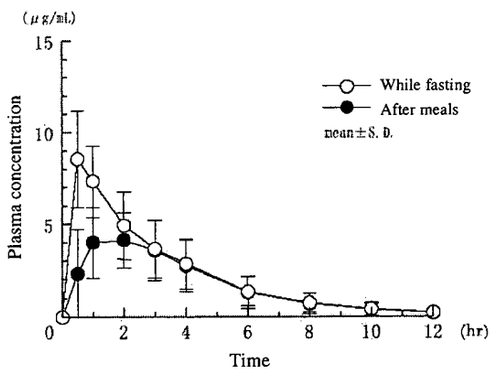


Fig. 2 Plasma concentration with oral administration of a single dose after meals and while fasting

Table 3. Pharmacokinetic parameters

Dose (mg)		n	Cmax (μg/mL)	Tmax (hr)	$AUC_{0\text{-}48}$ (μg·hr/mL)	$T_{1/2}$ (hr)
400	After meals	6	4.88 ± 1.72	1.83 ± 0.75	22.13 ± 10.63	1.77 ± 0.55
	While fasting		9.24 ± 1.74	0.58 ± 0.20	29.10 ± 11.77	1.96 ± 0.55

(Measurement method: HPLC) (mean ± S.D.)

3. Distribution

(Reference)

When a single dose of 100 mg/kg of [^{14}C]-pirfenidone was orally administered to rats, the organs and tissues having a higher radioactivity concentration than plasma included the liver, kidneys, pancreas, and preputial glands. The radioactivity concentration of the majority of the organs and tissues peaked 5 to 30 minutes after administration and then disappeared by a half-life of 4 to 7 hours, but the half-life of preputial glands was longer than that of other tissues at about 15 hours[10].

4. Metabolism

This drug is metabolized by multiple CYP molecular species (CYP1A2, 2C9, 2C19, 2D6, and 2E1) in human liver microsomes[11]. (*in vitro*)

It is estimated that this drug is not susceptible to CYP inhibition by other drugs since multiple CYP molecules are involved in metabolism reaction.

5. Excretion

When a single dose of 200, 400 or 600 mg was orally administered to 6 healthy men while fasting, the 48-hour urinary excretion rate was less than 1% for unaltered drug and approximately 90% for pirfenidone-5-carboxylate form (main metabolite) regardless of the dose[9].

6. Others

Serum protein binding rate: When a single dose of 600 mg was orally administered to healthy adults while fasting, the serum protein binding rate as measured by ultrafiltration was 54-62% 1 hour and 3 hours after administration[9].

CLINICAL STUDIES

A placebo-controlled double blind study performed before NDA approval showed that when compared with placebo, administration of pirfenidone inhibits a reduction in vital capacity (Table 4). The subjects of this study were patients who were diagnosed as having idiopathic pulmonary fibrosis according to the 4th Revised Edition of Criteria for Clinical Diagnosis of Idiopathic Interstitial Pneumonia of the Diffuse Pulmonary Disease Research Group of the Ministry of Health, Labour and Welfare and who, when subjected to a 6-minute treadmill walking test before administration, showed an SpO_2 minimum value on exertion of 85% or higher and a difference from the resting SpO_2 of 5% or higher.[12].

Table 4. Comparison of change in vital capacity [1]

Group		No. of cases evaluated for efficacy	Adjusted mean (L)	Standard deviation	Comparison with placebo group	
					Difference of adjusted mean (90% confidence interval)	Bilateral p value
Pirfenidone	1800 mg/day	104	-0.09	0.02	0.07 (0.01, 0.13)	0.0416
	1200 mg/day	54	-0.08	0.03	0.09 (0.02, 0.16)	0.0394
Placebo		103	-0.16	0.02	-	-

[1]Covariance analysis using pre-administration value as covariate.

PHARMACOLOGY

This drug has a production-modulating effect against various cytokines and growth factors in that it inhibits the production of inflammatory cytokines (TNF-α, IL-1, IL-6, etc.) and facilitates the production of anti-inflammatory cytokine (IL-10); it inhibits a reduction in IFN-γ level, leading to an improvement in the tendency toward the Th2 type (modification of Th1-Th2 balance); it inhibits the production of growth factors involved in fibrosis (TGF-β1, b-FGF, and PDGF); etc. This drug also has fibroblast growth inhibitory action and collagen production inhibitory action. This drug is considered to show an antifibrotic effect on the basis of these combined effects[13].

PHYSICOCHEMISTRY

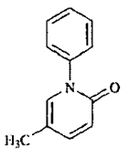
Nonproprietary name: Pirfenidone (JAN)

Chemical name: 5-Methyl-1-phenyl-1*H*-pyridin-2-one

Molecular formula: $C_{12}H_{11}NO$

Molecular weight: 185.22

Structural formula:



Description: A white to pale yellowish-white crystalline powder.

Freely soluble in methanol, ethanol (99.5), or dimethyl sulfoxide, and sparingly soluble in water.

Melting point: 108.2°C

PACKAGING

Pirespa® tablet 200 mg: Bottles of 500 tablets

100 tablets in press-through packages (10 tablets × 10)

REFERENCES

[Reference request No.]

1) Internal data (transfer to placenta and fetus) [200801753]
2) Internal data (reproductive development toxicity test) [200801754]
3) Internal data (transfer to breast milk) [200801755]
4) Internal data (photogenotoxicity) [200801779]
5) Internal data (skin photosensitization study and skin phototoxicity study) [200801778]

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6) Internal data (carcinogenicity study) [200801756]
7) Internal data (genotoxicity study) [200801757]
8) Internal data (pharmacological safety study, cardiovascular system) [200801758]
9) Internal data (clinical pharmacokinetics) [200801760]
10) Internal data (transfer to internal tissues in rats) [200801761]
11) Internal data (identification of CYP molecular species involved in oxidative metabolism) [200801762]
12) Internal data (phase III clinical trial) [200801759]
13) Internal data (mechanism of antifibrotic effect) [200801766]

REQUEST FOR LITERATURE (INCLUDING INTERNAL DATA) SHOULD BE MADE TO:
Drug Information Center
SHIONOGI & CO., LTD.
1-8, Doshomachi 3-chome, Chuo-ku, Osaka 541-0045, Japan
TEL: 0120-956-734
FAX: 06-6202-1541
http://www.shionogi.co.jp/med/

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March 10, 2009

CERTIFICATION OF TRANSLATION

This is to certify that the attached Japanese to English translation has been checked by a qualified translator competent in both languages, and verified to be an accurate and complete rendering of the content of the original document to the best of our ability. The following document is included in this certification: Package Insert for Pirespa® Tablets 200 mg, prepared in October 2008 (1st version).

Marlo R. Martin, Ph.D.
Director

2008年10月作成（第1版）

貯　　法：室温保存
使用期限：外箱等に表示（使用期間4年）

日本標準商品分類番号
873999

抗線維化剤
劇薬，指定医薬品，処方せん医薬品[注1)]

ピレスパ®錠200mg ①

ピルフェニドン錠
Pirespa®

	①
承認番号	22000AMX02373
薬価収載	薬価基準未収載
販売開始	
国際誕生	2008年10月

シオノギ製薬

【警告】

1. 本剤の使用にあたっては，光遺伝毒性試験において染色体構造異常を示し，光曝露に伴う皮膚の発がんの可能性があることを患者に十分に説明し，理解したことを確認した上で投与を開始すること。[「重要な基本的注意」及び「その他の注意」の項参照]
2. 本剤の使用は，特発性肺線維症の治療に精通している医師のもとで行うこと。

【禁忌（次の患者には投与しないこと）】

本剤の成分に対し過敏症の既往歴のある患者

【組成・性状】

1. 組成

販売名	ピレスパ錠200mg
成分・含量（1錠中）	ピルフェニドン200mg
添加物	乳糖水和物，カルメロースカルシウム，ヒドロキシプロピルセルロース，ステアリン酸マグネシウム，ヒプロメロース，クエン酸トリエチル，酸化チタン，タルク，黄色三二酸化鉄

2. 性状

販売名	ピレスパ錠200mg
性状・剤形	淡黄色～淡黄褐色の楕円形のフィルムコーティング錠である。
外形	 表面　裏面　側面
大きさ	長径 約12.2mm 短径 約6.4mm 厚さ 約4.5mm
重量	約0.30g
識別コード	521：200

【効能・効果】

特発性肺線維症

【用法・用量】

通常，成人にはピルフェニドンとして初期用量1回200mgを1日3回（1日600mg）食後に経口投与し，患者の状態を観察しながら1回量を200mgずつ漸増し，1回600mg（1日1800mg）まで増量する。
なお，症状により適宜増減する。

＜用法・用量に関連する使用上の注意＞

1. 本剤は初期用量として1回200mg（1日600mg）から開始し，2週間を目安に1回200mgずつ漸増し，1回600mg（1日1800 mg）で維持することが望ましい。
2. 胃腸障害等の発現時には必要に応じて減量又は休薬を検討すること。なお，症状が軽減した場合，1.に従い漸増し，維持用量の目安を1回400mg（1日1200mg）以上とすることが望ましい。
3. 食後投与と比べ空腹時投与では，本剤の血漿中濃度が高値を示し，副作用があらわれるおそれがあるので，食後に投与すること。[「薬物動態」の項参照]

【使用上の注意】

1. 慎重投与（次の患者には慎重に投与すること）

(1) 肝機能障害のある患者［肝機能障害を悪化させるおそれがある。］
(2) 腎機能障害のある患者［使用経験が少ない。］
(3) 高齢者［「高齢者への投与」の項参照］

2. 重要な基本的注意

(1) **光線過敏症があらわれることがあり，また，光曝露に伴う皮膚の発がんの可能性があるため，**投与にあたっては，事前に患者に対し以下の点について十分に指導すること。
1) 外出時には長袖の衣服，帽子等の着用や日傘，日焼け止め効果の高いサンスクリーン（SPF50＋，PA＋＋＋）の使用により，紫外線にあたることを避けるなど，光曝露に対する防護策を講じること。[「その他の注意」の項参照]
2) 発疹，そう痒等の皮膚の異常が認められた場合には，速やかに医師に連絡すること。
(2) 眠気，めまい，ふらつきが起こることがあるので，本剤投与中の患者には**自動車の運転等危険を伴う機械の操作**に従事させないように注意すること。
(3) AST（GOT），ALT（GPT）等の上昇を伴う**肝機能障害，黄疸があらわれる**ことがあるので，本剤投与中は定期的に検査を行い，患者の状態を十分に観察すること。[「重大な副作用」の項参照]

3. 副作用

承認時における安全性評価対象例265例中，副作用は233例（87.9%）に認められた。主なものは，光線過敏症137例（51.7%），食欲不振61例（23.0%），胃不快感37例（14.0%），嘔気32例（12.1%）であった。
また，臨床検査値の異常変動は安全性評価対象例265例中120例（45.3%）に認められた。主なものは，γ-GTP上昇53例（20.0%）であった。

(1) **重大な副作用**

肝機能障害，黄疸（0.1～1%未満）：AST（GOT），ALT（GPT）等の上昇を伴う肝機能障害，黄疸があらわれ，肝不全に至ることがあるので，定期的に検査を行うなど観察を十分に行い，異常が認められた場合には投与を中止し，適切な処置を行うこと。

(2) **その他の副作用**

次のような副作用があらわれた場合には，必要に応じて，減量又は投与を中止するなど適切な処置を行うこと。

種類＼頻度	5%以上	1～5%未満	1%未満
皮膚	光線過敏症（51.7%），発疹	そう痒，紅斑，湿疹，扁平苔癬	
消化器	食欲不振（23.0%），胃不快感（14.0%），嘔気（12.1%），下痢，胸やけ	腹部膨満感，嘔吐，便秘，逆流性食道炎，口内炎，腹部不快感，腹痛，口唇炎	口唇びらん
循環器		動悸	
精神神経系	眠気，めまい，ふらつき（感）	頭痛，頭重	
肝臓	γ-GTP上昇（20.0%），AST（GOT）上昇，ALT（GPT）上昇，Al-P上昇，LDH上昇	ビリルビン上昇	
血液		白血球増加，好酸球増加，白血球減少	血小板減少

000014

注1）注意-医師等の処方せんにより使用すること

種類＼頻度	5%以上	1～5%未満	1%未満
その他	倦怠感	体重減少，発熱，味覚異常，筋骨格痛，ほてり	

4. 高齢者への投与

一般に高齢者では生理機能が低下しているので，慎重に投与すること。

5. 妊婦，産婦，授乳婦等への投与

(1) 妊婦又は妊娠している可能性のある婦人には投与しないことが望ましい。[ラットにおいて，妊娠期間の延長及び出生率の低下，胎児への移行が認められている。また，ウサギでは，流産又は早産が認められている。なお，いずれの動物試験においても催奇形性は認められなかった[1),2)]。]

(2) 授乳中の婦人には本剤投与中は授乳を避けさせること。[ラットにおいて，乳汁中への移行及び哺育中期以降に出生児の体重増加抑制が認められている[2),3)]。]

6. 小児等への投与

低出生体重児，新生児，乳児，幼児又は小児に対する安全性は確立していない。[使用経験がない。]

7. 適用上の注意

薬剤交付時：PTP包装の薬剤はPTPシートから取り出して服用するよう指導すること。(PTPシートの誤飲により，硬い鋭角部が食道粘膜へ刺入し，更には穿孔を起こして縦隔洞炎等の重篤な合併症を併発することが報告されている。)

8. その他の注意

(1) チャイニーズハムスター肺由来培養細胞を用いた光染色体異常試験において，光照射による染色体構造異常誘発性が認められており，光毒性（光線過敏症）が惹起される血漿中濃度と光遺伝毒性を生じる薬物濃度に乖離がないことから，光曝露に伴う皮膚の発がんの可能性がある[4)]。

(2) モルモットを用いた皮膚光毒性試験において，皮膚光毒性を有することが認められた。なお，SPF50＋，PA＋＋＋のサンスクリーンで光毒性の発現を予防できることが確認されている[5)]。

(3) マウス，ラットを用いた長期がん原性試験（104週）において，肝細胞腫瘍（マウス800mg/kg/日以上，ラット750mg/kg/日以上）及び子宮腫瘍（ラット1500mg/kg/日）の発生増加が認められたが，いずれもげっ歯類に特異的な機序によるものと考えられる[6)]。なお，遺伝毒性試験の結果は陰性であった[7)]。

(4) ラット，イヌを用いた心血管系試験において，血圧低下（ラット300mg/kg），心拍数増加（ラット，イヌともに100mg/kg以上）が観察され，心電図では，房室ブロック（ラット100mg/kg以上），連発性の心室性期外収縮（ラット300mg/kg），QTc間隔への影響（イヌ100mg/kg以上）が認められた。なお，*in vitro* 心臓電気生理学的試験では，心筋活動電位やhERG電流に対する影響は少ないことが確認されている[8)]。

【薬物動態】

1. 血漿中濃度

(1) 空腹時単回投与

健康成人男性各6例に200mg，400mg及び600mgを空腹時単回経口投与したときの血漿中濃度及び薬物動態パラメータを図1・表1に示す。

Cmax，AUCはいずれも投与量にほぼ比例して増加した[9)]。

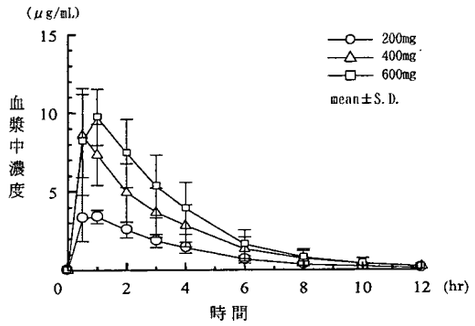


図1 空腹時単回経口投与時の血漿中濃度

表1 薬物動態パラメータ

投与量 (mg)	n	Cmax (μg/mL)	Tmax (hr)	AUC_{0-48} (μg·hr/mL)	$T_{1/2}$ (hr)
200	6	3.88±0.82	0.75±0.27	13.97±2.71	2.10±0.45
400	6	9.24±1.74	0.58±0.20	29.10±11.77	1.96±0.55
600	6	10.57±1.78	0.83±0.26	37.03±11.97	1.76±0.40

(測定法:HPLC) (mean±S.D.)

(2) 反復投与

健康成人男性12例に200mg，400mg及び600mgを漸増法でそれぞれ1日3回朝，昼，夕の毎食後6日間（投与第1日目及び6日目は朝と昼投与の1日2回）計18日間反復経口投与したときの薬物動態パラメータを表2に示す。

各投与量における投与第1日目と6日目の血漿中濃度はほぼ同様の時間推移を示し，投与第1日目のCmax，AUCはいずれも投与量の増加に従い比例的に増大した[9)]。

表2 薬物動態パラメータ

1回投与量 (mg)	n	投与日 (通算)	$Cmax_{0-4}$[a)] (μg/mL)	$Tmax_{0-4}$[a)] (hr)	$Cmax_{4-24}$[b)] (μg/mL)	$Tmax_{4-24}$[b)] (hr)
200	12	1	2.71±0.91	1.08±0.47	2.83±1.12	6.04±1.05
		6	3.06±1.28	1.08±0.82	2.70±0.51	6.29±0.96
400		1(7)	4.94±1.29	1.79±0.89	6.22±1.59	5.79±1.36
		6(12)	6.19±1.89	1.17±0.54	5.91±2.09	6.38±1.15
600		1(13)	8.20±1.29	1.25±0.45	9.21±1.97	6.33±1.15
		6(18)	8.19±1.54	1.71±0.54	10.00±1.70	6.13±1.00

1回投与量 (mg)	n	投与日 (通算)	AUC_{0-24}[c)] (μg·hr/mL)	$T_{1/2}$ (hr)
200	12	1	19.17± 6.46	2.17±0.30
		6	22.03± 5.47	2.25±0.29
400		1(7)	46.13±10.01	2.42±0.48
		6(12)	48.69±11.21	2.36±0.38
600		1(13)	77.22±15.44	2.53±0.42
		6(18)	82.31±16.50	2.55±0.45

a) 朝投与における値
b) 昼投与における値
c) 1日2回投与における値

(測定法：HPLC) (mean±S.D.)

2. 食事の影響

健康成人男性6例に400mgを食後及び空腹時単回経口投与したときの血漿中濃度及び薬物動態パラメータを図2・表3に示す。

食事によりCmax，AUCは有意に低下し，Tmaxは有意に遅延した[9)]。

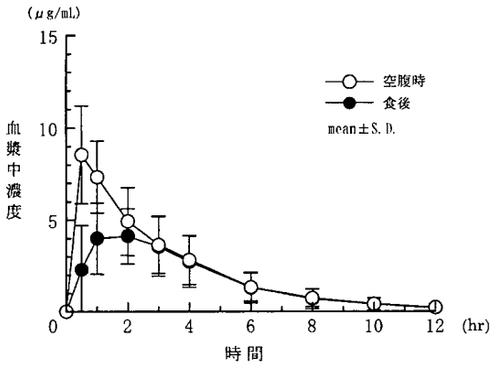


図2 食後及び空腹時単回経口投与時の血漿中濃度

表3 薬物動態パラメータ

投与量 (mg)		n	Cmax (μg/mL)	Tmax (hr)	AUC_{0-48} (μg·hr/mL)	$T_{1/2}$ (hr)
400	食後	6	4.88±1.72	1.83±0.75	22.13±10.63	1.77±0.55
	空腹時		9.24±1.74	0.58±0.20	29.10±11.77	1.96±0.55

(測定法：HPLC) (mean±S.D.)

3. 分布

(参考)

ラットに[^{14}C]-ピルフェニドン100mg/kgを単回経口投与したとき，血漿より高い放射能濃度を示す臓器・組織は，肝臓，腎臓，膵臓及び包皮腺であった。大部分の臓器・組織中放射能濃度は，投与後5～30分に最高濃度を示した後，半減期4～7時間で消失したが，包皮腺の半減期は他組織に比べ長く約15時間であった[10]。

4. 代謝

ヒト肝ミクロソームにおいて複数のCYP分子種（CYP1A2，2C9，2C19，2D6，2E1）によって代謝される[11]。(*in vitro*)

代謝反応に複数のCYP分子種が関与するため，他剤によるCYP阻害の影響を受けにくいと推察される。

5. 排泄

健康成人男性6例に200mg，400mg及び600mgを空腹時単回経口投与したとき，いずれの投与量においても48時間までの尿中排泄率は未変化体1%未満，ピルフェニドン-5-カルボン酸体（主代謝物）約90%であった[9]。

6. その他

血清蛋白結合率：健康成人に600mgを空腹時単回経口投与したとき，限外ろ過法にて測定した血清蛋白結合率は，投与後1時間及び3時間後において，54～62%であった[9]。

【臨床成績】

承認時におけるプラセボを対照とした二重盲検比較試験において，ピルフェニドン投与はプラセボに比べて肺活量の低下を抑制することが示された（表4）。なお，本試験の対象は，厚生労働省びまん性肺疾患調査研究班第4次改訂の特発性間質性肺炎の臨床的診断基準に基づき特発性肺線維症と診断され，投与前に実施したトレッドミルを用いた6分間歩行試験時の労作時SpO_2最低値が85%以上かつ安静時SpO_2との差が5%以上である患者とした[12]。

表4 肺活量の変化量の比較[注1]

群		有効性評価対象例数	調整平均 (L)	標準誤差	プラセボ群との比較	
					調整平均の差 (90%信頼区間)	両側p値
ピルフェニドン	1800mg/日	104	-0.09	0.02	0.07 (0.01，0.13)	0.0416
	1200mg/日	54	-0.08	0.03	0.09 (0.02，0.16)	0.0394
プラセボ		103	-0.16	0.02	−	−

注1：投与前値を共変量とした共分散分析

【薬効薬理】

炎症性サイトカイン（TNF-α，IL-1，IL-6等）の産生抑制と抗炎症性サイトカイン（IL-10）の産生亢進を示し，Th2型への偏りの改善（Th1・Th2バランスの修正）につながるIFN-γレベルの低下の抑制を示し，線維化形成に関与する増殖因子（TGF-β1，b-FGF，PDGF）の産生抑制を示すなどの各種サイトカイン及び増殖因子に対する産生調節作用を有する。また，線維芽細胞増殖抑制作用やコラーゲン産生抑制作用も有する。これらの複合的な作用に基づき抗線維化作用を示すと考えられる[13]。

【有効成分に関する理化学的知見】

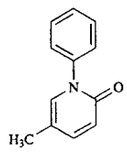
一般的名称：ピルフェニドン（JAN）
Pirfenidone

化学名：5-Methyl-1-phenyl-1*H*-pyridin-2-one

分子式：$C_{12}H_{11}NO$

分子量：185.22

化学構造式：



性状：白色～微黄白色の結晶性の粉末である。
メタノール，エタノール（99.5）又はジメチルスルホキシドに溶けやすく，水にやや溶けにくい。

融点：108.2℃

【包装】

ピレスパ錠200mg：瓶500錠
PTP100錠（10錠×10）

【主要文献】

〔文献請求番号〕

1) 社内資料（胎盤・胎児移行性）〔200801753〕
2) 社内資料（生殖発生毒性試験）〔200801754〕
3) 社内資料（乳汁移行性）〔200801755〕
4) 社内資料（光遺伝毒性）〔200801779〕
5) 社内資料（皮膚光感作性試験及び皮膚光毒性試験）〔200801778〕
6) 社内資料（がん原性試験）〔200801756〕
7) 社内資料（遺伝毒性試験）〔200801757〕
8) 社内資料（安全性薬理試験，心血管系）〔200801758〕
9) 社内資料（臨床における薬物動態）〔200801760〕
10) 社内資料（ラットにおける体内組織への移行性）〔200801761〕
11) 社内資料（酸化的代謝に関与するCYP分子種の同定）〔200801762〕
12) 社内資料（第Ⅲ相臨床試験）〔200801759〕
13) 社内資料（抗線維化作用メカニズム）〔200801766〕

【文献請求先】

主要文献に記載の社内資料につきましても下記にご請求ください。

塩野義製薬株式会社 医薬情報センター
〒541-0045 大阪市中央区道修町3丁目1番8号
電話 0120-956-734
FAX 06-6202-1541
http://www.shionogi.co.jp/med/

製造販売元
塩野義製薬株式会社
〒541-0045 大阪市中央区道修町3丁目1番8号

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ANEXO B

Guidance for Industry

Drug-Induced Liver Injury: Premarketing Clinical Evaluation

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Ruyi He at 301-796-0910, (CDER) Thomas Moreno at 301-796-2247, or (CBER) Bruce Schneider at 301-827-8343.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2007
Drug Safety

Guidance for Industry

Drug-Induced Liver Injury: Premarketing Clinical Evaluation

Additional copies are available from:

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Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
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http://www.fda.gov/cder/guidance/index.htm

or

Office of Communication, Training, and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
(Tel) 800-835-4709 or 301-827-1800
http://www.fda.gov/cber/guidelines.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2007
Drug Safety

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Contains Nonbinding Recommendations
Draft — Not for Implementation

Guidance for Industry[1]
Drug-Induced Liver Injury: Premarketing Clinical Evaluation

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist the pharmaceutical industry and other investigators who are conducting new drug development in assessing the potential for a drug[2] to cause ***severe*** liver injury (i.e., fatal, or requiring liver transplantation). In particular, the guidance addresses how laboratory measurements that signal the potential for such drug-induced liver injury (DILI) can be obtained and evaluated during drug development. This evaluation is important because most drugs that cause severe DILI do so infrequently; typical drug development databases with up to a few thousand subjects exposed to a new drug will not show any cases. Databases do, however, often show evidence of a drug's *potential* for severe DILI if the clinical and laboratory data are properly evaluated for evidence of lesser injury that may not be severe, but may predict the ability to cause more severe injuries. This guidance describes an approach that can be used to distinguish signals of DILI that identify drugs likely to cause significant hepatotoxicity from signals that do not suggest such a potential. This guidance does not address issues of preclinical evaluation for potential DILI, nor the detection and assessment of DILI after drug approval and marketing.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

[1] This guidance has been prepared by the Division of Gastroenterology Products, the Office of Medical Policy, and the Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA).

[2] This guidance uses the term *drug* or *product* to refer to all products, except whole blood and blood components, regulated by CDER and CBER, including vaccines, and uses the term *approval* to refer to both drug approval and biologic licensure.

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cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND: HEPATOTOXICITY

Hepatotoxicity has been the most frequent single cause of safety-related drug marketing withdrawals for the past 50 years (e.g., iproniazid), continuing to the present (e.g., ticrynafen, benoxaprofen, bromfenac, troglitazone, nefazodone). Hepatotoxicity discovered after approval for marketing also has limited the use of many drugs, including isoniazid, labetalol, trovafloxacin, tolcapone, and felbamate (Temple 2001). Several drugs have not been approved in the United States because European marketing experience revealed their hepatotoxicity (e.g., ibufenac, perhexiline, alpidem). Finally, some drugs were not approved in the United States because premarketing experience provided evidence of potential toxicity (e.g., dilevalol, tasosartan, ximelagatran). Although most significant hepatotoxins have caused predominantly hepatocellular injury, indicated by leakage of aminotransferase (AT) enzymes from injured liver cells without prominent evidence of hepatobiliary obstruction, the pattern of injury can vary. Many drugs cause cholestasis, but in general this condition is reversible after administration of the offending drug has stopped. Cholestatic injuries are less likely to lead to death or transplant, although there have been exceptions.

Drugs cause liver injuries by many different mechanisms. These injuries resemble almost all known liver diseases and there are no pathognomonic findings, even upon liver biopsy, that make diagnosis of DILI certain. Therefore, when possible DILI is suspected, it is essential to gather additional clinical and laboratory information, to observe the time course of the injury, and to seek alternative causes of the liver injury, such as acute viral hepatitis A, B, or C, autoimmune or alcoholic hepatitis, biliary tract disorders, and circulatory problems of hypotension or right heart congestive failure that may cause ischemic or hypoxic hepatopathy. It is also prudent to assess the subject for previously existing liver disease, such as chronic hepatitis C or nonalcoholic steatohepatitis (NASH), that may or may not have been recognized before exposure to the experimental drug.

Only the most overt hepatotoxins can be expected to show cases of severe DILI in the 1,000 to 3,000 subjects typically studied and described in a new drug application (NDA). Overtly hepatotoxic agents (e.g., carbon tetrachloride, chloroform, methylene chloride) are toxic to anyone receiving a large enough dose, and drugs that cause such predictable and dose-related injury generally are discovered and rejected in preclinical testing. More difficult to detect is toxicity that is not predictable or clearly dose-related, but seems to depend on individual susceptibilities that have, to date, not been characterized. Most of the drugs withdrawn from the market for hepatotoxicity have had rates of death or transplantation in the range of ≤ 1 per 10,000, so that a single case of such an event would not be reliably found even if several thousand subjects were studied. Cases of severe DILI have rarely been seen in drug development programs of significantly hepatotoxic drugs.

What are regularly seen during drug development are mild liver injuries, often laboratory signals without any symptoms. The problem is that both drugs capable of severe DILI and drugs that

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have a low potential for causing severe injury (e.g., aspirin, tacrine, heparin, hydroxyl-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (*statins*)) can generate these types of signals. Therefore, an approach is needed that can distinguish drugs likely to cause severe DILI from drugs unlikely to do so.

In general, the type of liver injury that leads to severe DILI is a predominantly hepatocellular injury. Hepatocellular injury is indicated by rises in serum AT activities reflecting release of alanine or aspartate aminotransferase (ALT or AST) from injured liver cells. The ability to cause some hepatocellular injury, however, is not a reliable predictor of a drug's potential for severe DILI. Many drugs that cause transient rises in serum AT activity do not cause progressive or severe DILI, even if drug administration is continued. It is only those drugs that cause hepatocellular injury extensive enough to affect the liver's functional ability to clear bilirubin from the plasma or to synthesize prothrombin and other coagulation factors that cause severe DILI. It is important to identify those drugs as rapidly as possible.

The drugs that have caused severe DILI in humans have not shown clear hepatotoxicity in animals, generally have not shown dose-related toxicity, and, as noted, generally have caused low rates of severe injury in humans (1 in 5,000 to 10,000 or less). These reactions thus appear to reflect host factors and individual susceptibility. Consequently, they have been termed *idiosyncratic*, meaning dependent upon the individual person's particular constitution. Whether they are the result of genetic or acquired differences has not yet been established, and to date no genetic, metabolic, or other characteristic has been found to predict severe DILI in an individual.

Some severe DILI examples have been different from the more commonly seen hepatocellular idiosyncratic type. Perhexiline, an anti-anginal drug marketed in Europe, produced toxicity within months that had the histological appearance of alcoholic cirrhosis (Pessayre and Biachara et al. 1979). Fialuridine caused modest acute liver injury, but most strikingly led to severe metabolic acidosis and multiorgan failure as mitochondrial oxidative capacity was obliterated over a period of months (Kleiner and Gaffey et al. 1997; Semino-Mora and Leon-Monzon et al. 1997). Valproic acid causes hyperammonemic encephalopathy even without notable rises in serum AT activities. Benoxaprofen (Oraflex) induced intrahepatic cholestasis that over many months led to significant, sometimes fatal, liver injury, especially in elderly patients (Taggart and Alderdice 1982).

Retrospective evaluation of earlier experiences, augmented by recent experience, lead us to believe that appropriate testing and analysis in premarketing studies may improve the early detection of drugs that can cause severe hepatocellular injury.

III. SIGNALS OF DILI AND HY'S LAW

Because hepatocellular injury (AT elevations) is caused both by drugs that rarely, if ever, cause severe DILI (e.g., aspirin, HMG-CoA reductase inhibitors, heparin) and drugs that do cause such injury, evidence of hepatocellular injury is a necessary, but not sufficient, indicator of a potential for severe DILI. The frequency of AT elevation is not a good indicator either, as drugs such as tacrine (not a cause of severe DILI) can cause AT elevations in as many as 50 percent of

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patients. The degree of AT elevation may be a better indicator of potential for severe DILI, but the most specific indicator is evidence of altered liver function.

As noted, a typical NDA or BLA database usually will not show any cases of severe DILI, even for a drug that can cause such injury. Many drugs, however, including both significant hepatotoxins and drugs that do not cause severe liver injury, cause laboratory evidence of hepatic injury, with leakage of liver enzymes and the appearance in blood of elevations in serum AT to levels of 3-, 5-, and greater times the upper limits of normal (ULN). Generally, ALT is considered a more liver-specific aminotransferase than AST, although it also occurs in many tissues (Green and Flamm 2002). The finding of a higher rate of such elevations in drug-treated subjects than in a control group is a sensitive signal of a potential to cause severe DILI, but it is not a very specific signal. A more specific signal of such potential is a higher rate of more marked peak AT elevations (10x-, 15xULN), with cases of increases >1,000 U/L causing increased concern. The single clearest (most specific) predictor found to date of a drug's potential for severe hepatotoxicity, however, is evidence of reduced overall liver *function* in one or more subjects, manifested by increased serum total bilirubin (TBL), in conjunction with AT elevation, not explained by any other cause, together with an increased rate of AT elevation in the overall study population compared to control.

Recognition of the importance of altered liver function, in addition to liver injury, began with Hyman Zimmerman's observation that drug-induced hepatocellular injury (i.e., aminotransferase elevation) accompanied by jaundice had a poor prognosis, with a 10 to 50 percent mortality from acute liver failure (in pretransplantation days) (Zimmerman 1978, 1999). The reason for this now seems clear. The liver has a large excess of bilirubin-excreting capacity; injury to hepatocytes sufficient to cause jaundice or near jaundice (i.e., a bilirubin >2 mg/dL) represents an extent of damage so great that recovery may not be possible in some patients. Zimmerman's observation that hepatocellular injury sufficient to impair bilirubin excretion was ominous has been used at the Food and Drug Administration (FDA) over the years to identify drugs likely to be capable of causing severe liver injury, as distinct from drugs that cause lesser hepatocellular injury (i.e., AT elevation without bilirubin elevation) but are not as likely to cause severe injury (e.g., aspirin, tacrine, heparin). The observation of the critical importance of altered liver function has been referred to informally as *Hy's Law* (Temple 2001; Reuben 2004).

Briefly, Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by more frequent 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control agent or placebo.
2. Among subjects showing such AT elevations, often with ATs much greater than 3xULN, some subjects also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (serum alkaline phosphatase (ALP) activity >2xULN).
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury.

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Finding one Hy's Law case in clinical trials is ominous; finding two is highly predictive of a potential for severe DILI. Clinical trials of the beta blocker dilevalol (enantiomer of labetalol, a diastereoisomeric mixture), showed two such cases in about 1,000 exposures. The drug was not approved in the United States, and examination of a postmarketing study in Portugal revealed fatal liver injury. Clinical trials of tasosartan, an angiotensin II blocking agent, showed a single Hy's Law case. The manufacturer was asked to do a large-scale safety study before the drug could be approved. The study was never conducted.

As a rule of thumb, based on Zimmerman's original estimate of 10 to 50 percent mortality associated with hepatocellular injury sufficient to impair the liver bilirubin excretory function, severe DILI can be estimated to occur at a rate of at least one-tenth the rate of so-called Hy's Law cases (Temple 2001). This observation was recently confirmed in large studies of DILI in Spain (Andrade and Lucena et al. 2005) and in Sweden (Björnsson and Olsson 2005) in which approximately 10 percent of subjects with hyperbilirubinemia or jaundice died or needed liver transplants.

Recent examples of some drugs causing idiosyncratic hepatotoxicity (e.g., bromfenac, troglitazone, ximelagatran) further illustrate the predictive value of Hy's Law, where findings during clinical trials were noted and severe DILI occurred after marketing. These examples are described in detail in Appendix A.

Past experience, including the three examples, shows that there is a set of laboratory abnormality signals that have the ability to predict a potential for severe DILI with reasonable sensitivity and specificity in a database of several thousand subjects. Although it is not yet possible to provide precise specificity and sensitivity estimates for the various signals, guidance can be provided on use of these major indicators of a potential for severe DILI, as follows:

- **An excess of AT elevations to >3xULN compared to a control group**

  AT elevations to >3xULN are relatively common and may be seen in all groups, but an excess of these elevations compared to a control group is nearly always seen for drugs that ultimately prove severely hepatotoxic at relatively high rates (1/10,000). Therefore, the sensitivity of an excess of >3xULN AT elevations as a predictor of a potential for severe DILI is high. But many drugs show this signal without conferring a risk of severe injury (e.g., tacrine, statins, aspirin, heparin), indicating low specificity for an excess of AT elevations alone. There are no good data analyses at this time on how great this excess should be compared to control (e.g., 2-fold, 3-fold) to suggest an increased risk of DILI.

- **Marked elevations of AT to 5x-, 10x-, or 20xULN in smaller numbers of subjects in the test drug group and not seen (or seen much less frequently) in the control group**

  Virtually all severely hepatotoxic drugs show such cases, indicating high sensitivity for predicting severe DILI, but, again, some drugs such as tacrine and others that are not severely hepatotoxic also can cause AT elevations to this degree, so that specificity of this finding is suboptimal.

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- **One or more cases of elevated bilirubin to >2xULN in a setting of pure hepatocellular injury (no evidence of obstruction, such as elevated ALP in gall bladder or bile duct disease, malignancy), with no other explanation (viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs), accompanied by an overall increased rate of AT elevations >3xULN in the test drug group compared to placebo**

  The sensitivity of this observation appears high for any given rate of severe DILI if enough people are exposed to the drug. Thus, if the true incidence of severe injury is 1/10,000, and the rate of Hy's Law cases is 1/1,000, about 3,000 subjects (*Rule of 3*) would be needed to have a 95 percent probability of observing a Hy's Law case in the treated population (Rosner 1995). The sensitivity of this finding appears very high if at least two cases are seen (e.g., dilevalol, bromfenac, troglitazone, ximelagatran). We are not aware of false positive Hy's Law findings. Therefore, the finding of two Hy's Law cases, and probably even one, is a strong predictor of a significant rate of severe liver injury. Failure to find a case, however, does not imply that a drug with AT elevations is free of a risk of severe DILI. The degree of assurance depends on the population exposed for a long enough time and on the rate of severe DILI that would be of interest.

The implications of these three findings may be different in patients with existing liver disease such as fatty liver disease, NASH, or chronic hepatitis C or B, with bilirubin metabolism abnormalities (Gilbert's syndrome), and in patients on drugs that treat liver disease or that inhibit bilirubin glucuronidation, such as indinavir or atazanavir (Zhang and Chando et al. 2005).

IV. CLINICAL EVALUATION OF DILI

A. General Considerations

For most drugs in development that reach phase 3 testing, the chances of encountering severe DILI are low. An increased frequency of mild hepatotoxicity (AT elevations) in early trials usually results in heightened screening to detect and evaluate liver injury during phase 3 testing. It is critical, however, to determine whether mild hepatotoxicity reflects a potential for severe DILI or reflects a capacity for only limited injury. To make this distinction, it is essential to detect any cases of more severe injury and to examine such cases closely, observing the course and outcome of the injury, and seeking additional information that might identify other causes. The following general recommendations for evaluating and monitoring potential drug-induced hepatotoxicity may not be suitable for all situations and should be modified for special populations, such as people with preexisting liver disease or malignancies, and in light of accumulating data. In addition, clinical trials of cellular and gene therapies and of vaccines pose specific challenges related to trial size and design, persistence of vectors, and tissue specificity. Applicants are encouraged to discuss these issues with the review division.

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1. Patients with Liver Abnormalities or Disease

Patients are sometimes excluded from clinical trials because of baseline liver test abnormalities or a history of liver disease, but there is no well-established reason to do this, except perhaps to avoid confusion between the previous disease and an effect of the test drug. These patients generally should be included in at least the phase 3 trials because they are likely to be treated with the drug if it is marketed. Preexisting liver disease is not known to make patients more susceptible to DILI (Zimmerman 1978, 1999), but it may be that a diminished *liver reserve* or the ability to recover could make the consequences of injury worse, making it appear that such patients were more susceptible to severe DILI. If the drug is intended to be prescribed or marketed to such patients after approval, they should be studied during controlled trials. It may be prudent, however, to first determine if DILI occurs in people with previously normal livers, before studying patients with well-characterized and stable chronic liver disease.

2. Detection of DILI

In general, early studies of a drug in study subjects with presumably normal liver function should involve obtaining liver tests every 2 to 4 weeks, at least for a few months. It is uncertain whether early symptoms (e.g., anorexia, nausea, fatigue, right upper abdominal discomfort, vomiting) precede or follow the first laboratory signs of hepatic injury (rising ALT, AST, or ALP) and the pattern of clinical and laboratory changes may vary with different drugs and recipients. In most cases, however, the first evidence of a problem is elevated AT or ALP. In longer trials, if there is no sign of liver injury after a reasonable length of exposure (e.g., 3 months), the monitoring interval can be increased to once every 2 to 3 months. Later trials also can use less frequent liver chemistry monitoring if there is no indication of hepatotoxicity.

If symptoms compatible with DILI precede knowledge of serum abnormalities, liver enzyme measurements should be made immediately, regardless of when the next visit or monitoring interval is scheduled. In some cases, symptoms may be an early sign of injury. Reliance on early symptoms, rather than serum enzyme monitoring, has become the standard for monitoring isoniazid therapy for prophylaxis of tuberculosis and seems to prevent severe liver injury if acted upon promptly (Nolan and Goldberg et al. 1999). Attention to symptoms does not supplant routine periodic assessment of AT, TBL, and ALP in trials of investigational drugs.

3. Confirmation

In general, an increase of serum AT to >3xULN should be followed by repeat testing within 48 to 72 hours of all four of the usual serum measures (ALT, AST, ALP, and TBL) to confirm the abnormalities and to determine if they are increasing or decreasing. There also should be inquiry about symptoms. Serum AT may rise and fall quite rapidly, and waiting a week or two before obtaining confirmation of elevations may lead to a false conclusion that the initially observed abnormality was spurious, or, of greater concern, to severe worsening if the initial abnormality was the herald of a severe reaction to follow. The need for prompt repeat testing is especially great if AT is much greater than 3xULN or TBL is greater than 2xULN. For outpatient studies, or studies in which subjects are far away from the study site, it may be difficult for the subjects to return to the study site promptly. In this case, the subjects should be retested locally, but

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normal laboratory ranges should be recorded, results should be made available to study investigators immediately, and the data should be included in the case reports. If symptoms persist or repeat testing shows AT >3xULN for the subjects with normal baseline measures or 2-fold increases above baseline values for subjects with elevated values before drug exposure, it is appropriate to initiate close observation to determine whether the abnormalities are improving or worsening.

4. Close Observation

Close observation is defined as follows:

- Repeating liver tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or study drug has been discontinued and subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., International Normalized Ratio (INR)).
- Considering gastroenterology or hepatology consultation.

It is critical to initiate close observation immediately upon detection and confirmation of early signals of possible DILI, and not to wait until the next scheduled visit or monitoring interval. A threshold of a greater than 3xULN aminotransferase level is reasonable, as lesser elevations are common and nonspecific. If additional testing is done, beyond that specified in the study protocol, it is important that the subject's information be added to the case report forms or database.

5. Decision to Stop Drug Administration

It has been observed that *dechallenge* (stopping drug administration) does not always, or even usually, result in immediate improvement in abnormal lab values. Abnormal test values and symptoms may progress for several days or even weeks after discontinuation of the drug that caused the abnormality. For example, rising TBL usually follows serum AT increases by a few days to weeks. The primary goal of close observation is to determine as quickly as possible whether observed abnormal findings are transient and will resolve spontaneously or are progressive. For most DILI, no specific antidotes are available (except N-acetylcysteine for acute acetaminophen overdose if given promptly, and, possibly, intravenous carnitine for valproic acid hepatotoxicity). Promptly stopping administration of the offending drug usually is the only potentially effective therapy.

A difficult question is when to stop administration of the investigational drug. Because transient rises and falls of ALT or AST are common, and progression to severe DILI or acute liver failure is uncommon, automatic discontinuation of study drug upon finding a greater than 3xULN

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elevation of ALT or AST may be unnecessary. For most people, the liver appears capable of adapting to injury by foreign chemical substances, which may render a person tolerant to the drug despite continuation of exposure. Stopping a drug at the first hint of mild injury does not permit learning whether adaptation will occur, as it does for drugs such as tacrine that cause liver injury but do not cause severe DILI. On the other hand, continuing drug administration too long can be dangerous once there is marked transaminase elevation or evidence of *functional* impairment appearing after hepatocellular injury, as indicated by rising bilirubin or INR, which represent substantial damage. Although there is no published consensus on when to stop a drug in the face of laboratory abnormalities, and the decision will be affected by information on related drugs, the accumulating clinical experience, the nature of the patient, and many other factors, the following can be considered a basic guide. In general, treatment should be stopped if:

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN **and** (TBL >2xULN **or** INR >1.5)
- ALT or AST >3xULN with the appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia

6. Evaluating Data for Alternative Causes

One of the critical purposes of close observation is to gather additional clinical information to determine the most likely cause or causes of the observed abnormalities, and specifically, whether there is a cause other than the study drug, such as one of the following common causes. Other less common causes also may need to be considered.

- **Acute viral hepatitis.** The usual onset of hepatocellular DILI is indistinguishable from acute viral hepatitis A or B. Hepatitis C is much less often acute in its onset and tends to be insidious, but it sometimes can resemble acute drug injury. The presence of acute viral hepatitis A, B, and C should always be evaluated by serological markers. Viral hepatitis D (requires concomitant hepatitis B infection) and E are relatively rare in the United States. Hepatitis E is more common in developing countries, including Southeast Asia, and should be considered in recent travelers to those countries. Also rare is liver injury caused by Epstein-Barr virus and cytomegalovirus, although this is seen more commonly in immuno-suppressed individuals. Adolescent and young adult patients with possible DILI should be tested for Epstein-Barr virus. Hepatitis is common among transplant patients with CMV disease.

- **Alcoholic and autoimmune hepatitis.** Acute alcoholic hepatitis usually is recurrent, with a history of binging exposure to alcohol preceding episodes, and it has some characteristic features, such as associated fever, leukocytosis, right upper quadrant pain and tenderness, and AST >ALT, that may help distinguish it from other causes of liver injury. Autoimmune hepatitis may be acute or even fulminant in its onset; it does not always respond immediately to corticosteroids, but may have serological markers of value. Alcoholic and autoimmune hepatitis should be assessed by history and serologic testing (e.g., antinuclear antibodies).

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- **Biliary tract disorders.** Biliary tract disease more often causes cholestatic injury initially and should be investigated with gall bladder and ductal ultrasound study, especially if ALP is increased. Malignant interruption of the biliary tract also should be considered.

- **Cardiovascular causes.** Cardiovascular disease, especially right heart failure and hypotension, may cause acute centrilobular hypoxic cell necrosis (*ischemic hepatitis*) with spectacular increases of serum AT (e.g., AT >10,000). Cardiovascular dysfunction, including hypotension or right heart failure, should be assessed by physical examination and history.

Exclusion of the two ABCs (i.e., viral hepatitis A, B, or C; alcoholic or autoimmune hepatitis, biliary disorders, and circulatory disorders) as causes of liver injury should be attempted in all cases of suspected DILI, and the results should be recorded. There is a practical limit as to how much testing should be done to exclude less common liver diseases, such as acute Wilson's disease or alpha-1-antitrypsin deficiency.

It is also critical to discover concomitant treatment that might be responsible for injury. Many people take multiple drugs, perhaps less often in controlled clinical trials because of exclusion criteria, but subjects may not report taking disallowed drugs or other agents. The possible exposure to potentially toxic herbal or dietary supplement mixtures of unknown composition, nonprescription medications such as acetaminophen, or to occupational chemical agents may not be volunteered unless subjects are specifically questioned.

7. Follow-Up to Resolution

All study subjects showing possible DILI should be followed until all abnormalities return to normal or to the baseline state. DILI may develop or progress even after the causative drug has been stopped. Results should be recorded on the case report form and in the database. Note that still longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be DILI, indicating that liver injury was related to an underlying liver disease.

8. Rechallenge

Whether or not to rechallenge a subject who showed mild DILI is a difficult question. Re-exposure may initiate a sometimes explosive and more severe reaction, as was observed with halothane several decades ago. Some cases of DILI show indicators of immunological reaction such as eosinophilia, rash, fever, or other symptoms or findings, and it is possible that such cases are more prone to recur with re-exposure. On the other hand, most people can adapt to xenobiotic substances such as new drugs and develop tolerance for them, as has been found even for drugs that can cause severe injury, such as isoniazid. The large majority of people showing hepatocellular injury on isoniazid recover fully or recover while continuing to take the drug, and some, but not all, can resume or continue taking the drug without further adverse consequence. If such tolerance develops, the use of rechallenge to verify drug causation would give a false negative result.

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Generally, rechallenge of subjects with significant (>5xULN) AT elevations should not be attempted. If such subjects are rechallenged, they should be followed closely. Rechallenge can be considered if the subject has shown important benefit from the drug and other options are not available or if substantial accumulated data with the test drug do not show potential for severe injury. The subject should be made aware of the potential risk, and consent to the rechallenge.

9. Research Opportunities

It is not known why only a few people show severe DILI in response to a hepatotoxic drug while others show nothing or seem to adapt. The current thinking is that there may be a genetic basis for such differences, but acquired factors may be equally important. The period of close observation provides a major opportunity to gather and store serial samples of blood and urine, to investigate characteristics of subjects who show evidence of mild or severe DILI, and to see how they differ from each other and from people who do not show any effects despite being similar in age, sex, and drug exposure. These serial samples can be studied by genomic, proteomic, and metabolomic methods to determine how subjects differ, and to seek biomarkers that identify the susceptible persons.

As part of the Critical Path Initiative,[3] the FDA is working with industry, academia, and other experts to broaden our understanding of the biochemical and genetic bases of DILI. In June 2006, the FDA co-sponsored a scientific workshop to determine the feasibility of developing a mathematical (in-silico) model for DILI from which other predictive experimental models can be derived to characterize potential hepatotoxicity. The long-term goal is to develop a model, or models, that can help researchers identify criteria for determining when early clinical intervention (i.e., stopping the drug) is appropriate. It is also hoped that predictive bioassays and biomarkers can be identified that will help determine which patients most likely will suffer liver toxicity from specific compounds.

This urgently needed research is not a regulatory requirement, but is an important opportunity. At present, we are able only to search among patients with drug-induced injury to predict what might happen to others. Ideally, we should seek to identify individuals at increased risk before administering a drug that they cannot tolerate. The goal is to be able to identify persons who should never be exposed to a given drug because they are idiosyncratically hypersusceptible to, or unable to recover from, DILI caused by it. If tests that screen for people susceptible to severe DILI can be developed, a hepatotoxic drug could remain available to people who are not susceptible to severe DILI, instead of having to withdraw the drug from the market, allowing no one to benefit from it.

In addition, identification of common genotypic characteristics among patients experiencing DILI in response to one or more class-related hepatotoxic agents might permit the development of in vitro or ex vivo tests or genetically altered animal strains that can be used to better predict serious hepatotoxic potential, or the lack thereof, of new drugs belonging to the same or closely related classes.

[3] See http://www.fda.gov/oc/initiatives/criticalpath.

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B. Case Report Forms

In addition to collecting information on laboratory abnormalities, clinical symptoms, and the potential cause of any hepatic illness, case report forms should include the following information for cases in which liver injury is found (including control subjects with such injury):

- Time and date from start of drug administration to start of illness
- Time and date of cessation of drug, or interruption of drug administration
- Space for recording free text to describe the course of illness, including abnormalities of aminotransferases, ALP, and TBL
- Risk factors, especially alcohol use history
- Use of all concomitant drugs (dose, start and stop dates, whether drug is known to be hepatotoxic, rechallenge and dechallenge information)
- Evaluation of nondrug causes: recent hepatitis A, B, and C serology, evidence for biliary obstruction, acute alcoholic hepatitis (AST >2xALT), recent history of severe hypotension or congestive heart failure, underlying other viral disease
- Rechallenge and dechallenge information with suspect drug, with details of time and dose
- All supplemental information, including tests in local laboratories, unscheduled tests and physical exam reports, consultation reports, narrative information, and special studies

Any potential Hy's Law case should be handled as a serious unexpected adverse event associated with the use of the drug and reported to the FDA promptly. Reporting should include all available information and should initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

C. Interpretation of Signals of DILI or Acute Liver Failure

1. Frequency and Magnitude of Liver AT Abnormalities

The presence of even a single case of severe liver failure resulting from treatment in the premarketing clinical trials database is an indicator of a high level of hepatotoxic risk. More commonly, however, there will be no identifiable cases of severe liver injury, but rather varying degrees of serum AT abnormalities that need to be interpreted. As previously noted, slight abnormalities of this kind (to <3xULN) are common in untreated and placebo-treated subjects and are not informative about the potential for the development of severe DILI.

Therefore, it has become standard practice to look at greater deviations, such as AT values ≥3x-, 5x-, or 10xULN. Because these abnormalities can occur in placebo-treated groups, it is important to compare their rate in drug-exposed subject groups relative to control groups (i.e., placebo or products that do not cause elevation of transaminases). An excess of AT abnormalities >3xULN is a signal of a potential for severe DILI, but, even though it has high sensitivity, it is not specific. Comparison of rates of AT elevations during drug treatment to a control group is probably less critical for abnormalities of greater magnitude (e.g., 10xULN), as such elevations are rarely seen spontaneously. Therefore, these greater AT elevations can be examined in the whole clinical trials database, not just in the controlled trials. It should be appreciated that serum AT activity is a relatively volatile measurement, often rising and falling

within days. It cannot be concluded from one measurement that a peak value has been seen, so that detection of an abnormal rise is a call for serial measures to determine which way the abnormality is moving, whether increasing or decreasing.

A number of factors may confound interpretation of AT abnormalities seen in NDA or BLA databases. Although the more extreme AT elevations may be better predictors of toxicity than smaller elevations, it is possible that close monitoring could affect the magnitude of abnormalities seen if it leads to earlier cessation of drug treatment that prevents the greater abnormalities from appearing. In addition, the contribution of drug treatment to an exacerbation of preexisting liver disease may be difficult to determine. Finally, normalization of abnormalities on continued treatment is not proof that the abnormality was not drug-caused, but may result from liver adaptation to the drug.

2. Combined Elevations of Aminotransferases and Bilirubin

When AT abnormalities indicating hepatocellular injury are accompanied by evidence of impaired hepatic function (bilirubin elevation >2xULN), in the absence of evidence for biliary obstruction (i.e., significant elevation of ALP) or some other explanation of the injury (e.g., viral hepatitis, alcohol hepatitis), the combined finding (i.e., Hy's Law cases) represents a signal of a potential for severe DILI. Experience has indicated that the occurrence of even one or two well-documented cases of this combination is ominous, indicating a likelihood that the drug will cause severe liver injury.

The absence of Hy's Law cases in an NDA or BLA database may allow an estimate of an upper limit of the rate for severe DILI, using the Rule of 3 derived from simple binomial calculation. There will be at least a 95 percent chance of seeing one or more cases of DILI in 3n study subjects if its true incidence is 1 in **n** subjects, and the group is well observed. Thus, if no cases of AT and bilirubin elevations are seen in 3,000 well-observed subjects, it can be concluded with 95 percent confidence that the true rate of such occurrences is not more than 1 per 1,000. This calculation would then suggest a rate of expected severe liver injury ≤1 per 10,000 exposed patients, assuming that the rate of severe injury when AT and TBL are both elevated is about 10 percent (Andrade and Lucena et al. 2005; Björnsson and Olsson 2005).

D. Analysis of Signals of DILI

Based on our experience, we recommend that the following analyses related to liver injury potential be carried out and included in an NDA or BLA, or included in an investigational new drug application when DILI is suspected and being evaluated.

1. Assessment of Drug Metabolism

The metabolism of a drug can have serious consequences for the safety profile of the drug. A drug may be metabolized to a hepatotoxic metabolite (e.g., acetaminophen, halothane, and isoniazid). Most hepatotoxic drugs have been oxidatively metabolized by the CYP450 system.

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Several in vitro methods are available to detect and quantify binding for a drug or its metabolites to liver proteins, including radiochemical and immunological methods.

2. Assessment of Liver-Related Adverse Events in Controlled Trials

Analysis of incidence rates of liver-related adverse events (abnormal AT, bilirubin, and ALP levels) seen in subjects in controlled trials with at least one dose of drug exposure should be provided, generally for pooled data, although study-to-study differences may be of interest. Rates can be given as the number of events per number of subjects exposed, or as the number of events per subject-years of exposure, preferably both. For many drugs, it appears that a minimum duration of exposure is required before DILI occurs. Therefore, it is useful to give the rates of liver-related adverse events for subjects who have had the minimum duration of exposure (e.g., rate in subjects with at least 1-month exposure). Rates for pooled data should include, but are not limited to:

- 3x-, 5x-, 10x-, and 20xULN elevations of AST, ALT, and either ALT or AST.
- Any elevations of bilirubin; elevated bilirubin to >1.5xULN, and to >2xULN.
- Any elevations of ALP >1.5xULN.
- Elevation of AT (>3xULN) accompanied by elevated bilirubin (>1.5xULN, >2xULN).
- Possibly liver-related deaths and liver-related treatment discontinuations. These cases should be described and time-to-event analyses should be performed. Follow-up status also should be provided. There should be a description of any histologic and rechallenge data.

All rates should be calculated separately for drug-, placebo-, and active-controlled groups. Normal ranges for all tests should be provided. Time-to-event analyses for elevated rates of significant individual events (e.g., elevated AT, bilirubin) should be provided. The contribution of sex, age, risk factors, and drug dose or regimen to the abnormalities seen should be explored.

3. Assessment of Liver-Related Adverse Events in the Entire Clinical Trials Database

Analysis of rates of liver-related adverse events (abnormal AT, bilirubin, and ALP levels) for the total clinical trials database, including subjects with exposure of at least one dose of study drug in phase 1 or phase 2 trials, or in uncontrolled, open label, extension trials should be provided. We recommend the same evaluation as for the controlled trials database discussed in section IV.D.2. Time-to-event analyses, mortality rates, study withdrawals, and similar data should be provided for significant abnormalities. The contribution of sex, age, and drug dose or regimen to the abnormalities seen should be explored.

4. Assessment of Hy's Law Cases in the Clinical Trials Database

NDA and BLA submissions should include a listing of possible Hy's Law cases identified by treatment group (e.g., subjects with any elevated AT of >3xULN, ALP <2xULN, and associated with an increase in bilirubin ≥2xULN). A narrative summary for each Hy's Law case should be provided. Narrative summaries should not only provide, in text format, the data that are already

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presented in the case report tabulation, but also should provide a complete synthesis of all available clinical data and an informed discussion of the case, allowing for a better understanding of what the subject experienced. For a narrative summary to be useful, it should contain the following information:

- Subject's age, sex, weight, and height
- Discussion of signs and symptoms related to hepatotoxicity: type and timing
- Relationship of exposure duration and dose to the development of the liver injury
- Pertinent medical history
- Concomitant medications with dates and doses
- Pertinent physical exam findings
- Test results (e.g., laboratory data, biopsy data and reports, with dates and normal ranges)
- Time course of serum enzyme and bilirubin elevations
- A summary of all available clinical information including, if known:
  - Prior or current history of ethanol use
  - Evidence for pre- or co-existing viral hepatitis, or other forms of liver disease
  - Symptoms and clinical course including follow-up to resolution
  - Special studies, radiologic examinations, liver biopsy results
  - Presence or absence of possible confounders, including concomitant illness, use of concomitant medications that are known hepatotoxins, such as acetaminophen
- Discussion of hepatotoxicity as supported by available clinical data and overall assessment of treating physician, consultants, and applicants as to the likelihood of DILI
- Treatment provided
- Dechallenge and rechallenge results, if done
- Outcomes and follow-up information
- Copies of hospital discharge summaries, pathology and autopsy reports

The availability of liver biopsy, explant, or autopsy slides for pathology review by review staff or external expert consultants has been helpful in the FDA's assessment of such cases. Reports of external consultant opinions solicited by the applicant should be provided to the FDA.

Complete narrative summaries that include the components previously listed also should be provided for all subjects who died of hepatic illness, or who discontinued study drugs for hepatotoxicity, including subjects with abnormalities consistent with protocol-specific stopping rules.

5. Overall Assessment of a Drug's Potential to Cause DILI

The overall assessment should characterize a drug's potential for DILI and should consider at least the following questions:

- Was liver monitoring sufficiently frequent and thorough to characterize DILI risk?
- Were there any cases of probably drug-induced serious or severe DILI?
- Were there signals of a potential for DILI (e.g., AT elevations, Hy's Law cases) and how were these signals assessed?

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- What doses and durations of exposure were associated with hepatotoxicity signals?
- What approximate incidence of mild, moderate, and severe DILI could be expected postmarketing?
- Is the trial information sufficient to inform an overall risk-benefit assessment?
- Was there sufficient drug exposure (i.e., number of study subjects and duration of treatment of each study subject) and adequate liver test monitoring to reliably set an upper boundary for risk of severe DILI after marketing?
- What rate of severe injury (assuming Hy's Law cases occur at about 10 times the rate of severe injury) has been suggested or has been ruled out (e.g., no Hy's Law cases in 3,000 subjects implies a rate of such cases of <1/1,000 and thus a rate of severe DILI of <1/10,000)? This consideration should reflect the presence or absence of other signals, such as marked elevations of AT.
- Will some form of monitoring, by symptoms or serum testing, be needed? Usually, this would be considered only if there was evidence of severe liver injury or the potential for it. If so, effectiveness of monitoring in the NDA database should be discussed.

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APPENDIX A: ILLUSTRATIVE EXAMPLES OF DILI

Duract (bromfenac)

Bromfenac was a nonsteroidal anti-inflammatory drug (NSAID) studied for both short-term analgesia and long-term arthritis treatment. There was little evidence of hepatotoxicity in the short-term analgesic trials, but during longer term clinical trials in arthritis, ALT elevations >3xULN were seen in 2.8 percent of patients on bromfenac, compared to none in placebo group. Among 1,195 exposed patients, there were two cases in which there was elevated TBL as well as AT elevation in the clinical trial data submitted for review in the NDA. Concerns about possible liver toxicity led to the approval of bromfenac in July 1997 for short-term use only and not for osteoarthritis or rheumatoid arthritis. As an NSAID, however, it was prescribed long-term off-label in arthritic patients, and severe hepatotoxicity emerged. Within 6 months of approval, reports of severe hepatic failure, including two cases requiring liver transplant, were received. All severe cases involved the use of bromfenac for more than 10 days, the maximum duration of treatment recommended in the labeling.

In response, the FDA and the manufacturer strengthened the warnings in the package insert with a boxed warning, and issued a Dear Health Care Professional letter. Despite these efforts, the manufacturer and the FDA continued to receive reports of severe injuries, including reports of death or need for liver transplantation (Moses and Schroeder et al. 1999; Hunter and Johnston et al. 1999; Rabkin and Smith et al. 1999; Fontana and McCashland et al. 1999). Given the availability of other NSAIDs of equal effectiveness and safety, bromfenac was withdrawn from the market in June 1998. The two Hy's Law cases in the long-term-exposed population of about 1,000 subjects during drug development predicted an occurrence of severe hepatotoxicity during chronic use at a rate of about 1/5,000 to 10,000 people. Following approval, rates of acute liver failure for bromfenac were estimated to be in the range of 1/10,000 (Goldkind and Laine 2006).

Rezulin (troglitazone)

Troglitazone was approved by the FDA in January 1997 for the treatment of Type 2 diabetes mellitus. In reviews of the clinical trials of troglitazone conducted before approval there were no cases of liver failure among 2,510 subjects exposed to the drug in the NDA database, but 1.9 percent of troglitazone-treated subjects had ALT >3xULN compared to 0.3 percent of placebo-treated subjects, 1.7 percent had ALT >5xULN, and 0.2 percent (5 subjects) had ALT >30xULN (2 subjects in the last group also experienced jaundice). The median duration of troglitazone therapy before peak ALT elevation was 121 days. In the Diabetes Prevention Trial at the National Institutes of Health (NIH) performed after approval, 4.3 percent of 585 troglitazone-treated subjects had ALT ≥3xULN, 1.5 percent had ALT >8xULN, and 2 subjects had ALT >30xULN, compared to 3.6 percent of subjects with ALT ≥3xULN in the placebo group (Knowler and Hamman et al. 2005). One of the subjects with ALT >30xULN developed liver failure and died, despite receiving a liver transplant. The second subject recovered. These data suggest that the rate of severe liver injury would be about 1 in 3,000 to 10,000.

After marketing, there were numerous reports (Gitlin and Julie et al. 1998; Vella and deGroen et al. 1998; Herrine and Choudary 1999) of acute liver failure associated with troglitazone use, and

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four letters were sent to practicing physicians between 1997 and 1999, urging monthly monitoring and careful use. These letters did not significantly affect the monitoring done by physicians, and AT monitoring recommended in the Dear Health Care Professional letters and in the package insert was not regularly performed (Graham and Drinkard et al. 2001). Moreover, an analysis of 94 cases of liver failure reported spontaneously to the FDA showed that the progression from normal hepatic test results to irreversible liver injury occurred in less than a month (the recommended monitoring interval) in 19 patients. The onset of injury began after 3 days to more than 2 years of troglitazone use (Graham and Green et al. 2003a; Graham and Drinkard et al. 2003b). Time from jaundice to hepatic encephalopathy, liver transplantation, or death usually was rapid, averaging 24 days. Troglitazone was withdrawn from the United States market in March 2000, when other agents (rosiglitazone, pioglitazone) with similar efficacy but little or no hepatotoxicity became available.

Apart from constituting another example of the predictive value of evidence of hepatocellular injury accompanied by even two cases of elevated bilirubin, there were other lessons learned from the troglitazone experience: 1) monitoring recommendations, even after several warning letters to all practicing physicians, may not be well followed; and 2) some cases of severe hepatotoxicity occur rapidly, within less than a reasonable and practical recommended interval for monitoring, indicating that monitoring would provide at best only partial protection, even if recommendations were followed. In addition, following the withdrawal of troglitazone, many companies began to search for toxigenomic answers to determining individual susceptibility to DILI, and a national network was funded by NIH in 2003 to study the problem (Watkins 2005).

Exanta (ximelagatran)

Exanta (ximelagatran), an oral anticoagulant (antithrombin), was not marketed in the United States because of hepatotoxicity and other concerns discovered during clinical trials. Issues related to potential liver toxicity of ximelagatran were presented and discussed at an FDA advisory committee meeting in September 2004 (He 2004). During short-term clinical trials of the drug for prevention of thromboembolic complications after joint replacement surgical procedures, there was no increased rate of transaminase elevations in the ximelagatran group compared to the enoxaparin-warfarin group, and no serious hepatotoxicity was seen. But in longer-term (>35 days) trials in patients with chronic atrial fibrillation to prevent embolic or thrombotic strokes, an increase in ALT >3xULN occurred in 7.6 percent of 6,948 patients compared to 1.1 percent of patients receiving warfarin treatment; and 1.5 percent of ximelagatran-treated patients had ALT >10xULN.

Increases in AT typically occurred 1 to 6 months after the initiation of ximelagatran administration with peak levels within 2 to 3 months post-randomization. Among the 531 ximelagatran patients with ALT >3xULN, 39 percent completed the study on treatment, while 61 percent discontinued the drug. Almost all patients with ALT >3xULN returned to <2xULN whether the drug was stopped or not, although the return to normal was faster if ximelagatran was stopped. Of 18 patients who resumed drug after ALT returned to normal, only 2 had elevations recur. Concomitant elevations of ALT >3xULN and bilirubin >2xULN were observed in 37 of about 7,000 patients, at least 13 of whom had no alternative explanation for the concomitant ALT and bilirubin elevation. Nine of the 37 patients died, but the deaths were not

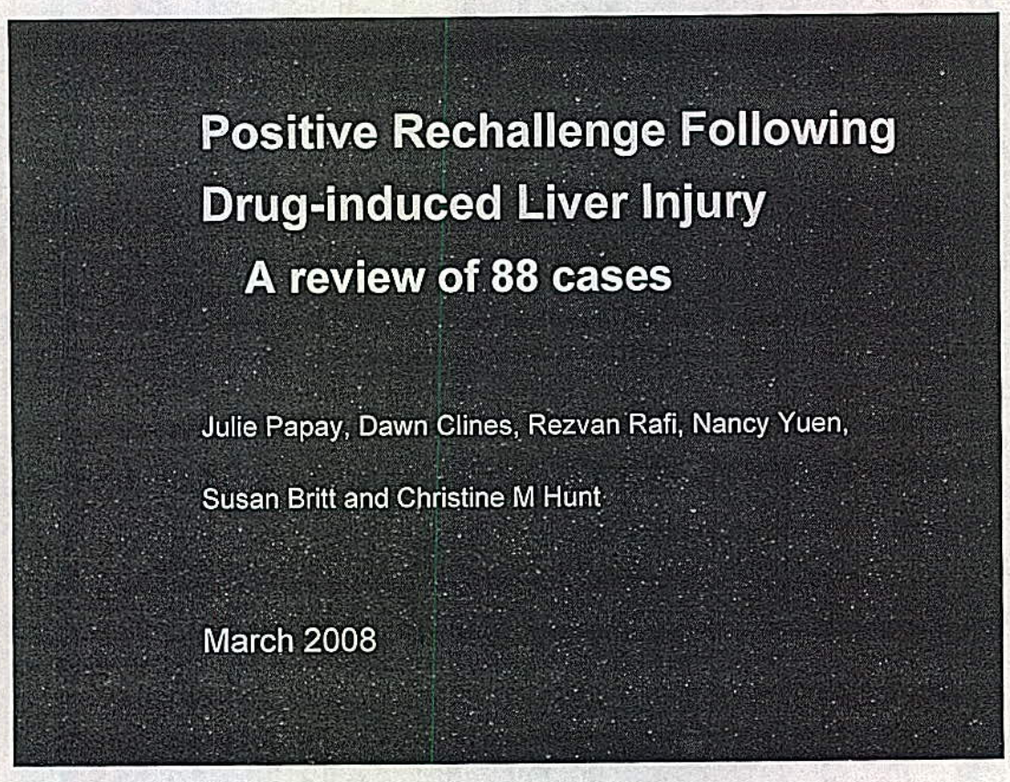
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clearly hepatotoxicity-related in most cases. Only one autopsy was done and it showed a small, friable and diffusely mottled liver suggestive of severe diffuse hepatic necrosis, but liver failure from ximelagatran might have contributed to some of the other deaths (He 2004; Lewis 2006; Kaplowitz 2006; Senior 2006; Temple 2006). Because severe hepatotoxicity was observed in an orthopedic surgery trial in an extended treatment of 35 days, Exanta was withdrawn in February 2006 from the 22 countries in which it had been approved, and further development in the United States was abandoned.

Again, short-term tolerance of ximelagatran, with resolution of even substantial elevations of ALT in most cases did not predict long-term safety. The relatively high rate of Hy's Law cases, about 0.2 percent or 1/500 (13 cases among 7,000 exposed patients), predicted the occurrence of severe hepatotoxicity, at a rate of about 1/5,000 (10 percent of the rate of Hy's Law cases). In fact, at least one death occurred among the 7,000 exposed patients subsequent liver toxicity, further supporting such an estimate.

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ANEXO C



DR. SELIGMAN: Our final speaker of this session is Dr. Julie Papay from GSK. Dr. Papay.

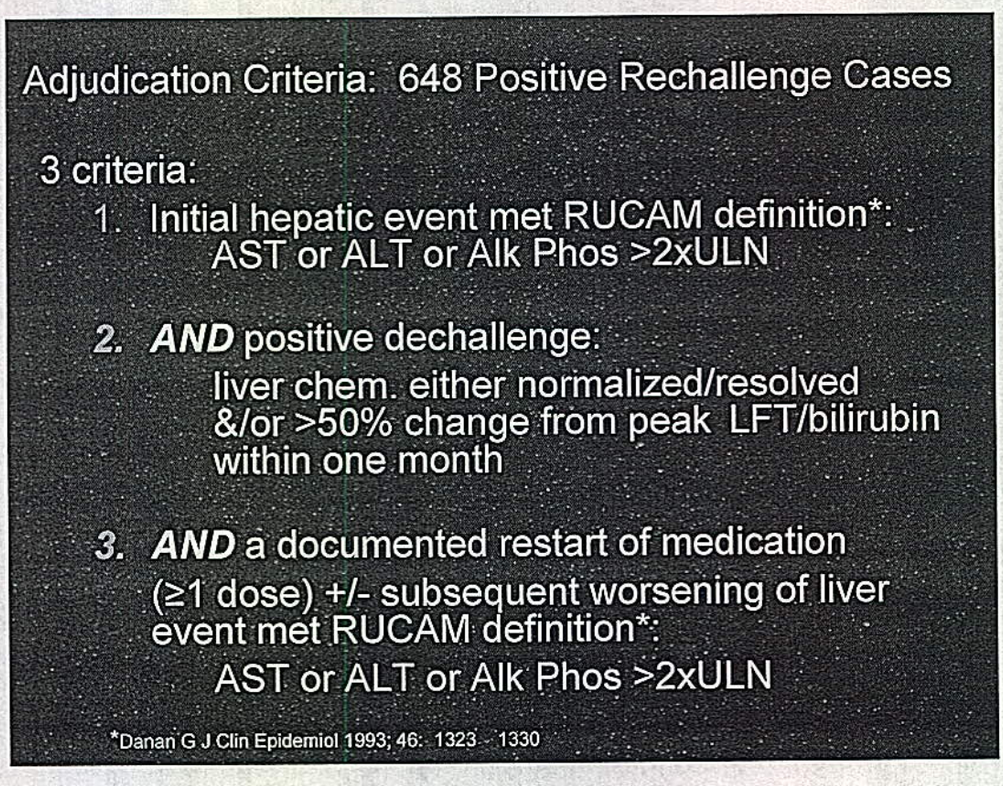
DR. PAPAY: Let me just do a quick check on the audio. I think that's a bit better. I'd certainly like to thank John Senior as well as Lana Pauls for the opportunity to present this information on positive drug rechallenge.

This was an analysis done by a group of us, and I would like to recognize my colleagues who are in the audience who helped support this analysis. Dawn Clines, Susan Britt, Nancy Yuen and Chris Hunt, who were able to make it here today as well as Rezvan Rafi, who unfortunately couldn't be here.

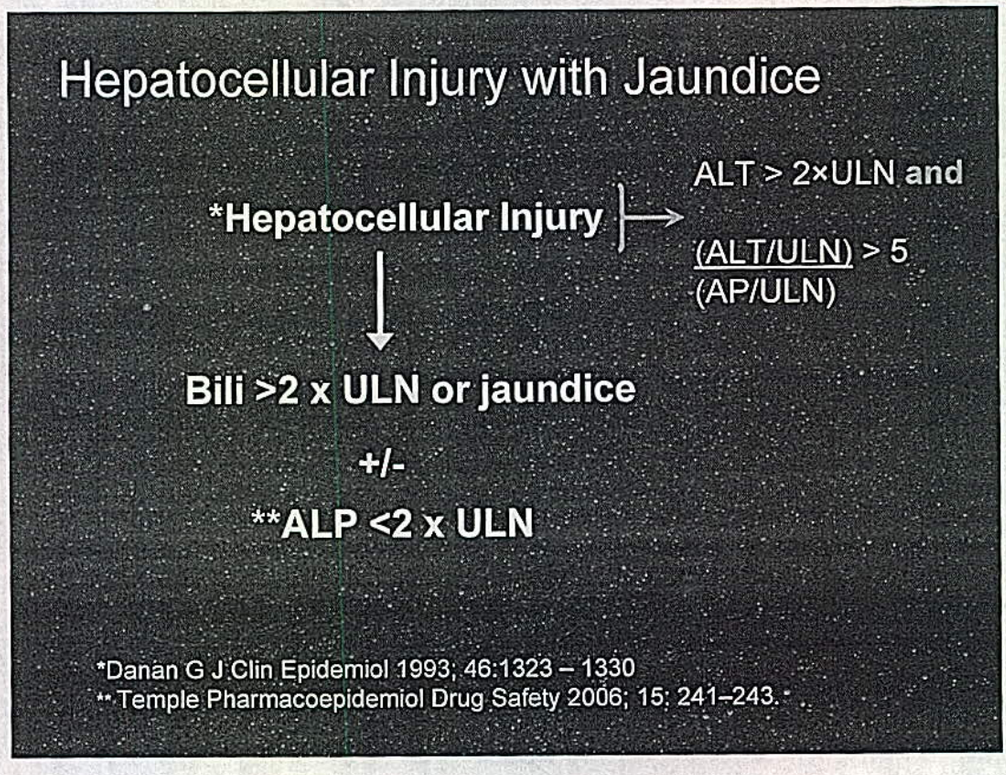
Positive Rechallenge Following Drug-induced Liver Injury

- **Methods**
- Results
- FDA Guidance
- Conclusion

What I'd like to talk to you today is about positive drug rechallenge following drug-induced liver injury, a review of 88 cases. In the time allotted, I'd like to tell you a little bit about what we did, what we found, how our analysis complements the draft FDA Guidance and end with some concluding remarks.



A positive drug rechallenge was defined using the following three criteria. First, the case had to demonstrate an initial hepatic event that met the RUCAM definition published by Danan, et al., an internationally recognized criteria of an AST, ALT or alkaline phosphatase of greater than two times upper limit of normal. Second, the cases had to show a clear positive rechallenge to rule out chronic liver disease, and that was defined by liver chemistries that either normalized or resolved and/or had a greater than 50 percent change from peak LFT or bilirubin within one month. And finally, all cases in this analysis had to show a documented restart of medication of at least one dose with or without subsequent worsening of a liver event, that once again met the RUCAM definition of elevated AST, ALT or alkaline phosphatase greater than two times the upper limit of normal.



Cases were also evaluated for hepatocellular injury with jaundice better known as Hy's Rule, Hy's Law, Hy's Hypothesis, but originally identified by Dr. Hy Zimmerman. It's a hepatocellular injury defined as an ALT greater than two times the upper limit of normal with a ratio of ALT to alkaline phosphatase of greater than five, with concomitant bilirubin elevations of at least two times upper limit of normal or overt jaundice.

Causality Criteria: 648 Positive Rechallenge Cases

- 1991 Causality Classification in Pharmacovigilance in the European Community, from the CPMP Working Party on Pharmacovigilance
- Only cases possibly or probably related to suspect drug were included:
  - Probable "A" Reports including good reason and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely but not necessarily highly probable.
  - Possible "B" Reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible or not unlikely, although the connection is uncertain or doubtful, for example because of missing data or insufficient evidence
  - Unclassified "O" Reports where causality is, for one reason or another, not assessable e.g., because of insufficient evidence, conflicting data, or poor documentation.

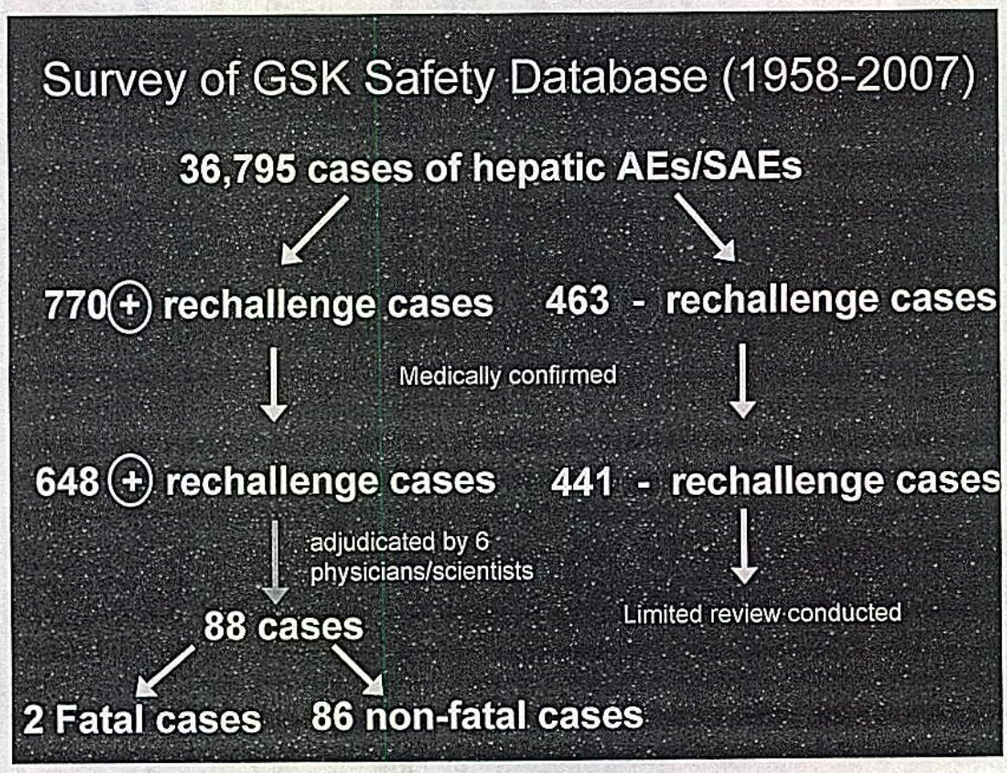
Meyboom RHB Pharmacoepidemiol Drug Safety 1992;1:87-97

In addition, cases were evaluated for alkaline phosphatase, whether or not it met a normal threshold. All cases were also evaluated using the causality score defined by the 1991 Causality Classification in Pharmacovigilance. Only cases that were possibly or probably drug related were included in this analysis.

Positive Rechallenge Following Drug-induced Liver Injury

- Methods
- **Results**
  - Demographics
  - Outcomes
  - Comparison of Select Therapies
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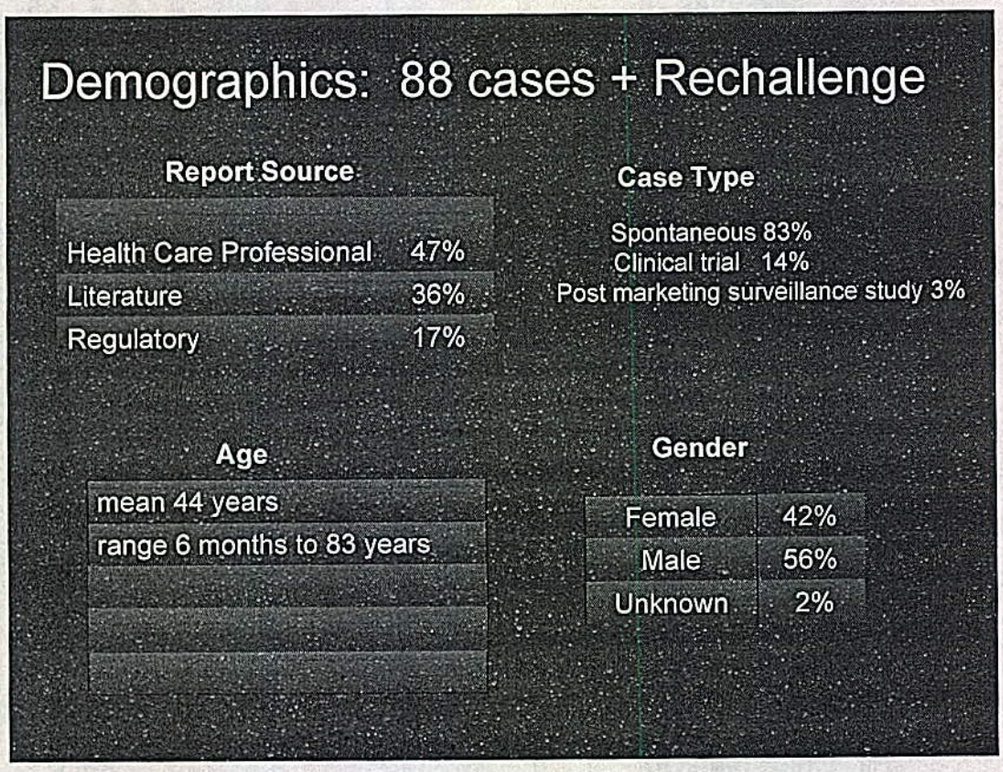
In other words, any reports that were considered unclassified, in which there was an inadequate amount of information, insufficient data or conflicting data, were not included in this analysis.



So to tell you a little bit about what we found, what I'd like to do is focus your attention on the left-hand side of the screen first. This analysis represents a survey of the GSK safety database which spans nearly 50 years of data. It is an international database of several merged PhRMA companies.

In our analysis, over 36,000 cases of hepatic adverse events and/or serious adverse events were identified including 770 positive rechallenge cases. Only those cases that were medically confirmed or reported by a regulatory agency were considered in this analysis. The majority of the cases were medically confirmed at 648, and this is where the real work came in, and this is where my colleagues helped out immensely. We had a team of six physicians and scientists who adjudicated 648 cases for all of the criteria that were discussed previously for positive rechallenge which resulted in 88 cases, 2 of which were fatal. So that's the positive rechallenge data set.

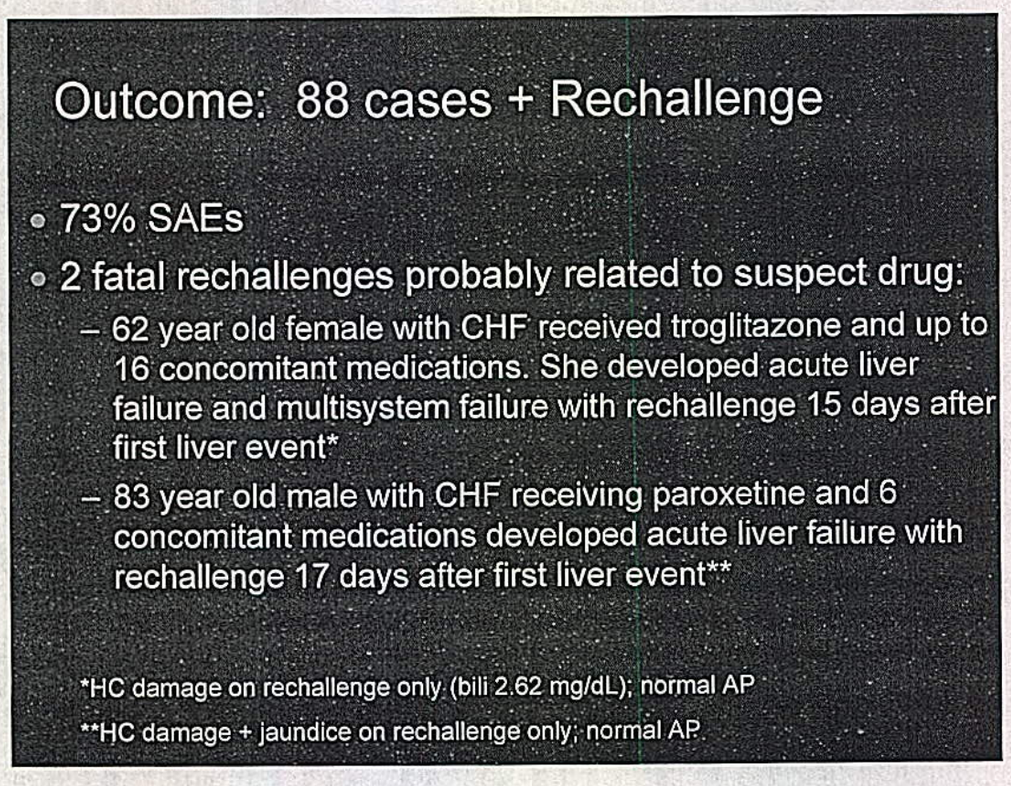
In addition, we did a limited review on negative rechallenge cases which is to the right of the screen. There were 463 cases that were identified in the database as negative rechallenge of which 441 were medically confirmed or reported by a regulatory agency, and a limited review was conducted on this data set.



But for the remainder of the talk, for the next few slides, I'd like to focus on the 88 cases of positive rechallenge that met rigorous criteria. The majority of these cases were reported by healthcare professionals, 47 percent. Of note, a third, over a third, 36 percent were reported in the literature and 17 percent were reported by regulatory agencies.

Surprisingly, this data subset was represented by a relatively young patient population at 44 years of age, although the range was fairly wide, 6 months to 83 years. When we look at the age breakouts, namely those patients who were over 55 years of age who were thought to be at increased risk of drug-induced liver injury, that represented almost a third of the data set but the vast majority were adults between the ages of 20 and 55 years.

In terms of who was reporting these positive drug rechallenges, most of the cases were reported spontaneously, 83 percent, although we did have 12 cases that were reported during our clinical trials of which half were the HIV portfolio. There were more men surprisingly in this data set of 56 percent versus women.



To characterize this data set a little bit further, 73 percent met the FDA criteria for serious adverse events, that is they either resulted in a fatality, required hospitalization or were life threatening. This included two fatal rechallenges that were probably related to the drug. Both of these fatalities occurred in elderly patients who interestingly enough had congestive heart failure.

The first case occurred in a 62-year-old female with congestive heart failure who received troglitazone and multiple medications, up to 16 concomitant medications. She unfortunately developed acute liver failure and multisystem failure with rechallenge 15 days after the liver event.

The second fatality occurred in an 83-year-old male who received paroxetine and 6 concomitant medications. He also developed acute liver failure with rechallenge 17 days after the first event.

Drug Class in 88 Cases of Positive Rechallenge	Number of cases
Antibiotics (half are Augmentin)	21 (24%)
HIV meds (majority are NRTIs AZT, lamivudine, stavudine, abacavir, ddi)	13 (15%)
Azathioprine	14 (16%)
H2 antagonists (majority are ranitidine)	9 (10%)
5-HT3 antagonists (ondansetron/granisetron)	7 (8%)
Oncology meds (mercaptopurine, chlorambucil, pazopanib)	7 (8%)
Antidepressants (bupropion, paroxetine, tranylcypromine)	4 (5%)
Albendazole	3 (3%)
Antiviral – acyclovir, valaciclovir	2 (2%)
Cardiac meds (labetalol, carvedilol)	2 (2%)
Diabetic drugs (troglitazone, rosiglitazone)	3 (3%)
Allopurinol	1 (1%)
Phentermine	1 (1%)
Tranilast (for asthma)	1 (1%)
Total	88

What drugs were represented? Well, there was a broad class of drugs that we found in our data set. The majority of drugs fell into either the antibiotic class, half of which were amoxicillin-clavulanic acid and HIV medications. The largest set were represented by nucleoside reverse transcriptase inhibitors. Other drugs that were found in this data set include azathioprine, the H2 antagonists, 5-HT3 blockers and oncology medications. But as you can see there were a wide variety of medications that were found in this rechallenged analysis.

88 Positive Rechallenge Cases

Symptoms
Yes = 37 No = 15

PMH for liver disease
Yes = 15 No = 56

Type of Liver Injury
HC 51%, Cholestatic 24%,
Mixed 10%, unknown 15%

Autoantibodies
Neg in 5 cases; +2 ANA in one

Concomitant Medications (n=69)	
None recorded	18%
1 Med	20%
2 Med	14%
3 Med	14%
≥4 Meds	34%

When symptoms were reported, the majority of patients described some symptoms of hepatitis or jaundice, over 70 percent. However, the majority of patients did not have a past medical history for liver disease.

The type of injury was overwhelmingly hepatocellular, 51 percent followed by cholestatic and mixed disease, and very rarely autoantibodies were reported. Six cases actually documented that autoantibodies were measured, and they were negative in five case. Only one case reported amoxicillin-clavulanic acid demonstrated positive 2 ANA.

Many patients were receiving multiple medications, and I think of note what's impressive to me is the fact that 34 percent received more than 4 medications concurrently.

Time to Rechallenge

52% were rechallenged with same drug within one month

Timeframe	Number of cases
1 week (0-7 days)	6
2 weeks (8-14 days)	9
3 weeks (15-21 days)	16
4 weeks (22-30 days)	15
2 months (31-60 days)	10
3 months (61-90 days)	7
4 months	3
5 months	2
6 months	2
9 months	1
1 year	2
1-2 years	1
Unknown	14

→ All 3 cases were amoxicillin + clavulanate

Most of the rechallenges were inadvertent and over half of the patients were rechallenged with the same drug within one month. There were three cases that were outliers that occurred at one to two years and all of these cases occurred with the antibiotic amoxicillin-clavulanate.

Time to Onset of Drug Induced Liver Injury

Event 1

Timeframe	Number of cases
1 week (0-7 days)	16
2 weeks (8-14 days)	12
3 weeks (15-21 days)	8
4 weeks (22-30 days)	9
2 months (31-60 days)	15
3 months (61-90 days)	8
4 months	1
5 months	1
9 months	1
10 months	1
1 year	2
1-2 years	2
Unknown	12

Rechallenge Event

Timeframe	Number of cases
1 week (0-7 days)	40
2 weeks (8-14 days)	11
3 weeks (15-21 days)	7
4 weeks (22-30 days)	5
2 months (31-60 days)	3
5 months	1
Unknown	21

Event 1: Mean 3 weeks (1d-18 mos)

Event 2: Mean 1 week (hrs 5 mos)

In terms of time to onset for the DILIN event, rechallenge, the time to onset with rechallenge occurred much more rapidly, a mean of one week versus the initial event a mean of three weeks. And in particular, I'd like to draw your attention to the fact that 40 of the cases, almost half of the data set, on rechallenge experienced drug-induced liver injury within 1 week.

Negative Rechallenge Cases (n=441)

- Limited negative rechallenge case review and comparison to positive rechallenge cases revealed:
  - Similar demographics
    - mean age 43 yrs; 56% male
  - Similar drugs
    - antiretrovirals & antibiotics constituted 40%
  - No factors evident to explain differing response

Now I'd like to transition and tell you a little bit about what we found with negative rechallenge cases. A limited review was conducted on the negative rechallenge cases to compare to the positive rechallenge data set, and overall the demographics were similar with a mean age of 43 years, more men than women. In terms of breaking out by age, there was a similar amount, about a quarter of the cases were over the age of 55 years. Similar drug classes were implicated with negative rechallenge, although the number 1 and number 2 spot were flipped for negative rechallenge. Antiretrovirals were number 1 and antibiotics were number 2 and constituted 40 percent of the data set.

We didn't see any evident risk factors to explain the differences between the positive and negative rechallenge.

Positive Rechallenge Event Summary (n=88)

- Most rechallenge events occurred within one month of initial drug induced liver injury, many within one week
- Most exhibited symptoms of jaundice or hepatitis, when data available (71%, 37/52)
- Most received multiple meds besides suspect drug (82%, 57/69)
- Few had underlying liver disease (21%, 15/71)
- Hepatocellular injury most common type of injury (51%)

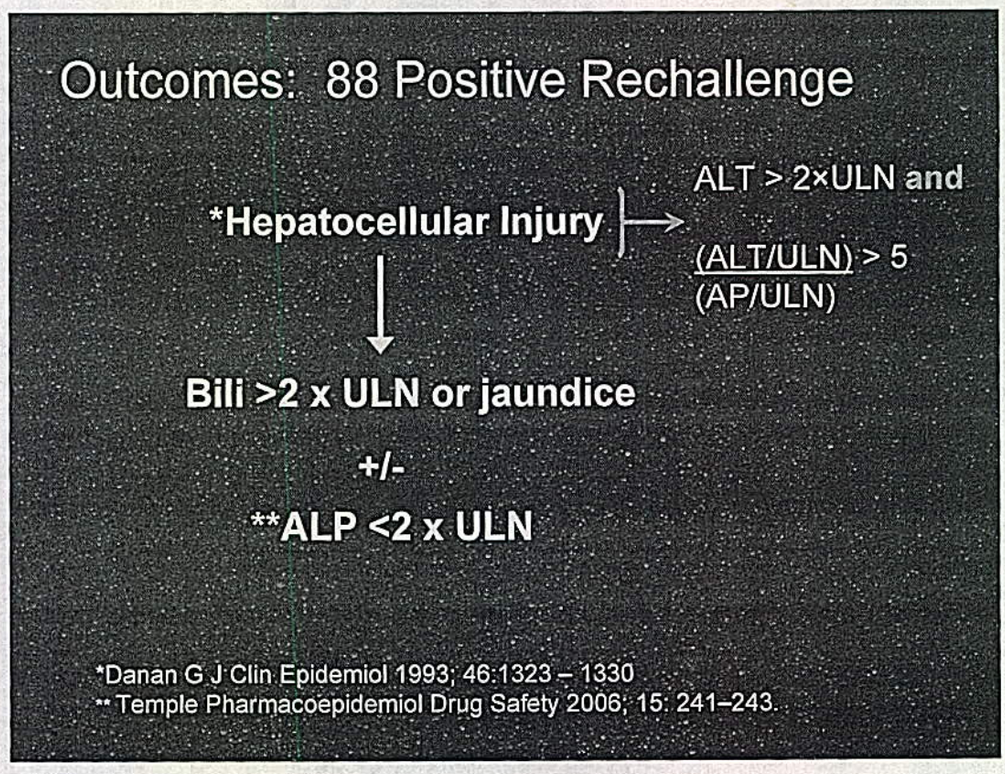
- A limited review of negative rechallenge cases (n=441) revealed similar demographics, drugs, with no clear trends

So just to summarize the data that we've reviewed thus far, most rechallenge events occurred within one month of the initial injury and many occurred within one week. Seventy-one percent of patients reported signs or symptoms of hepatitis or jaundice when symptoms were reported. Most received multiple medications and few had underlying liver disease, with hepatocellular injury as the most predominant form of injury. And a limited review of negative rechallenged cases on the data set of 441, revealed similar demographics, drugs and no clear trends.

Positive Rechallenge Following Drug-induced Liver Injury

- Methods
- **Results**
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  - **Outcomes**
  - Comparison of Select Therapies
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- Conclusion

Let's talk a bit about the outcomes.



I'm showing you this slide just to reorient you. I think most folks in the room are familiar with Hy's Law but these cases were also evaluated for evidence of hepatocellular injury with elevations in bilirubin with or without normal alkaline phosphatase which tells about biliary obstruction.

Outcomes (n=12)*: 88 + Rechallenge

Initial event only (n=3)	25%
Upon rechallenge only (n=2 fatalities)	17%
Both events (n=3)	25%
Jaundice described on rechallenge (n=4) (no labs provided for rechallenge)	33%

"Recurrent Hy's Law"

*including 8 cases (67%) with normal alk phos <2x ULN

Bilirubin >3 mg/dL in 11 of 12 cases

In the data set of positive rechallenge cases, 12 cases met Hy's Law. This included 11 cases that reported bilirubin that exceeded 3 milligrams per deciliter and I'd also like to note that 8 cases had normal alkaline phosphatase of less than 2 times upper limit of normal.

Cases Worse on Rechallenge (non-fatal): Recurrent Hy's law (n= 7)

Bilirubin & Transaminases on Initial Event & Rechallenge

Age/ Gender	Suspect Drugs	Time to Rechall	Outcome
58 Years/F	Azathioprine[1]	6 days	Improved
46 Year/M	Amoxicillin[2] trihydrate + potassium clavulanate	1 year	Hepatocell. hepatitis Resolved
*41 Years/M	Amoxicillin[3] trihydrate + potassium clavulanate	>23 months	Hepatocell. hepatitis Liver transplant

*Normal alk phos <2x ULN

[1]Sterneck M Hepatology 1991;14:806–810; [2] Breuskin F Acta Clinica Belgica 2001;56:255 257; [3]Andrade RJ Hepatology 2006; 44: 1581 1588.

The next few slides I'd like to focus your attention on seven cases that actually had recurrent Hy's Law, that is they had Hy's Law on the initial event followed by Hy's Law on rechallenge. This slide shows you 3 of the 7 cases that described increased bilirubin and transaminases on initial event and rechallenge, and this was represented by a case of a 58-year-old woman who received azathioprine. Fortunately, her Hy's Law case improved. This patient actually received azathioprine following liver transplant for chronic Hepatitis C infection. The other two cases received amoxicillin- clavulanate, one in a 46-year-old male, also whose drug-induced liver injury resolved. It also represents a 41-year-old male who unfortunately went on to liver transplant. All of these cases by the way are published in literature and the references are provided.

Cases Worse on Rechallenge (non-fatal; cont'd): Recurrent Hy's law (n= 7)

Jaundice Reported on Rechallenge Only

Age/Gender	Suspect Drugs	Time to Rechallenge	Outcome
*28 Years/M	Azathioprine[1]	30 days	Unknown
48 Years/F	Azathioprine[1]	Unknown	Unknown
49 Years/F	Azathioprine[1]	20 days	Unknown
*35 Years/M	Ondansetron HCl[2]	Unknown (probably <2 months)	Resolved

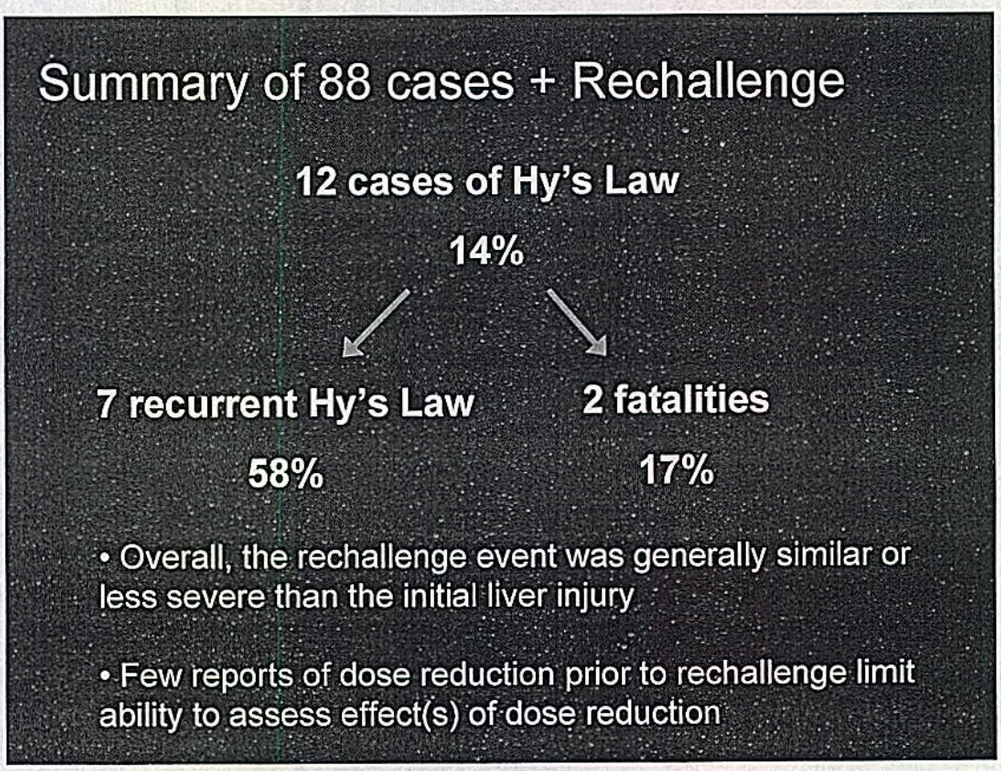
*Normal alk phos <2 xULN

[1]Ramahlo HJ Tranplantation Proceedings 1989;21:1716 1717

[2] Verrill M Lancet 1994;344:190-191

The remaining four cases that experienced recurrent on rechallenge of Hy's Law only reported jaundice but for completeness sake, that data is represented here. This includes three cases of azathioprine that were published by Ramahlo, et al. These patients received Azathioprine following renal transplant and of note, had normal liver function tests prior to transplantation.

The last case is an interesting case published by Verrill, et al., with ondansetron, and this patient was receiving IV doses of ondansetron prior to chemotherapy, received the first dose of IV ondansetron with chemotherapy, experienced elevations in LFTs and increased bilirubin, came in for a second course of chemotherapy and was again pretreated with ondansetron for chemotherapy-induced emesis, saw a recurrence of this event. With the third round of chemotherapy he was actually switched to granisetron, and there were no ill effects with respect to the liver.



So to summarize hepatocellular injury with jaundice, over half of the cases, 58 percent, actually experienced recurrence with rechallenge and this subset also included two fatalities

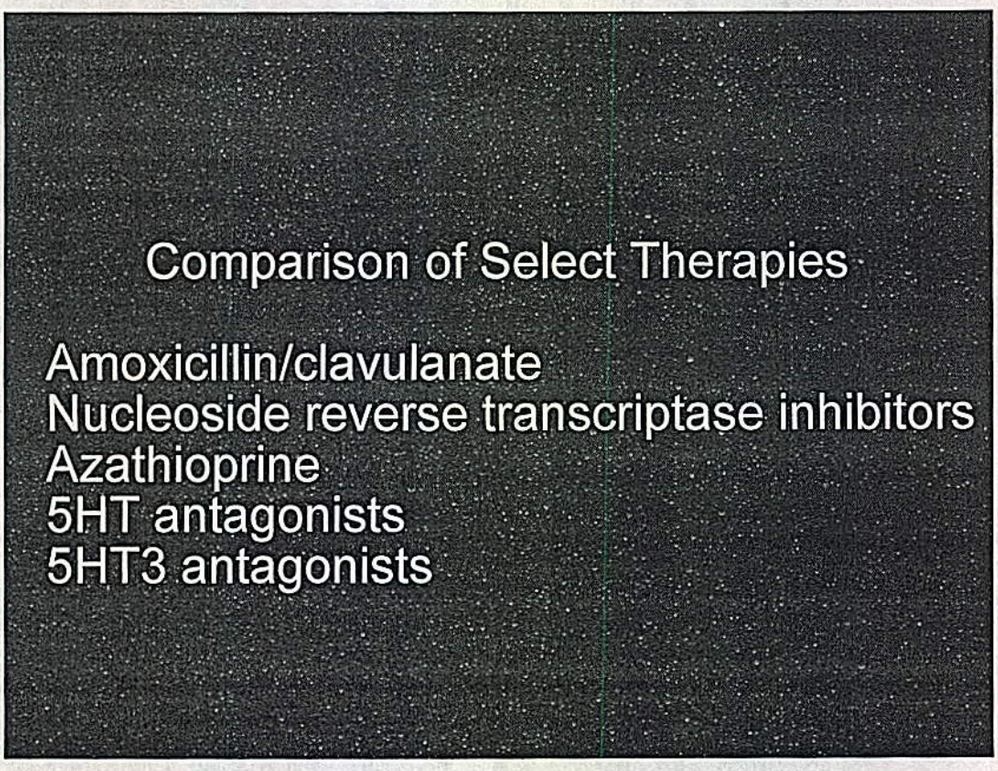
That said, overall the rechallenge event was generally similar or less severe than the initial injury in those cases that did not meet Hy's Law.

We did evaluate the effective dose and unfortunately there were just too few cases to evaluate for reducing the dose prior to rechallenge to note any trends or meaningful information.

Positive Rechallenge Following Drug-induced Liver Injury

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Comparison of select therapies:



...these five drug classes represent over 80 percent of the drug classes that were observed with the 88 cases of positive rechallenge, and I'd like to talk to you a little bit about each of these in greater depth.

Possible Confounders in Select Therapies

NRTIs N=11	5 cases hepatitis C 3 alcohol use
Azathioprine N=14	1 liver transplant for hepatitis C
H2 antagonists N=9	1 case alcoholic liver disease 2 cases PMH drug allergy including one case with drug induced hepatitis with pyrazinamide/rash
5 HT3 antagonists n=7	1 case metastatic cancer with liver metastases 1 case h/o erythromyin-induced hepatitis 1 case (47 yo F) with positive EBV antibody

Confounders affected a minority of cases and occurred most frequently in HIV subjects receiving NRTIs

There were possible confounders with select therapies which included hepatitis C, past medical history for drug allergy, alcohol abuse, et cetera. However, most of the confounders affected the nuceloside reverse transcriptase inhibitor patients with HIV.

Amoxicillin/clavulanic acid (n=10)

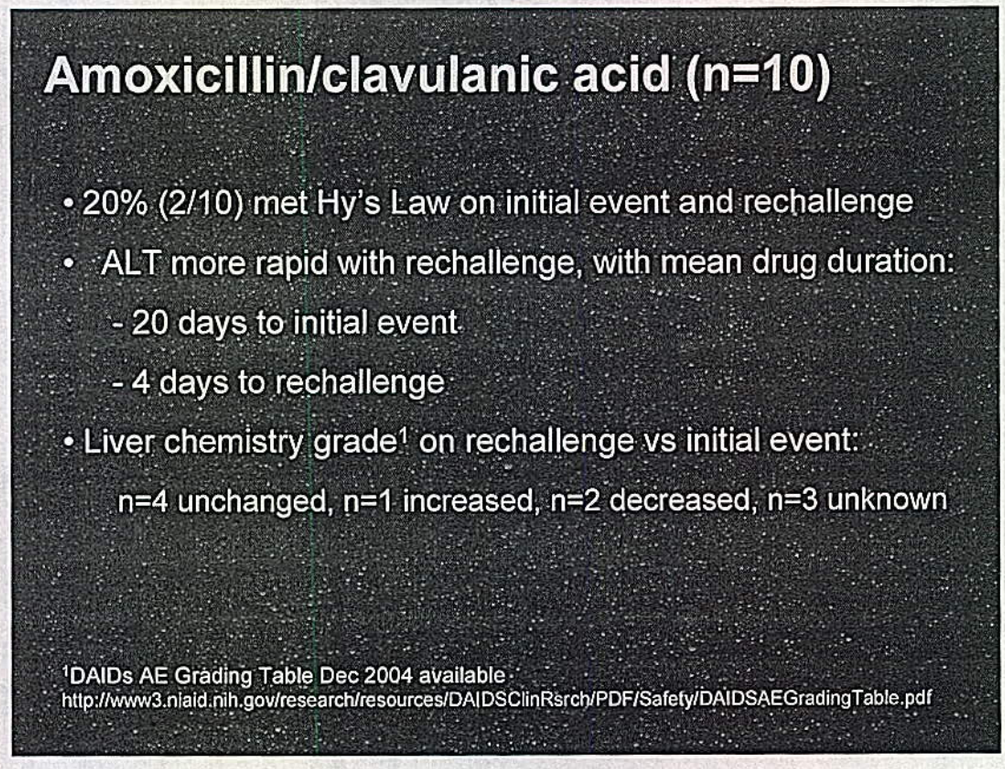
Demographics:

- Mean age 50 years (40-78 years)
- 6 female; 4 male

- Presentation: 90% (9/10) developed jaundice after 1-4 wks; usually post-treatment
- Rechallenge cases similar to data published by Lucena et al.[1]

[1]Lucena Hepatology 2006;44:850 856.

In terms of what was found with the 10 case of amoxicillin-clavulanic acid, the mean age was 50 years. All of these cases represented adult patients. Six males and four females were represented in this data set. And, 90 percent involved jaundice after 1 to 4 weeks of starting their antibiotic. Usually these changes were seen a few days after finishing their antibiotic regimen.



And the information that we found in our data set is similar to the Spanish registry published by the Lucena, et al., who reported that in patients over the age of 55, there were higher elevations of bilirubin. Our data set corroborates that information in that patients who were over the age of 55 had an average bilirubin elevation of 14 milligrams per deciliter, versus younger patients, less than 55, only had bilirubin elevations of about 7 milligrams per deciliter. So very similar data.

In addition, two of the cases met Hy's Law on the initial event and rechallenge. The rises in ALT were much more rapid on rechallenge than the initial event, with 4 days versus 20 days and when you look at the Division of AIDS, liver AE grading tables, we wanted to see how bad were the elevations on rechallenge or did you tend to see some adaptation. Four cases, their DAIDS grade scoring remained unchanged, one increased, two decreased and three didn't provide enough information to make an assessment.

Nucleoside Reverse Transcriptase Inhibitors (n=11)

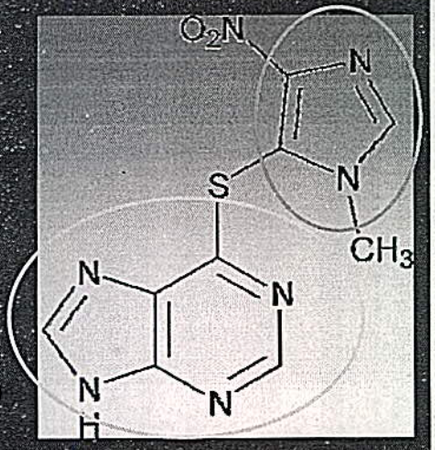
- Median age 41 (6 mos - 57 years), 9 male/1 female/1 unk
- Most events asymptomatic (jaundice in two cases)
- No Hy's Law cases
- Mean duration of drug therapy to first event: 2.6 months
- Liver injury frequently hepatocellular:
  - 55% hepatocellular (abacavir)
  - 27% cholestatic (zidovudine/lamivudine)
  - 18% unassessable
- Liver chemistry grade[1] on rechallenge vs initial DILI:
  n=6 unchanged, n 1 increased, n=3 decreased, n=1 unknown

[1]DAIDs AE Grading Table Dec 2004

In contrast, with the NRTIs most of the liver injury was hepatocellular in nature, and many of these cases had asymptomatic elevations in their ALTs that occurred months after starting therapy. So a very different picture than amoxicillin-clavulanate. The mean age was 41 years although there was a broad range. One case reported exposure in a six-month old. There were no Hy's Law cases in this subset and liver chemistry grade on rechallenge versus the initial, six remained unchanged, one increased and three decreased.

Azathioprine n=14

- Mean age 46 years (21-63); 9 male/5 female
- Presentation:
  - 57% (8/14) developed asymptomatic ↑ LFTs
  - 43% (6/14) developed jaundice that reappeared on rechallenge
- Liver injury usually hepatocellular:
  - 71% hepatocellular
  - 21% cholestatic
  - 7% mixed
- 2 cases w/eosinophilic portal infiltrate on bx
- 29% (4/14) met Hy's law on initial injury & rechallenge[1,2]
- ALT more rapid with rechallenge, with mean drug duration:
  - 3 months to initial event
  - 10 days to rechallenge event



[1]Sterneck M Hepatology 1991;14:806–810;
[2]Ramahlo HJ Tranplantation Proceedings 1989;21:1716-1717

In the interest of time, I'll quickly go through the next three data sets, but suffice it to say that for azathioprine, the 5HT3 antagonists and H2 blockers, the form of liver injury was hepatocellular in nature, had a quicker time to onset after rechallenge than the initial event and azathioprine, like the NRTIs, typically the injury occurred months after starting the drug.

H2 Antagonists (n=7 ranitidine, 2 cimetidine)

- Mean age 49 years (40-78), 5 male/4 female
- Liver injury frequently hepatocellular:
  - 55% hepatocellular
  - 22% mixed
  - 22% unassessable
- 22% (2/9) met Hy's Law on *initial injury only*
- ALT more rapid with rechallenge, with mean drug duration:
  - 33 days to initial event
  - 7 days to rechallenge
- Liver chemistry grade[1] on rechallenge vs initial DILI:
  n=2 unchanged, n 1 increased, n=3 decreased, n=3 unknown

[1]DAIDs AE Grading Table Dec 2004; [2]Luparini RL Ann Ital Med Int 2000;15:214-217;
[3]Hiesse C Lancet 1985;1:1280

For H2 blockers, the form of liver injury was hepatocellular in nature, had a quicker time onset after rechallenge than the initial event and, typically the injury occurred months after starting the drug.

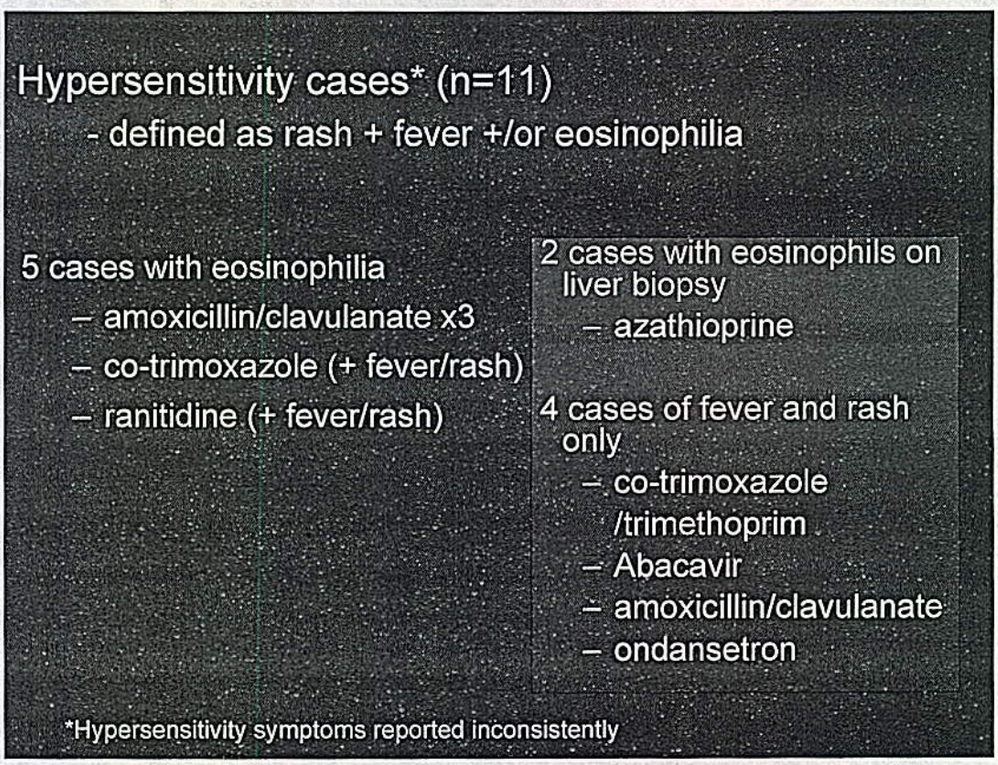
5HT3 Antagonists (n=6 ondansetron, 1 granisetron)

- Mean age 46 years (11-69), 3 male/4 female
- Liver injury usually hepatocellular:
  - 71% hepatocellular
  - 29% unassessable
- 1 case met Hy's law on initial injury & rechallenge[1]
- Liver chemistry grade[1] on rechallenge vs initial DILI:
  n=2 unchanged, n=4 decreased, n=1 unknown

[1]Verrill M Lancet 1994;344:190-191

[2]DAIDs AE Grading Table Dec 2004

With 5HT3 antagonists, the form of liver injury was hepatocellular in nature, had a quicker time onset after rechallenge than the initial event and typically the injury occurred months after starting the drug.



Just to stay on track with time, there has been a fair amount discussed about hypersensitivity and the role that might play in drug-induced liver injury. We evaluated cases for rash, fever and/or eosinophilia and five case were documented with eosinophilia including three with amoxicillin-clavulanate, one with cotrimoxazole and one with ranitidine. And I should pause and say here that out of all the data shown on this slide, there's only one case that occurred with amoxicillin-clavulanic acid in which the patient had eosinophilia and also met with Hy's Law.

In addition, there were two cases with eosinophilia infiltrates that were noted on the liver biopsy. Both of those cases occurred with azathioprine. None of those case met Hy's Law. And there were four cases of fever and rash reported only, and that included one case with abacavir hypersensitivity reaction.

Positive Rechallenge Following Drug-induced Liver Injury

- Methods
- Results
- **FDA Guidance**
- Conclusion

So how does this information complement the draft FDA Guidance, and I think it complements it quite well.

FDA Draft Guidance – Drug Induced Liver Injury

- Rechallenge should only be considered when:
  - ALT elevations do not exceed 5x ULN
  - a patient has shown clear therapeutic benefit from the drug & other options are not available OR
  - substantial accumulated data does not show potential for severe injury
  - requires subject consent & monitor closely

*FDA Draft Guidance. DILI Premarketing Clinical Evaluation. October 2007

The FDA draft Guidance suggests that rechallenge should only be considered when you see ALT elevations that do not exceed more than five times upper limit of normal and when a patient has shown a clear therapeutic benefit from the drug when other options are not available or you know there's enough data out there to suggest that the drug is not the likely offender. It obviously requires the patient understand the risk benefit and give consent before rechallenge.

ALT<5xULN in 16/88 rechallenge cases

- 13/16 cases: event no worse on rechallenge
- 3/16 cases: event similar/more severe on rechallenge; no fatalities
  - 61yoM with rheumatoid arthritis & azathioprine hypersensitivity hepatitis on liver biopsy with fever, chills, malaise, **jaundice**, cholestatic hepatitis with eosinophils on biopsy, and acute interstitial nephritis[1]
    - Concom. meds: naproxen (rapidly tapered)
  - 35yoM with neuroectodermal cancer with fever, **jaundice** with ondansetron initial and rechallenge liver events[2]
    - Concom. meds: ifosfamide, doxorubicin, vincristine, Mesna
  - 75yoM with chronic lymphocytic leukemia and hypothyroidism with hepatocellular injury on chlorambucil rechallenge exhibited doubling of ALT and AST in rechallenge event compared with initial event[3]
    - Concom. meds: prednisone, thyroxine
- Evidence base suggests that ALT≤5xULN without jaundice a better threshold for drug rechallenge after probable drug-induced liver injury

1. Meys J Rheumatol 1992;19(5):807, 2. Verrill Lancet 1994;344:190, 3. spontaneous report

So the first criterion, for ALT elevations that did not exceed five times upper limit of normal, we went back and reviewed our data set of 88 cases of positive rechallenge and we found that 13 of 16 cases that did not have worsening other than on rechallenge. However, there were 3 cases that did get worse on rechallenge who had ALTs less than five. Two of those patients reported concurrent jaundice with the ALT less than five and one patient, a 75-year-old male, who had leukemia who received chlorambucil experienced a doubling of the LFTs following the challenge.

Positive Rechallenge Following Drug-induced Liver Injury

- Methods
- Results
- FDA Guidance
- **Conclusion**

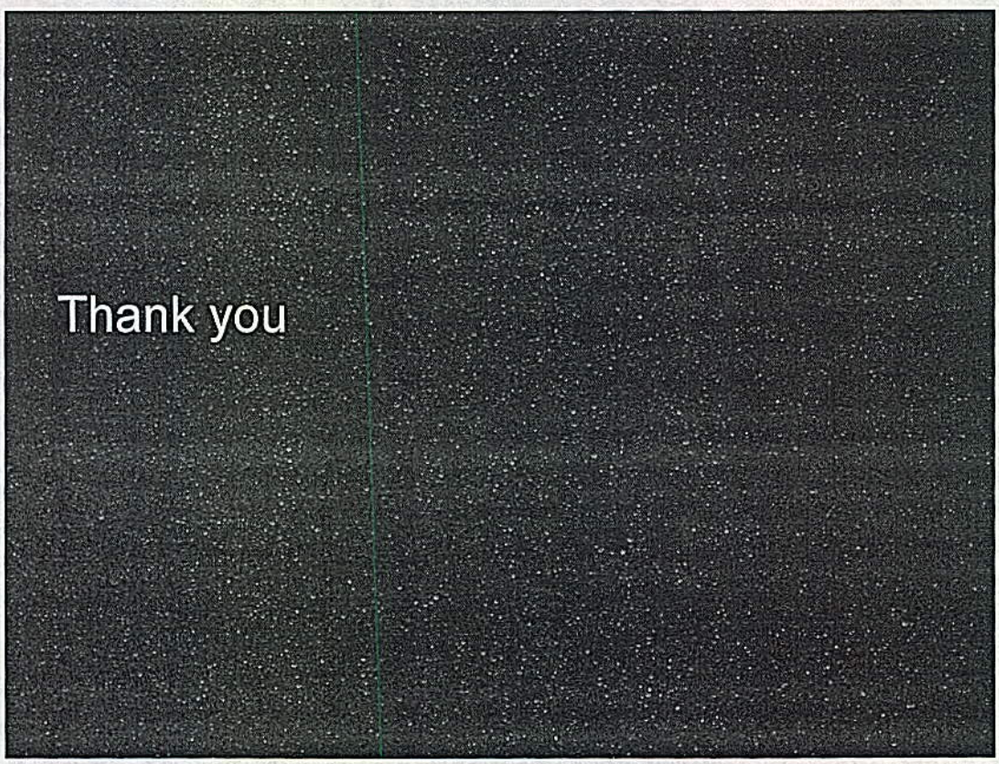
So I think it would complement the FDA Guidance quite nicely if inclusion of rechallenge might be considered in patients who have ALTs less than five times upper limit of normal without jaundice.

Conclusions

- Drug rechallenge following drug-induced liver injury may result in recurrence of adverse effects
- 2 fatalities, although HC injury occurred with initial event, HC injury with ↑ bilirubin (>2 mg/dL) only occurred on rechallenge
- The short time interval (<1mo) between initial drug-induced liver injury and rechallenge suggests that drug rechallenge could be prevented by:
  - improved recognition of drug-induced liver injury
  - HCP communication to patients (as per allergies)
  - improved health records

And just some concluding remarks, drug rechallenge following DILI may result in the recurrence of adverse effects. We had a fair number of recurrence of Hy's Law on rechallenge. Fatalities can happen and in our data set, the two fatalities, demonstrated Hy's Law upon rechallenge only. The initial liver injury was hepatocellular in nature and did not meet Hy's Law.

The short time interval, less than one month between the initial drug-induced liver injury and rechallenge, suggests that we can do a better job and prevent rechallenge first by improving the recognition of drug-induced liver injury from clinicians who are seeing patients as well as communicating to our patients that they had a potentially serious drug-induced liver injury with a drug, making sure that those patients understand that they've had the event and the name of the drug, not only the trade name but the generic name, perhaps even, you know, patients could wear a Medic Alert bracelet or carry a medication guide in their wallet because patients move, doctors change and unfortunately all health records are not electronic. And we can also do a better job of improving our health records. In our data set, inadvertent rechallenge was reported in one hospital on different floors.



So I think that there is learning that can be shared and improvement that can be made regarding drug-induced liver injury.

In conclusion, a heightened awareness is needed about positive rechallenge following drug-induced liver injury, given the potential for serious adverse events and sometimes fatal outcomes and in general, clinicians should avoid such rechallenges. Thank you.

(Applause.)

ANEXO D

Tracleer
BOSENTAN TABLETS

62.5 mg and 125 mg film-coated tablets

Use of TRACLEER® requires attention to two significant concerns: 1) potential for serious liver injury, and 2) potential damage to a fetus.

WARNING: Potential liver injury

TRACLEER® causes at least 3-fold (upper limit of normal; ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious liver injury, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly (see WARNINGS: Potential Liver Injury and DOSAGE AND ADMINISTRATION). In the post-marketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (>12 months) therapy with TRACLEER® in patients with multiple co-morbidities and drug therapies. There have also been rare reports of liver failure. The contribution of TRACLEER® in these cases could not be excluded.

In at least one case the initial presentation (after >20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of TRACLEER®. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment and the treatment algorithm, which includes stopping TRACLEER® with a rise of aminotransferases accompanied by signs or symptoms of liver dysfunction (see DOSAGE AND ADMINISTRATION).

Elevations in aminotransferases require close attention (see DOSAGE AND ADMINISTRATION). TRACLEER® should generally be avoided in patients with elevated aminotransferases (>3 × ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥2 × ULN, treatment should be stopped. There is no experience with the re-introduction of TRACLEER® in these circumstances.

CONTRAINDICATION: Pregnancy

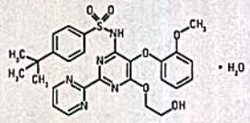
TRACLEER® (bosentan) is very likely to produce major birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals (see CONTRAINDICATIONS). Therefore, pregnancy must be excluded before the start of treatment with TRACLEER® and prevented thereafter by the use of a reliable method of contraception. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving TRACLEER® (see PRECAUTIONS: Drug Interactions). Therefore, effective contraception through additional forms of contraception must be practiced. Monthly pregnancy tests should be obtained.

Because of potential liver injury and in an effort to make the chance of fetal exposure to TRACLEER® (bosentan) as small as possible, TRACLEER® may be prescribed only through the TRACLEER® Access Program by calling 1 866 228 3546. Adverse events can also be reported directly via this number.

DESCRIPTION

Bosentan is the first of a new drug class, an endothelin receptor antagonist.

TRACLEER® (bosentan) belongs to a class of highly substituted pyrimidine derivatives, with no chiral centers. It is designated chemically as 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-[2,2']-bipyrimidin-4-yl]-benzenesulfonamide monohydrate and has the following structural formula:



Bosentan has a molecular weight of 569.64 and a molecular formula of $C_{27}H_{29}N_5O_6S \cdot H_2O$. Bosentan is a white to yellowish powder. It is poorly soluble in water (1.0 mg/100 mL) and in aqueous solutions at low pH (0.1 mg/100 mL at pH 1.1 and 4.0; 0.2 mg/100 mL at pH 5.0). Solubility increases at higher pH values (43 mg/100 mL at pH 7.5). In the solid state, bosentan is very stable, is not hygroscopic and is not light sensitive.

TRACLEER® is available as 62.5 mg and 125 mg film-coated tablets for oral administration, and contains the following excipients: corn starch, pregelatinized starch, sodium starch glycolate, povidone, glyceryl behenate, magnesium stearate, hydroxypropylmethylcellulose, triacetin, talc, titanium dioxide, iron oxide yellow, iron oxide red, and ethylcellulose. Each **TRACLEER®** 62.5 mg tablet contains 64.541 mg of bosentan, equivalent to 62.5 mg of anhydrous bosentan. Each **TRACLEER®** 125 mg tablet contains 129.082 mg of bosentan, equivalent to 125 mg of anhydrous bosentan.

CLINICAL PHARMACOLOGY

Mechanism of Action

Endothelin-1 (ET-1) is a neurohormone, the effects of which are mediated by binding to ET_A and ET_B receptors in the endothelium and vascular smooth muscle. ET-1 concentrations are elevated in plasma and lung tissue of patients with pulmonary arterial hypertension, suggesting a pathogenic role for ET-1 in this disease. Bosentan is a specific and competitive antagonist at endothelin receptor types ET_A and ET_B. Bosentan has a slightly higher affinity for ET_A receptors than for ET_B receptors.

Pharmacokinetics

General

After oral administration, maximum plasma concentrations of bosentan are attained within 3-5 hours and the terminal elimination half-life ($t_{1/2}$) is about 5 hours in healthy adult subjects. The exposure to bosentan after intravenous and oral administration is about 2-fold greater in adult patients with pulmonary arterial hypertension than in healthy adult subjects.

Absorption and Distribution

The absolute bioavailability of bosentan in normal volunteers is about 50% and is unaffected by food. The volume of distribution is about 18 L. Bosentan is highly bound (>98%) to plasma proteins, mainly albumin. Bosentan does not penetrate into erythrocytes.

Metabolism and Elimination

Bosentan has three metabolites, one of which is pharmacologically active and may contribute 10%-20% of the effect of bosentan. Bosentan is an inducer of CYP2C9 and CYP3A4 and possibly also of CYP2C19. Total clearance after a single intravenous dose is about 4 L/hr in patients with pulmonary arterial hypertension. Upon multiple oral dosing, plasma concentrations in healthy adults decrease gradually to 50-65% of those seen after single dose administration, probably the effect of auto-induction of the metabolizing liver enzymes. Steady-state is reached within 3-5 days. Bosentan is eliminated by biliary excretion following metabolism in the liver. Less than 3% of an administered oral dose is recovered in urine.

Special Populations

It is not known whether bosentan's pharmacokinetics is influenced by gender, body weight, race, or age.

Liver Function Impairment

In vitro and *in vivo* evidence showing extensive hepatic metabolism of bosentan suggests that liver impairment could significantly increase exposure of bosentan. In a study comparing 8 patients with mild liver impairment (as indicated by the Child-Pugh method) to 8 controls, the single- and multiple-dose pharmacokinetics of bosentan were not altered in patients with mild hepatic impairment. The influence of moderate or severe liver impairment on the pharmacokinetics of bosentan has not been evaluated. Bosentan should generally be avoided in patients with moderate or severe liver abnormalities and/or elevated aminotransferases >3 × ULN (see **DOSAGE AND ADMINISTRATION** and **WARNINGS**).

Renal Impairment

In patients with severe renal impairment (creatinine clearance 15-30 mL/min), plasma concentrations of bosentan were essentially unchanged and plasma concentrations of the three metabolites were increased about 2-fold compared to people with normal renal function. These differences do not appear to be clinically important (see **DOSAGE AND ADMINISTRATION**).

Clinical Studies

Pulmonary Arterial Hypertension

Two randomized, double-blind, multi-center, placebo-controlled trials were conducted in 32 and 213 patients. The larger study (BREATHE-1) compared 2 doses (125 mg b.i.d. and 250 mg b.i.d.) of **TRACLEER®** with placebo. The smaller study (Study 351) compared 125 mg b.i.d. with placebo. Patients had severe (WHO functional Class III-IV) pulmonary arterial hypertension: primary pulmonary hypertension (72%) or pulmonary hypertension secondary to scleroderma or other connective tissue diseases (21%), or to autoimmune diseases (7%). There were no patients with pulmonary hypertension secondary to other conditions such as HIV disease, or recurrent pulmonary emboli.

In both studies, **TRACLEER®** or placebo was added to patients' current therapy, which could have included a combination of digoxin, anticoagulants, diuretics, and vasodilators (e.g., calcium channel blockers, ACE inhibitors), but not epoprostenol. **TRACLEER®** was given at a dose of 62.5 mg b.i.d. for 4 weeks and then at 125 mg b.i.d. or 250 mg b.i.d. for either 12 (BREATHE-1) or 8 (Study 351) additional weeks. The primary study end point was 6-minute walk distance. In addition, symptoms and functional status were assessed. Hemodynamic measurements were made at 12 weeks in Study 351.

The mean age was about 49 years. About 80% of patients were female, and about 80% were Caucasian. Patients had been diagnosed with pulmonary hypertension for a mean of 2.4 years.

Submaximal Exercise Capacity

Results of the 6-minute walk distance at 3 months (Study 351) or 4 months (BREATHE-1) are shown in Table 1.

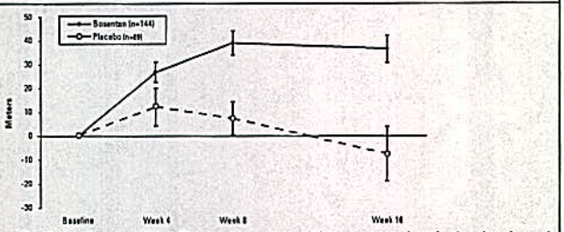
Table 1. Effects of bosentan on 6-minute walk distance

	BREATHE-1			Study 351	
	Bosentan 125 mg b.i.d. (n=74)	*Bosentan 250 mg b.i.d. (n=70)*	Placebo (n=69)	Bosentan 125 mg b.i.d. (n=21)	Placebo (n=11)
Baseline	*326 ± 73*	*333 ± 75*	344 ± 76	360 ± 86	355 ± 82
End point	*353 ± 115*	*379 ± 01*	336 ± 129	431 ± 66	350 ± 147
Change from baseline	*27 ± 75*	*46 ± 62*	-8 ± 96	70 ± 56	-6 ± 121
Placebo-subtracted	*35 [a]*	*54 [b]*		*76 [c]*	

Distance in meters: mean ± standard deviation. Changes are to week 16 for BREATHE-1 and to week 12 for Study 351.
[a]p=0.01; by Wilcoxon [b]p=0.0001 for 250 mg; by Wilcoxon [c]p=0.02; by Student's t-test

In both trials, treatment with **TRACLEER®** resulted in a significant increase in exercise capacity. The improvement in walk distance was apparent after 1 month of treatment (with 62.5 mg b.i.d.) and fully developed by about 2 months of treatment (Figure 1). It was maintained for up to 7 months of double-blind treatment. Walking distance was somewhat greater with 250 mg b.i.d., but the potential for increased liver injury causes this dose not to be recommended (see **DOSAGE AND ADMINISTRATION**). There were no apparent differences in treatment effects on walk distance among subgroups analyzed by demographic factors, baseline disease severity, or disease etiology, but the studies had little power to detect such differences.

Figure 1. Mean Change in 6-min Walk Distance (BREATHE-1)



Change from baseline in 6-minute walking distance from start of therapy to week 16 in the placebo and combined bosentan (125 mg b.i.d. and 250 mg b.i.d.) groups. Values are expressed as mean ± standard error of the mean.

Hemodynamic Changes

Invasive hemodynamic parameters were assessed in Study 351. Treatment with **TRACLEER®** led to a significant increase in cardiac index (CI) associated with a significant reduction in pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), and mean right atrial pressure (RAP) (Table 2).

Table 2. Change from Baseline to Week 12: Hemodynamic Parameters

	Bosentan 125 mg b.i.d		Placebo
Mean CI (L/min/m²)	N=20		N=10
Baseline	2.35±0.73		2.48±1.03
Absolute Change	0.50±0.46		-0.52±0.48
Treatment Effect		1.02[a]	
Mean PAP (mmHg)	N=20		N=10
Baseline	53.7±13.4		55.7±10.5
Absolute Change	-1.6±5.1		5.1±8.8
Treatment Effect		-6.7[b]	
Mean PVR (dyn•sec•cm⁻⁵)	N=19		N=10
Baseline	896±425		942±430
Absolute Change	-223±245		191±235
Treatment Effect		-415[a]	
Mean RAP (mmHg)	N=19		N=10
Baseline	9.7±5.6		9.9±4.1
Absolute Change	-1.3±4.1		4.9±4.6
Treatment Effect		-6.1[b]	

Values shown are means ± SD
[a]$p \leq 0.001$ [b]$p < 0.02$

000093

Symptoms and Functional Status

Symptoms of pulmonary arterial hypertension were assessed by Borg dyspnea score, WHO functional class, and rate of "clinical worsening." Clinical worsening was assessed as the sum of death, hospitalizations for PAH, discontinuation of therapy because of PAH, and need for epoprostenol. There was a significant reduction in dyspnea during walk tests (Borg dyspnea score), and significant improvement in WHO functional class in **TRACLEER®**-treated patients. There was a significant reduction in the rate of clinical worsening (Table 3 and Figure 2). Figure 2 shows the log-rank test reflecting clinical worsening over 28 weeks.

Table 3. Incidence of Clinical Worsening, Intent To Treat Population

	BREATHE-1		Study 351	
	Bosentan 125/250 mg b.i.d. (N=144)	**Placebo (N=69)**	**Bosentan 125 mg b.i.d. (N=21)**	**Placebo (N=11)**
Patients with clinical worsening [n (%)]	9 (6%)[a]	14 (20%)	0 (0%)[b]	3 (27%)
Death	1 (1%)	2 (3%)	0 (0%)	0 (0%)
Hospitalization for PAH	6 (4%)	9 (13%)	0 (0%)	3 (27%)
Discontinuation due to worsening of PAH	5 (3%)	6 (9%)	0 (0%)	3 (27%)
Receipt of epoprostenol[c]	4 (3%)	3 (4%)	0 (0%)	3 (27%)

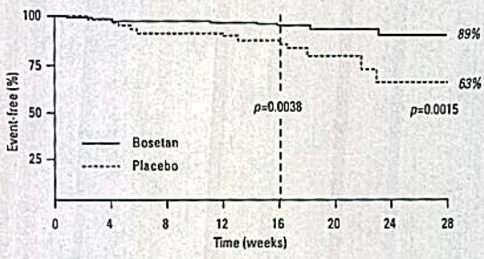
Note: Patients may have had more than one reason for clinical worsening.

[a] $p=0.0015$ vs. placebo by log-rank test. There was no relevant difference between the 125 mg and 250 mg b.i.d. groups.

[b] $p=0.033$ vs. placebo by Fisher's exact test.

[c] Receipt of epoprostenol was always a consequence of clinical worsening.

Figure 2. Time to Clinical Worsening (BREATHE-1)



Time from randomization to clinical worsening with Kaplan-Meier estimate of the proportions of failures in BREATHE-1. All patients (N=144 in the bosentan group and N=69 in the placebo group) participated in the first 16 weeks of the study. A subset of this population (N=35 in the bosentan group and 13 in the placebo group) continued double-blind therapy for up to 28 weeks.

Pulmonary Arterial Hypertension Related to Congenital Heart Defect

A small study with patients with Eisenmenger physiology demonstrated effects of bosentan on exercise and safety that were similar to those seen in other trials in patients with PAH (WHO Group I).

Congestive Heart Failure (CHF)

In a pair of studies, 1613 subjects with NYHA Class III-IV heart failure, left ventricular ejection fraction <35%, on diuretics, ACE inhibitor, and other therapies, were randomized to placebo or **TRACLEER®** (62.5 mg b.i.d. titrated as tolerated to 125 mg b.i.d.) and followed for up to 70 weeks. Use of **TRACLEER®** was associated with no benefit on patient global assessment (the primary end point) or mortality. However, hospitalizations for heart failure were more common during the first 4 to 8 weeks after bosentan was initiated. Based on these results, bosentan is not effective in the treatment of congestive heart failure with left ventricular dysfunction.

Long-term Treatment

The long-term follow-up of the patients who were treated with **TRACLEER®** in the two pivotal studies and their open-label extensions (N=235) shows that 93% and 84% of patients were still alive at 1 and 2 years, respectively, after the start of treatment with **TRACLEER®**. These uncontrolled observations do not allow comparison with a group not given **TRACLEER®** and cannot be used to determine the long-term effect of **TRACLEER®** on mortality.

INDICATIONS AND USAGE

TRACLEER® is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with WHO Class III or IV symptoms, to improve exercise ability and decrease the rate of clinical worsening (see **Clinical Studies**).

CONTRAINDICATIONS

See **BOX WARNING** for **CONTRAINDICATION** to use in pregnancy.

Pregnancy Category X. TRACLEER® is expected to cause fetal harm if administered to pregnant women. Bosentan was teratogenic in rats given oral doses ≥60 mg/kg/day (twice the maximum recommended human oral dose of 125 mg, b.i.d., on a mg/m² basis). In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face and large blood vessels. Bosentan increased stillbirths and pup mortality at oral doses of 60 and 300 mg/kg/day (2 and 10 times, respectively, the maximum recommended human dose on a mg/m² basis). Although birth defects were not observed in rabbits given oral doses of up to 1500 mg/kg/day, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs. There are no data on the use of **TRACLEER®** in pregnant women.

Pregnancy must be excluded before the start of treatment with **TRACLEER®** and prevented thereafter by use of reliable contraception. It has been demonstrated that hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives may not be reliable in the presence of **TRACLEER®** and should not be used as the sole contraceptive method in patients receiving **TRACLEER®** (see **Drug Interactions: Hormonal Contraceptives, Including Oral, Injectable, Transdermal and Implantable Contraceptives**). Input from a gynecologist or similar expert on adequate contraception should be sought as needed.

TRACLEER® should be started only in patients known not to be pregnant. For female patients of childbearing potential, a prescription for **TRACLEER®** should not be issued by the prescriber unless the patient assures the prescriber that she is not sexually active or provides negative results from a urine or serum pregnancy test performed during the first 5 days of a normal menstrual period and at least 11 days after the last unprotected act of sexual intercourse.

Follow-up urine or serum pregnancy tests should be obtained monthly in women of childbearing potential taking **TRACLEER®**. The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, she must notify the physician immediately for pregnancy testing. If the pregnancy test is positive, the physician and patient must discuss the risk to the pregnancy and to the fetus.

Cyclosporine A: Co-administration of cyclosporine A and bosentan resulted in markedly increased plasma concentrations of bosentan. Therefore, concomitant use of **TRACLEER®** and cyclosporine A is contraindicated.

Glyburide: An increased risk of liver enzyme elevations was observed in patients receiving glyburide concomitantly with bosentan. Therefore co-administration of glyburide and **TRACLEER®** is contraindicated.

Lopinavir/ritonavir or other ritonavir-containing HIV regimens: Co-administration of lopinavir/ritonavir and bosentan resulted in markedly increased plasma concentrations of bosentan. Therefore, concomitant use of **TRACLEER®** and lopinavir/ritonavir or other ritonavir-containing HIV regimens is contraindicated (see **PRECAUTIONS: Drug Interactions**).

Hypersensitivity: TRACLEER® is also contraindicated in patients who are hypersensitive to bosentan or any component of the medication.

WARNINGS

Potential Liver Injury (see **BOX WARNING**)

Elevations in ALT or AST by more than 3 × ULN were observed in 11% of bosentan-treated patients (N=658) compared to 2% of placebo-treated patients (N=280). Three-fold increases were seen in 12% of 95 PAH patients on 125 mg b.i.d. and 14% of 70 PAH patients on 250 mg b.i.d. Eight-fold increases were seen in 2% of PAH patients on 125 mg b.i.d. and 7% of PAH patients on 250 mg b.i.d. Bilirubin increases to ≥3 × ULN were associated with aminotransferase increases in 2 of 658 (0.3%) of patients treated with bosentan.

The combination of hepatocellular injury (increases in aminotransferases of >3 × ULN) and increases in total bilirubin (≥3 × ULN) is a marker for potential serious liver injury.[1]

Elevations of AST and/or ALT associated with bosentan are dose-dependent, occur both early and late in treatment, usually progress slowly, are typically asymptomatic, and usually have been reversible after treatment interruption or cessation. Aminotransferase elevations also may reverse spontaneously while continuing treatment with **TRACLEER®**.

Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated (see **DOSAGE AND ADMINISTRATION**). If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥2 × ULN, treatment should be stopped. There is no experience with the re-introduction of **TRACLEER®** in these circumstances.

Pre-existing Liver Impairment

Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. **TRACLEER®** should generally be avoided in patients with moderate or severe liver impairment (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**). In addition, **TRACLEER®** should generally be avoided in patients with elevated aminotransferases (>3 × ULN) because monitoring liver injury in these patients may be more difficult (see **BOX WARNING**).

Decreased Sperm Counts

An open-label, single arm, multicenter safety study evaluated the effect on testicular function of **TRACLEER®** 62.5 mg b.i.d. for 4 weeks, followed by 125 mg b.i.d for 5 months. Twenty-five male patients with WHO functional class III and IV PAH and normal baseline sperm count were enrolled. Twenty-three completed the study and 2 discontinued due to adverse events not related to testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment with **TRACLEER®**. Sperm count remained within the normal range in all 22 patients with data after 6 months, and no changes in sperm morphology, sperm motility, or hormone levels were observed. One patient developed marked oligospermia at 3 months, and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. **TRACLEER®** was discontinued and after two months the sperm count had returned to baseline levels. Based on these findings and preclinical data from endothelin receptor antagonists, it cannot be excluded that endothelin receptor antagonists such as **TRACLEER®** have an adverse effect on spermatogenesis.

PRECAUTIONS

Hematologic Changes

Treatment with **TRACLEER®** caused a dose-related decrease in hemoglobin and hematocrit. Hemoglobin levels should be monitored after 1 and 3 months of treatment and then every 3 months. The overall mean decrease in hemoglobin concentration for bosentan-treated patients was 0.9 g/dL (change to end of treatment). Most of this decrease of hemoglobin concentration was detected during the first few weeks of bosentan treatment and hemoglobin levels stabilized by 4-12 weeks of bosentan treatment. In placebo-controlled studies of all uses of bosentan, marked decreases in hemoglobin (>15% decrease from baseline resulting in values <11 g/dL) were observed in 6% of bosentan-treated patients and 3% of placebo-treated patients. In patients with pulmonary arterial hypertension treated with doses of 125 and 250 mg b.i.d., marked decreases in hemoglobin occurred in 3% compared to 1% in placebo-treated patients.

A decrease in hemoglobin concentration by at least 1 g/dL was observed in 57% of bosentan-treated patients as compared to 29% of placebo-treated patients. In 80% of those patients whose hemoglobin decreased by at least 1 g/dL, the decrease occurred during the first 6 weeks of bosentan treatment.

During the course of treatment the hemoglobin concentration remained within normal limits in 68% of bosentan-treated patients compared to 76% of placebo patients. The explanation for the change in hemoglobin is not known, but it does not appear to be hemorrhage or hemolysis.

It is recommended that hemoglobin concentrations be checked after 1 and 3 months, and every 3 months thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment.

Fluid Retention

In a placebo-controlled trial of patients with severe chronic heart failure, there was an increased incidence of hospitalization for CHF associated with weight gain and increased leg edema during the first 4-8 weeks of treatment with **TRACLEER®**. In addition, there have been numerous post-marketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting **TRACLEER®**. Patients required intervention with a diuretic, fluid management, or hospitalization for decompensating heart failure (see **Clinical Studies**; *Congestive Heart Failure*).

Pulmonary Veno-Occlusive Disease (PVOD)

Should signs of pulmonary edema occur when **TRACLEER®** is administered, the possibility of associated PVOD should be considered and **TRACLEER®** should be discontinued.

Information for Patients

Patients are advised to consult the **TRACLEER®** Medication Guide on the safe use of **TRACLEER®**.

The physician should discuss with the patient the importance of monthly monitoring of serum aminotransferases and urine or serum pregnancy testing and of avoidance of pregnancy. The physician should discuss options for effective contraception and measures to prevent pregnancy with their female patients. Input from a gynecologist or similar expert on adequate contraception should be sought as needed.

Drug Interactions

Bosentan is metabolized by CYP2C9 and CYP3A4. Inhibition of these enzymes may increase the plasma concentration of bosentan (see ketoconazole). Concomitant administration of both a CYP2C9 inhibitor (such as fluconazole or amiodarone) and a strong CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, ritonavir) or a moderate CYP3A4 inhibitor (e.g., amprenavir, erythromycin, fluconazole, diltiazem) with bosentan will likely lead to large increases in plasma concentrations of bosentan. Co-administration of such combinations of a CYP2C9 inhibitor plus a strong or moderate CYP3A4 inhibitor with **TRACLEER®** is not recommended.

Bosentan is an inducer of CYP3A4 and CYP2C9. Consequently plasma concentrations of drugs metabolized by these two isozymes will be decreased when **TRACLEER®** is co-administered. Bosentan had no relevant inhibitory effect on any CYP isozyme *in vitro* (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4). Consequently, **TRACLEER®** is not expected to increase the plasma concentrations of drugs metabolized by these enzymes.

Hormonal Contraceptives, Including Oral, Injectable, Transdermal, and Implantable Contraceptives: An interaction study demonstrated that co-administration of bosentan and the oral hormonal contraceptive Ortho-Novum® produced average decreases of norethindrone and ethinyl estradiol levels of 14% and 31%, respectively. However, decreases in exposure were as much as 56% and 66%, respectively, in individual subjects. Therefore, hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may not be reliable when **TRACLEER®** is co-administered. Women should practice additional methods of contraception and not rely on hormonal contraception alone when taking **TRACLEER®**.

Specific interaction studies have demonstrated the following:

Cyclosporine A: During the first day of concomitant administration, trough concentrations of bosentan were increased by about 30-fold. Steady-state bosentan plasma concentrations were 3- to 4-fold higher than in the absence of cyclosporine A. The concomitant administration of bosentan and cyclosporine A is contraindicated (see **CONTRAINDICATIONS**). Co-administration of bosentan decreased the plasma concentrations of cyclosporine A (a CYP3A4 substrate) by approximately 50%.

Tacrolimus: Co-administration of tacrolimus and bosentan has not been studied in man. Co-administration of tacrolimus and bosentan resulted in markedly increased plasma concentrations of bosentan in animals. Caution should be exercised if tacrolimus and bosentan are used together.

Glyburide: An increased risk of elevated liver aminotransferases was observed in patients receiving concomitant therapy with glyburide. Therefore, the concomitant administration of **TRACLEER®** and glyburide is contraindicated, and alternative hypoglycemic agents should be considered (see **CONTRAINDICATIONS**).

Co-administration of bosentan decreased the plasma concentrations of glyburide by approximately 40%. The plasma concentrations of bosentan were also decreased by approximately 30%. Bosentan is also expected to reduce plasma concentrations of other oral hypoglycemic agents that are predominantly metabolized by CYP2C9 or CYP3A4. The possibility of worsened glucose control in patients using these agents should be considered.

Ketoconazole: Co-administration of bosentan 125 mg b.i.d. and ketoconazole, a potent CYP3A4 inhibitor, increased the plasma concentrations of bosentan by approximately 2-fold. No dose adjustment of bosentan is necessary, but increased effects of bosentan should be considered.

Simvastatin and Other Statins: Co-administration of bosentan decreased the plasma concentrations of simvastatin (a CYP3A4 substrate), and its active β-hydroxy acid metabolite, by approximately 50%. The plasma concentrations of bosentan were not affected. Bosentan is also expected to reduce plasma concentrations of other statins that have significant metabolism by CYP3A4, such as lovastatin and atorvastatin. The possibility of reduced statin efficacy should be considered. Patients using CYP3A4 metabolized statins should have cholesterol levels monitored after **TRACLEER®** is initiated to see whether the statin dose needs adjustment.

Warfarin: Co-administration of bosentan 500 mg b.i.d. for 6 days decreased the plasma concentrations of both S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A4 substrate) by 29 and 38%, respectively. Clinical experience with concomitant administration of bosentan and warfarin in patients with pulmonary arterial hypertension did not show clinically relevant changes in INR or warfarin dose (baseline vs. end of the clinical studies), and the need to change the warfarin dose during the trials due to changes in INR or due to adverse events was similar among bosentan- and placebo-treated patients.

Digoxin, Nimodipine and Losartan: Bosentan has no significant pharmacokinetic interactions with digoxin and nimodipine, and losartan has no significant effect on plasma levels of bosentan.

Sildenafil: In healthy subjects, co-administration of multiple doses of 125 mg b.i.d bosentan and 80 mg t.i.d. sildenafil resulted in a reduction of sildenafil plasma concentrations by 63% and increased bosentan plasma concentrations by 50%. A dose adjustment of neither drug is necessary. This recommendation holds true when sildenafil is used for the treatment of pulmonary arterial hypertension or erectile dysfunction.

Iloprost: In a small, randomized, double-blind, placebo-controlled study (the STEP trial), 34 patients treated with bosentan 125 mg bid for at least 16 weeks tolerated the addition of inhaled iloprost (up to 5 mcg 6 to 9 times per day during waking hours). The mean daily inhaled dose was 27 mcg and the mean number of inhalations per day was 5.6.

Rifampicin: Coadministration of bosentan and rifampicin in normal volunteers resulted in a mean 6-fold increase in bosentan trough levels after the first concomitant dose, but about a 60% decrease in bosentan levels at steady-state. The effect of bosentan on rifampicin levels has not been assessed. When consideration of the potential benefits and known and unknown risks leads to concomitant use, measure LFTs weekly for the first 4 weeks before reverting to normal monitoring.

Lopinavir/ritonavir or other ritonavir-containing HIV regimens: Co-administration of **TRACLEER®** and lopinavir/ritonavir in healthy subjects resulted in initial and steady state trough plasma concentrations of bosentan that were approximately 48-fold and 5-fold higher, respectively, than those measured after **TRACLEER®** administered alone. This is most likely explained by inhibition by ritonavir of OATP-mediated uptake into hepatocytes, but the potential for increased toxicity cannot be excluded. Co-administration of bosentan and lopinavir/ritonavir or other ritonavir-containing HIV regimens is contraindicated (see **CONTRAINDICATIONS**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two years of dietary administration of bosentan to mice produced an increased incidence of hepatocellular adenomas and carcinomas in males at doses as low as 450 mg/kg/day (about 8 times the maximum recommended human dose [MRHD] of 125 mg b.i.d., on a mg/m² basis). In the same study, doses greater than 2000 mg/kg/day (about 32 times the MRHD) were associated with an increased incidence of colon adenomas in both males and females. In rats, dietary administration of bosentan for two years was associated with an increased incidence of brain astrocytomas in males at doses as low as 500 mg/kg/day (about 16 times the MRHD). In a comprehensive battery of *in vitro* tests (the microbial mutagenesis assay, the unscheduled DNA synthesis assay, the V-79 mammalian cell mutagenesis assay, and human lymphocyte assay) and an *in vivo* mouse micronucleus assay, there was no evidence for any mutagenic or clastogenic activity of bosentan.

Impairment of Fertility/Testicular Function

The development of testicular tubular atrophy and impaired fertility has been linked with the chronic administration of certain endothelin receptor antagonists in rodents.

Treatment with bosentan at oral doses of up to 1500 mg/kg/day (50 times the MRHD on a mg/m² basis) or intravenous doses up to 40 mg/kg/day had no effects on sperm count, sperm motility, mating performance or fertility in male and female rats. An increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as 125 mg/kg/day (about 4 times the MRHD and the lowest doses tested) for two years but not at doses as high as 1500 mg/kg/day (about 50 times the MRHD) for 6 months. Effects on sperm count and motility were evaluated only in the much shorter duration fertility studies in which males had been exposed to the drug for 4-6 weeks. An increased incidence of tubular atrophy was not observed in mice treated for 2 years at doses up to 4500 mg/kg/day (about 75 times the MRHD) or in dogs treated up to 12 months at doses up to 500 mg/kg/day (about 50 times the MRHD).

Pregnancy, Teratogenic Effects: Category X (see **CONTRAINDICATIONS**).

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, breastfeeding while taking **TRACLEER®** is not recommended.

Pediatric Use

Safety and efficacy in pediatric patients have not been established (see **DOSAGE AND ADMINISTRATION**).

Use in Elderly Patients

Clinical experience with **TRACLEER®** in subjects aged 65 or older has not included a sufficient number of such subjects to identify a difference in response between elderly and younger patients (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Adverse Events

See **BOX WARNING** for discussion of liver injury and **PRECAUTIONS** for discussion of hemoglobin and hematocrit abnormalities.

Safety data on bosentan were obtained from 12 clinical studies (8 placebo-controlled and 4 open-label) in 777 patients with pulmonary arterial hypertension, and other diseases. Doses up to 8 times the currently recommended clinical dose (125 mg b.i.d.) were administered for a variety of durations. The exposure to bosentan in these trials ranged from 1 day to 4.1 years (N=89 for 1 year; N=61 for 1.5 years and N=39 for more than 2 years). Exposure of pulmonary arterial hypertension patients (N=235) to bosentan ranged from 1 day to 1.7 years (N=126 more than 6 months and N=28 more than 12 months).

Treatment discontinuations due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension were more frequent on bosentan (5%; 8/165 patients) than on placebo (3%; 2/80 patients). In this database the only cause of discontinuations >1%, and occurring more often on bosentan was abnormal liver function.

The adverse drug reactions that occurred in ≥3% of the bosentan-treated patients and were more common on bosentan in placebo-controlled trials in pulmonary arterial hypertension at doses of 125 or 250 mg b.i.d. are shown in Table 4:

Table 4. Adverse events* occurring in ≥ 3% of patients treated with bosentan 125-250 mg b.i.d. and more common on bosentan in placebo-controlled studies in pulmonary arterial hypertension

Adverse Event	Bosentan N = 165		Placebo N = 80	
	No.	%	No.	%
Headache	36	22%	16	20%
Nasopharyngitis	18	11%	6	8%
Flushing	15	9%	4	5%
Hepatic function abnormal	14	8%	2	3%
Edema, lower limb	13	8%	4	5%
Hypotension	11	7%	3	4%
Palpitations	8	5%	1	1%
Dyspepsia	7	4%	0	0%
Edema	7	4%	2	3%
Fatigue	6	4%	1	1%
Pruritus	6	4%	0	0%

***Note: only AEs with onset from start of treatment to 1 calendar day after end of treatment are included. All reported events (at least 3%) are included except those too general to be informative, and those not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population.**

In placebo-controlled studies of bosentan in pulmonary arterial hypertension and for other diseases (primarily chronic heart failure), a total of 677 patients were treated with bosentan at daily doses ranging from 100 mg to 2000 mg and 288 patients were treated with placebo. The duration of treatment ranged from 4 weeks to 6 months. For the adverse drug reactions that occurred in ≥3% of bosentan-treated patients, the only ones that occurred more frequently on bosentan than on placebo (≥2% difference) were headache (16% vs. 13%), flushing (7% vs. 2%), abnormal hepatic function (6% vs. 2%), leg edema (5% vs. 1%), and anemia (3% vs. 1%).

Post-Marketing Experience: Hypersensitivity, Rash, Thrombocytopenia, Jaundice, Anemia requiring transfusion.

There have been several post-marketing reports of angioneurotic edema associated with the use of bosentan. The onset of the reported cases occurred within a range of 8 hours to 21 days after starting therapy. Some patients were treated with an antihistamine and their signs of angioedema resolved without discontinuing **TRACLEER®**.

In the post-marketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (>12 months) therapy with **TRACLEER®** in patients with multiple co-morbidities and drug therapies. There have also been rare reports of liver failure. The contribution of **TRACLEER®** in these cases could not be excluded (see **BOX WARNING**).

Laboratory Abnormalities

Increased Liver Aminotransferases (see BOX WARNING and WARNINGS).

Decreased Hemoglobin and Hematocrit (see **PRECAUTIONS**)

OVERDOSAGE

Bosentan has been given as a single dose of up to 2400 mg in normal volunteers, or up to 2000 mg/day for 2 months in patients, without any major clinical consequences. The most common side effect was headache of mild to moderate intensity. In the cyclosporine A interaction study, in which doses of 500 and 1000 mg b.i.d. of bosentan were given concomitantly with cyclosporine A, trough plasma concentrations of bosentan increased 30-fold, resulting in severe headache, nausea, and vomiting, but no serious adverse events. Mild decreases in blood pressure and increases in heart rate were observed.

In the postmarketing period, there was one reported overdose of 10,000 mg of bosentan taken by an adolescent male patient. He had symptoms of nausea, vomiting, hypotension, dizziness, sweating, and blurred vision. He recovered within 24 hours with blood pressure support.

Bosentan is unlikely to be effectively removed by dialysis due to high molecular weight and extensive plasma protein binding.

DOSAGE AND ADMINISTRATION

General

TRACLEER® treatment should be initiated at a dose of 62.5 mg b.i.d. for 4 weeks and then increased to the maintenance dose of 125 mg b.i.d. Doses above 125 mg b.i.d. did not appear to confer additional benefit sufficient to offset the increased risk of liver injury.

Tablets should be administered morning and evening with or without food.

Dosage Adjustment and Monitoring in Patients Developing Aminotransferase Abnormalities

ALT/AST levels	Treatment and monitoring recommendations
> 3 and ≤ 5 × ULN	Confirm by another aminotransferase test; if confirmed, reduce the daily dose or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, continue or re-introduce the treatment as appropriate (see below).
> 5 and ≤ 8 × ULN	Confirm by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pre-treatment values, consider re-introduction of the treatment (see below).
> 8 × ULN	Treatment should be stopped and re-introduction of **TRACLEER®** should not be considered. There is no experience with re-introduction of **TRACLEER®** in these circumstances.

If **TRACLEER®** is re-introduced it should be at the starting dose; aminotransferase levels should be checked within 3 days and thereafter according to the recommendations above.

If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥2 × ULN, treatment should be stopped. There is no experience with the re-introduction of **TRACLEER®** in those circumstances.

Use in Women of Child-bearing Potential

TRACLEER® treatment should only be initiated in women of child-bearing potential following a negative pregnancy test and only in those who practice adequate contraception that does not rely solely upon hormonal contraceptives, including oral, injectable, transdermal, or implantable contraceptives (see **DRUG INTERACTIONS: Hormonal Contraceptives, Including Oral, Injectable, Transdermal, and Implantable Contraceptives**). Input from a gynecologist or similar expert on adequate contraception should be sought as needed. Urine or serum pregnancy tests should be obtained monthly in women of childbearing potential taking **TRACLEER®**.

Dosage Adjustment in Renally Impaired Patients

The effect of renal impairment on the pharmacokinetics of bosentan is small and does not require dosing adjustment.

Dosage Adjustment in Geriatric Patients

Clinical studies of **TRACLEER®** did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Clinical experience has not identified differences in responses between elderly and younger patients. In general, caution should be exercised in dose selection for elderly patients given the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group.

Dosage Adjustment in Hepatically Impaired Patients

Because there is *in vitro* and *in vivo* evidence that the main route of excretion of bosentan is biliary, liver impairment could be expected to increase exposure (C_{max} and AUC) of bosentan. Mild liver impairment was shown not to impact the pharmacokinetics of bosentan. The influence of moderate or severe liver impairment on the pharmacokinetics of **TRACLEER®** has not been evaluated. There are no specific data to guide dosing in hepatically impaired patients (see **WARNINGS**); caution should be exercised in patients with mildly impaired liver function. **TRACLEER®** should generally be avoided in patients with moderate or severe liver impairment.

Dosage Adjustment in Children

Safety and efficacy in pediatric patients have not been established.

Dosage Adjustment in Patients with Low Body Weight

In patients with a body weight below 40 kg but who are over 12 years of age the recommended initial and maintenance dose is 62.5 mg b.i.d.

Discontinuation of Treatment

There is limited experience with abrupt discontinuation of **TRACLEER®**. No evidence for acute rebound has been observed. Nevertheless, to avoid the potential for clinical deterioration, gradual dose reduction (62.5 mg b.i.d. for 3 to 7 days) should be considered.

HOW SUPPLIED

62.5 mg film-coated, round, biconvex, orange-white tablets, embossed with identification marking "62,5", packaged in a white high-density polyethylene bottle and a white polypropylene child-resistant cap.

NDC 66215-101-06: Bottle containing 60 tablets.

125 mg film-coated, oval, biconvex, orange-white tablets, embossed with identification marking "125", packaged in a white high-density polyethylene bottle and a white polypropylene child-resistant cap.

NDC 66215-102-06: Bottle containing 60 tablets.

Rx only.

STORAGE

Store at 20°C – 25°C (68°F – 77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature].

Distributed by:
Actelion Pharmaceuticals US, Inc.
South San Francisco, CA
94080, USA

Reference:

1. Zimmerman HJ. Hepatotoxicity - The adverse effects of drugs and other chemicals on the liver. Second ed. Philadelphia: Lippincott, 1999.

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Medication Guide

Tracleer (tra-KLEER) Tablets
(bosentan)

Read this information carefully before you start taking Tracleer tablets. Read the information you get with Tracleer each time you refill your prescription. There may be new information. This information does not take the place of talking with your doctor.

What is the most important information I should know about Tracleer?

• Liver damage.

Tracleer can cause liver damage if liver problems are not found early. Therefore, you must have a blood test to check your liver function before you start Tracleer and each month after that. (See "What are the possible side effects of Tracleer?" for information about the signs of liver problems.)

• Major birth defects.

Tracleer can cause major birth defects if taken during pregnancy. Therefore, women must not be pregnant when they start taking Tracleer or during Tracleer treatment. Women who are sexually active must have a negative pregnancy test before beginning treatment. A negative test means you are not pregnant. The test should be during the first five days of a normal menstrual period and at least 11 days after the last unprotected sexual intercourse. **Pregnancy tests must be done each month during Tracleer treatment, if you are sexually active.**

Women who are able to get pregnant must use effective birth control while taking Tracleer. Birth control pills, shots, patches, implants, or other hormone-based birth control may not be enough when Tracleer is used. Talk with your doctor and, if needed, with a gynecologist (a doctor who specializes in female reproduction) or another doctor who knows about birth control, to find out how to avoid pregnancy. **Tell your doctor right away if you miss a period or think you may be pregnant.**

What is Tracleer?

Tracleer is a medicine to treat pulmonary arterial hypertension, which is high blood pressure in the lung arteries. You take it by mouth.

Tracleer can improve your ability to exercise and can slow the worsening of your physical condition and symptoms. Tracleer lowers high blood pressure in your lungs and lets your heart pump blood more effectively.

Who should not take Tracleer?

Do not take Tracleer if:

- **you are pregnant, plan to become pregnant, or become pregnant during Tracleer treatment. Tracleer can cause major birth defects.** All women should read the birth defects section of "What is the most important information I should know about Tracleer?" Severe birth defects from Tracleer happen early in pregnancy. Therefore, you must not be pregnant while taking Tracleer.
- **your blood test shows possible liver injury**
- **you are taking cyclosporine-A** (used for psoriasis and rheumatoid arthritis, and to prevent rejection of heart or kidney transplants), **glyburide** (used for diabetes), or **lopinavir/ritonavir or other ritonavir-containing HIV regimens.**
- **you are allergic to any ingredients in Tracleer.** The active ingredient is bosentan. Ask your doctor or pharmacist if you need to know the inactive ingredients.

Tell your doctor if you have moderate or severe liver problems. Tracleer may not be right for you.
Tell your doctor about **all** the medicines you use. They may affect how Tracleer works, or Tracleer may affect how the other medicines work. Be sure to tell your doctor if you take

- ketoconazole, fluconazole, itraconazole or voriconazole (used for fungal infections)
- hormone-based birth control, such as pills, shots, patches, and implants
- cyclosporine A (used for psoriasis and rheumatoid arthritis, and to prevent rejection of heart or kidney transplants)
- tacrolimus (used to prevent rejection of liver or kidney transplants)
- rifampicin (used for tuberculosis)
- glyburide (used for diabetes)
- cholesterol lowering medicines
- warfarin (used to prevent blood clots)
- lopinavir/ritonavir or other ritonavir-containing HIV regimens

How should I take Tracleer?

Tracleer will be mailed to you by a central pharmacy. Your doctor will give you complete details:

- In most cases, you will take 1 tablet in the morning and 1 in the evening.
- You can take it with or without food.
- Your doctor will tell you how much to take.
- It will be easier to remember to take Tracleer if you do it at the same time each morning and evening. If you have trouble remembering, ask a family member to remind you, or put written notes where you will be sure to see them.
- If you take more than the prescribed dose of Tracleer, call your doctor right away.
- If you miss a dose, take your tablet as soon as you remember. However, do not take 2 doses to make up for a missed dose. Take your next tablet at the regular time.
- Do not stop taking Tracleer unless your doctor tells you to do so. Suddenly stopping your treatment may cause your symptoms to get worse. If you need to stop taking Tracleer, your doctor may tell you to reduce the dose over a few days before stopping completely.

During treatment your doctor will test your blood for signs of side effects to your liver and red blood cells.

What should I avoid while taking Tracleer?

- **Do not get pregnant** while taking Tracleer. (See the birth defect section of "What is the most important information I should know about Tracleer?") If you miss a period, call your doctor.
- **Breast-feeding is not recommended** while taking Tracleer. It is not known if Tracleer can pass through your milk and harm the baby.
- **Do not use hormone-based birth control (pills, shots, patches, implants) as your only method of birth control.** These may not work when used with Tracleer. Ask your doctor about effective birth control choices.
- **Do not take cyclosporine-A.** This medicine can cause too much Tracleer in your blood and increase your chance of side effects.
- **Do not take glyburide.** This medicine can increase your chance of liver damage.
- **Do not take lopinavir/ritonavir or other ritonavir-containing HIV regimens.** They can cause too much Tracleer in your blood and increase your chance of side effects.

What are the possible side effects of Tracleer?

Tracleer can have serious side effects:

- **Liver damage.** Tracleer can cause liver damage if it is not found early. Because this side effect may not cause symptoms at first, only a blood test can show that you have early liver damage. Regular blood tests let your doctor change or stop your therapy before there is permanent damage. **Therefore, it is very important that you have a liver function blood test before you start treatment and every month after that.**

  Call your doctor right away if you have any of these symptoms of liver problems: nausea, vomiting, fever, unusual tiredness, abdominal (stomach area) pain, or yellowing of the skin or the whites of your eyes (jaundice).
- **Major birth defects.** All females should read the birth defects section of "What is the most important information I should know about Tracleer?"
- **Sperm count reduction.** Reduced sperm counts have been observed in some men on Tracleer, which might impair ability to father a child. Tell your doctor if remaining fertile is important to you.

Other possible side effects

The most common side effects of Tracleer are:

- low red blood cell levels (anemia)
- headache
- inflamed throat and irritated nose passages
- flushing (hot flashes)
- ankle and leg swelling
- low blood pressure
- irregular heart beats
- upset stomach
- tiredness
- rash
- itching

General advice about prescription medicines

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any concerns or questions about Tracleer, ask your doctor or other healthcare provider. This Medication Guide is only a summary of some important information about Tracleer. Your doctor can give you information about Tracleer that was written for healthcare professionals. Do not use Tracleer for a condition for which it was not prescribed. Do not share Tracleer with other people.

This Medication Guide has been approved by the US Food and Drug Administration.

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ACTELION

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ANEXO E

PARAFON FORTE® DSC

(chlorzoxazone)

Caplets 500 mg

For Painful Musculoskeletal Conditions

Prescribing Information

DESCRIPTION

Each caplet (capsule shaped tablet) contains:

Chlorzoxazone*.....500 mg

Inactive ingredients: FD&C Blue No. 1, microcrystalline cellulose, docusate sodium, lactose (hydrous), magnesium stearate, sodium benzoate, sodium starch glycolate, pregelatinized corn starch, D&C Yellow No. 10.

*5-chlorobenzoxazolinone

ACTIONS

Chlorzoxazone is a centrally-acting agent for painful musculoskeletal conditions. Data available from animal experiments as well as human study indicate that chlorzoxazone acts primarily at the level of the spinal cord and subcortical areas of the brain where it inhibits multisynaptic reflex arcs involved in producing and maintaining skeletal muscle spasm of varied etiology. The clinical result is a reduction of the skeletal muscle spasm with relief of pain and increased mobility of the involved muscles. Blood levels of chlorzoxazone can be detected in people during the first 30 minutes and peak levels may be reached, in the majority of the subjects, in about 1 to 2 hours after oral administration of chlorzoxazone. Chlorzoxazone is rapidly metabolized and is excreted in the urine, primarily in a conjugated form as the glucuronide. Less than one percent of a dose of chlorzoxazone is excreted unchanged in the urine in 24 hours.

INDICATIONS

PARAFON FORTE DSC chlorzoxazone is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort 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. Chlorzoxazone does not directly relax tense skeletal muscles in man.

CONTRAINDICATIONS

PARAFON FORTE DSC chlorzoxazone is contraindicated in patients with known intolerance to the drug.

WARNINGS

Serious (including fatal) hepatocellular toxicity has been reported rarely in patients receiving chlorzoxazone. The mechanism is unknown but appears to be idiosyncratic and unpredictable. Factors predisposing patients to this rare event are not known. Patients should be instructed to report early signs and/or symptoms of hepatotoxicity such as fever, rash, anorexia, nausea, vomiting, fatigue, right upper quadrant pain, dark urine, or jaundice. Chlorzoxazone should be discontinued immediately and a physician consulted if any of these signs or symptoms develop. Chlorzoxazone use should also be discontinued if a patient develops abnormal liver enzymes (e.g. AST, ALT, alkaline phosphatase and bilirubin).

The concomitant use of alcohol or other central nervous system depressants may have an additive effect.

Usage in Pregnancy: The safe use of PARAFON FORTE DSC chlorzoxazone has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible risks.

PRECAUTIONS

PARAFON FORTE DSC chlorzoxazone should be used with caution in patients with known allergies or with a history of allergic reactions to drugs. If a sensitivity reaction occurs such as urticaria, redness, or itching of the skin, the drug should be stopped.

If any symptoms suggestive of liver dysfunction are observed, the drug should be discontinued.

ADVERSE REACTIONS

Chlorzoxazone containing products are usually well tolerated. It is possible in rare instances that chlorzoxazone may have been associated with gastrointestinal bleeding. Drowsiness, dizziness, lightheadedness, malaise, or overstimulation may be noted by an occasional patient. Rarely, allergic-type skin rashes, petechiae, or ecchymoses may develop during treatment. Angioneurotic edema or anaphylactic reactions are extremely rare. There is no evidence that the drug will cause renal damage. Rarely, a patient may note discoloration of the urine resulting from a phenolic metabolite of chlorzoxazone. This finding is of no known clinical significance.

DOSAGE AND ADMINISTRATION

Usual Adult Dosage: One caplet three or four times daily. If adequate response is not obtained with this dose, it may be increased to 1½ caplets (750 mg) three or four times daily. As improvement occurs dosage can usually be reduced.

OVERDOSAGE

Symptoms: Initially, gastrointestinal disturbances such as nausea, vomiting, or diarrhea together with drowsiness, dizziness, lightheadedness or headache may occur. Early in the course there may be malaise or sluggishness followed by marked loss of muscle tone, making voluntary movement impossible. The deep tendon reflexes may be decreased or absent. The sensorium remains intact, and there is no peripheral loss of sensation. Respiratory depression may occur with rapid, irregular respiration and intercostal and substernal retraction. The blood pressure is lowered, but shock has not been observed.

Treatment: Gastric lavage or induction of emesis should be carried out, followed by administration of activated charcoal. Thereafter, treatment is entirely supportive. If respirations are depressed, oxygen and artificial respiration should be employed and a patent airway assured by use of an oropharyngeal airway or endotracheal tube. Hypotension may be counteracted by use of dextran, plasma, concentrated albumin or a vasopressor agent such as norepinephrine. Cholinergic drugs or analeptic drugs are of no value and should not be used.

HOW SUPPLIED

PARAFON FORTE® DSC (chlorzoxazone) 500 mg caplets, (capsule shaped tablet, colored light green, imprinted "PARAFON FORTE DSC" and "McNEIL," scored).

NDC 0045-0325-60, bottles of 100.

Dispense in tight container as defined in the official compendium.

Store at controlled room temperature (15°-30°C, 59°-86°F).

ORTHO-McNEIL

OMP DIVISION
ORTHO-McNEIL
PHARMACEUTICAL, INC.
Raritan, NJ 08869

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