PRODUCT MONOGRAPH

Pr TEVA-PIRFENIDONE

pirfenidone

Film coated tablets, 267 mg and 801 mg

Teva Standard

Anti-fibrotic/ Anti-inflammatory Agent

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Toronto, Ontario
M1B 2K9

Date of Revision:
May 17, 2021

Submission Control No: 252567

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PrTEVA-PIRFENIDONE

pirfenidone tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Film coated tablet / 267 mg, and 801 mg	Black iron oxide, colloidal silicon dioxide, croscarmellose sodium, iron oxide red (801 mg), iron oxide yellow, macrogol (polyethylene glycol), magnesium stearate, microcrystalline cellulose, polyvinyl alcohol-part hydrolyzed, povidone, talc, and titanium dioxide.

INDICATIONS AND CLINICAL USE

TEVA-PIRFENIDONE is indicated for the treatment of idiopathic pulmonary fibrosis (IPF) in adults.

Geriatrics (≥65 years of age):
No dose adjustment is necessary in patients 65 years and older (see ACTION AND CLINICAL PHARMACOLOGY).

Pediatrics (< 18 years of age):
The safety and effectiveness of pirfenidone in pediatric patients have not been established.

CONTRAINDICATIONS

- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- History of angioedema with pirfenidone (see WARNINGS AND PRECAUTIONS).
- Concomitant use of fluvoxamine (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).
- Severe hepatic impairment or end-stage liver disease (see WARNINGS AND PRECAUTIONS).
- Severe renal impairment (CrCl <30 mL/min) or end stage renal disease requiring

dialysis (see WARNINGS AND PRECAUTIONS).

WARNINGS AND PRECAUTIONS

General

Drug-Interactions with Inhibitors of CYP1A2 and Other CYP Isoenzymes

Fluvoxamine
TEVA-PIRFENIDONE is contraindicated in patients with concomitant use of fluvoxamine (a strong inhibitor of CYP1A2 with inhibitory effects on CYP2C9, 2C19, and 2D6). Fluvoxamine should be discontinued prior to the initiation of treatment with TEVA-PIRFENIDONE and avoided during pirfenidone therapy due to the potential for reduced clearance of pirfenidone (see CONTRAINDICATIONS and DRUG INTERACTIONS).

Ciprofloxacin
Co-administration of pirfenidone and 750 mg of ciprofloxacin (a moderate and selective inhibitor of CYP1A2) increased the exposure to pirfenidone by 81%. If ciprofloxacin at the dose of 750 mg twice daily (a total daily dose of 1500 mg) cannot be avoided, the dose of TEVA-PIRFENIDONE should be reduced to 1602 mg daily (a dose of 534 mg, three times a day). TEVA-PIRFENIDONE should be used with caution when ciprofloxacin is used at a total daily dose of 250 to 1000 mg (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION).

Strong and Selective Inhibitors of CYP1A2
In vitro-in vivo extrapolations indicate that strong and selective inhibitors of CYP1A2 have the potential to increase the exposure to pirfenidone by approximately 2 to 4-fold. If concomitant use of TEVA-PIRFENIDONE with a strong and selective inhibitor of CYP1A2 cannot be avoided, the dose of TEVA-PIRFENIDONE should be reduced to 801 mg daily (267 mg, three times a day). Patients should be closely monitored for emergence of adverse reactions associated with TEVA-PIRFENIDONE therapy. Discontinue TEVA-PIRFENIDONE if necessary (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION).

Other CYP1A2 Inhibitors
Agents or combinations of agents that are moderate to strong inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of pirfenidone (i.e., CYP2C9, 2C19, 2D6, and 2E1) should be avoided during TEVA-PIRFENIDONE treatment. TEVA-PIRFENIDONE should be used with caution in patients treated with moderate inhibitors of CYP1A2 that do not inhibit other CYP isoenzymes (see DRUG INTERACTIONS).

Treatment with TEVA-PIRFENIDONE should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of IPF.

TEVA-PIRFENIDONE should be taken with food to reduce the incidence of dizziness or nausea.

Physicians should monitor patients as frequently as clinically indicated for toxicities and for any additional medication used to treat the patient (see DOSAGE AND ADMINISTRATION and DRUG INTERACTIONS). For significant side effects, the treatment of symptoms and dose reduction or discontinuation of TEVA-PIRFENIDONE should be considered.

Fatigue
Fatigue has been reported in patients treated with pirfenidone. Therefore, patients should know how they react to TEVA-PIRFENIDONE before they engage in activities requiring mental alertness or coordination (e.g., driving or using machinery). If fatigue does not improve or if it worsens in severity, dose reduction or discontinuation of pirfenidone may be warranted.

Endocrine and Metabolism

Weight Loss
Anorexia and weight loss have been reported in patients treated with pirfenidone. Physicians should monitor patients' weight, and when appropriate, encourage increased caloric intake if weight loss is considered to be of clinical significance.

Gastrointestinal
Gastrointestinal events (e.g., nausea, diarrhoea, dyspepsia, vomiting) have been reported in patients treated with pirfenidone. Patients who experience gastrointestinal side effects should be reminded to take TEVA-PIRFENIDONE with food. If gastrointestinal events do not improve or worsen in severity, dose reduction or discontinuation of TEVA-PIRFENIDONE may be warranted (see DOSAGE AND ADMINISTRATION).

Hepatic/Biliary/Pancreatic
Drug-Induced Liver Injury (DILI) in the form of transient and clinically silent elevations in transaminases has been commonly reported in patients treated with pirfenidone. In rare cases, these elevations were associated with concomitant bilirubin increases, and serious clinical consequences including isolated cases with fatal outcome have been reported post-marketing (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions). Liver chemistry tests (ALT, AST, and bilirubin) should be performed prior to the initiation of treatment with TEVA-PIRFENIDONE, and subsequently at monthly intervals for the first 6 months and then every 3 months thereafter. In addition, liver function tests should be promptly measured in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. In the event of elevations of ALT and/or AST, or clinical signs and symptoms of liver injury, the dose of TEVA-PIRFENIDONE may need to be reduced or treatment discontinued (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and DOSAGE AND ADMINISTRATION- Recommendations in Case of ALT, AST, Bilirubin Elevations).

In patients with moderate hepatic impairment (i.e., Child-Pugh Class B), pirfenidone exposure

increased by 60%. TEVA-PIRFENIDONE should be used with caution in patients with pre-existing mild to moderate hepatic impairment (i.e., Child-Pugh Class A and B) given the potential for increased TEVA-PIRFENIDONE exposure. Patients should be monitored closely for signs of toxicity especially if they are concomitantly taking a known CYP1A2 inhibitor (see DRUG INTERACTIONS and ACTION AND CLINICAL PHARMACOLOGY). Pirfenidone has not been studied in individuals with severe hepatic impairment. TEVA-PIRFENIDONE should not be used in patients with severe hepatic impairment or end-stage liver disease (see CONTRAINDICATIONS).

Immune System

Angioedema

Reports of angioedema (some serious) such as swelling of the face, lips and/or tongue which may be associated with difficulty breathing or wheezing have been received in association with use of pirfenidone in the post-marketing setting. Therefore, patients who develop signs or symptoms of angioedema following administration of TEVA-PIRFENIDONE should immediately discontinue treatment. Patients with angioedema should be managed according to standard of care. TEVA-PIRFENIDONE should not be used in patients with a history of angioedema due to pirfenidone (see CONTRAINDICATIONS).

Neurologic

Dizziness

Dizziness has been reported in patients treated with pirfenidone. Therefore, patients should know how they react to TEVA-PIRFENIDONE before they engage in activities requiring mental alertness or coordination (e.g., driving or using machinery). Patients who experience intolerance to therapy due to dizziness should be reminded to take TEVA-PIRFENIDONE with food to reduce dizziness. If dizziness does not improve or worsens in severity, dose adjustment or discontinuation of TEVA-PIRFENIDONE may be warranted.

Renal

TEVA-PIRFENIDONE should not be used in patients with severe renal impairment, or end-stage renal disease requiring dialysis (CrCl <30 mL/min, per Cockcroft-Gault equation) (see CONTRAINDICATIONS). TEVA-PIRFENIDONE should be used with caution in patients with mild (CrCl 51-80 mL/min) and moderate renal impairment (CrCl 30-50 mL/min) (see ACTION AND CLINICAL PHARMACOLOGY - Renal Insufficiency).

Skin

Photosensitivity Reaction and Rash

Photosensitivity reaction and rash have been reported in patients treated with pirfenidone. Patients treated with TEVA-PIRFENIDONE should be advised to avoid or minimize exposure to direct and indirect sunlight, including through windows and from sunlamps, and to avoid other medicinal products known to cause photosensitivity. Patients should be instructed to use daily an effective sun block (at least SPF 50 against UVA and UVB), and to wear clothing that protects against sun exposure such as wide-brimmed hats and long sleeves. Patients should be instructed to report promptly to their physician symptoms of photosensitivity reaction or rash. Severe

photosensitivity reactions are uncommon. Dose reduction and temporary treatment discontinuation may be necessary in the event of photosensitivity reaction or rash. TEVA-PIRFENIDONE may be reintroduced with re-escalation to the tolerated dose in the same manner as the dose- escalation period (see DOSAGE AND ADMINISTRATION).

Special Populations

Pregnant Women

Pirfenidone has not been studied in pregnant women. In animals, placental transfer of pirfenidone and/or its metabolites to the foetus occurs with the potential for accumulation of pirfenidone and/or its metabolites in amniotic fluid.

At high doses (≥1000 mg/kg/day) rats exhibited prolongation of gestation and reduction in foetal viability.

The use of TEVA-PIRFENIDONE should be avoided during pregnancy.

Nursing Women

It is unknown whether pirfenidone or its metabolites are excreted in human milk. Available pharmacokinetic data in animals have shown rapid excretion of pirfenidone and/or its metabolites in milk with the potential for accumulation of pirfenidone and/or its metabolites in milk (see TOXICOLOGY). A risk to the breast-fed child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue TEVA-PIRFENIDONE therapy, taking into account the benefits of breast-feeding for the child and of pirfenidone therapy for the mother.

Fertility

No adverse effects on fertility were observed in preclinical studies (see TOXICOLOGY).

Pediatrics (< 18 years of age)

The safety and effectiveness of pirfenidone in pediatric patients have not been established.

Geriatrics (≥65 years of age):

No dose adjustment is necessary in patients 65 years and older (see ACTION AND CLINICAL PHARMACOLOGY).

Monitoring and Laboratory Tests

Liver chemistry tests (ALT, AST and bilirubin) should be performed prior to the initiation of treatment with TEVA-PIRFENIDONE, and subsequently at monthly intervals for the first 6 months and then every 3 months thereafter. In addition, liver function tests should be promptly measured in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. In the event of elevation in ALT, AST and/or bilirubin or clinical signs and symptoms of liver injury, the dose of TEVA-

PIRFENIDONE may need to be reduced or treatment discontinued (see DOSAGE AND ADMINISTRATION: *Recommendations in case of elevations in ALT, AST, bilirubin*).

If a patient exhibits any ALT and/or AST elevation accompanied by clinical signs and symptoms of liver injury or accompanied by hyperbilirubinaemia, TEVA-PIRFENIDONE should be discontinued promptly. The patient should be monitored closely until resolution of elevated ALT, AST and bilirubin and symptoms. The patient should NOT be re-challenged with TEVA-PIRFENIDONE.

If a patient exhibits ALT and/or AST elevation to ≥5 × ULN regardless of the level of serum bilirubin, TEVA-PIRFENIDONE should be discontinued promptly and the patient monitored closely until resolution of ALT and AST. The patient should NOT be re-challenged with TEVA-PIRFENIDONE.

ADVERSE REACTIONS

Adverse Drug Reaction

The safety of pirfenidone has been evaluated in more than 1400 subjects with over 170 subjects exposed to pirfenidone for more than 5 years in clinical trials.

The most common adverse reactions (≥10%) are nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, anorexia, gastro-esophageal reflux disease, sinusitis, insomnia, weight decreased, and arthralgia.

At the recommended dosage of 2403 mg/day, 14.6% of patients on pirfenidone capsules compared to 9.6% on placebo permanently discontinued treatment because of an adverse event and 42.7% of patients on pirfenidone capsules compared to 16.2% on placebo had a dose interruption or reduction because of an adverse event. The most common (>1%) adverse reactions leading to discontinuation were rash and nausea. The most common (>3%) adverse reactions leading to dosage reduction or interruption were rash, nausea, diarrhea, and photosensitivity reaction.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Pirfenidone capsules was studied in 3 randomized, double-blind, placebo-controlled trials (Studies PIPF-016, PIPF-004 and PIPF-006) in which a total of 623 patients received 2403 mg/day of pirfenidone capsules and 624 patients received placebo. Subjects ages ranged from 40

to 80 years (mean age of 67 years). Most patients were male (74%) and Caucasian (95%). The mean duration of exposure to pirfenidone capsules was 62 weeks (range: 2 to 118 weeks) in these 3 trials. Patients in these studies could elect to participate in an open-label extension study to examine the long-term safety of pirfenidone capsules (Study PIPF 012).

Table 1: Adverse Drug Reactions Occurring in ≥3% Patients on Pirfenidone Capsules and with Greater Frequency than Placebo in Studies PIPF-004, and PIPF-006, and PIPF-016

Adverse Drug Reactions	Number of Patients, n (%)	
	Randomized Patient Subset Updated	
	Pirfenidone (N = 623)	Placebo (N = 624)
Gastrointestinal Disorders		
Nausea	225 (36.1)	97 (15.5)
Abdominal pain[a]	165 (26.5)	103 (16.5)
Diarrhoea	161 (25.8)	127 (20.4)
Dyspepsia	115 (18.5)	43 (6.9)
Vomiting	83 (13.3)	39 (6.3)
Gastro-oesophageal reflux disease	69 (11.1)	44 (7.1)
Dry mouth	19 (3.0)	17 (2.7)
General Disorders and Administration Site Conditions		
Fatigue	162 (26.0)	119 (19.1)
Asthenia	40 (6.4)	24 (3.8)
Non-cardiac chest pain	32 (5.1)	25 (4.0)
Infections and Infestations		
Upper respiratory tract infection	167 (26.8)	158 (25.3)
Sinusitis	68 (10.9)	64 (10.3)
Influenza	41 (6.6)	38 (6.1)
Gastroenteritis viral	29 (4.7)	17 (2.7)
Rhinitis	20 (3.2)	19 (3.0)
Injury, Poisoning And Procedural Complications		
Sunburn	23 (3.7)	11 (1.8)
Investigations		
Weight decreased	63 (10.1)	34 (5.4)
Gamma-Glutamyltransferase increased	24 (3.9)	11 (1.8)
Alanine Aminotransferase increased	20 (3.2)	9 (1.4)
Metabolism and Nutrition Disorders		
Anorexia	81 (13.0)	31 (5.0)
Decreased appetite	50 (8.0)	20 (3.2)

Adverse Drug Reactions	Number of Patients, n (%)	
	Randomized Patient Subset Updated	
	Pirfenidone (N = 623)	Placebo (N = 624)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	62 (10.0)	44 (7.1)
Musculoskeletal Pain	24 (3.9)	22 (3.5)
Musculoskeletal Chest Pain	19 (3.0)	7 (1.1)
Nervous System Disorders		
Headache	137 (22.0)	120 (19.2)
Dizziness	112 (18.0)	71 (11.4)
Dysgeusia	36 (5.8)	14 (2.2)
Somnolence	22 (3.5)	18 (2.9)
Psychiatric Disorders		
Insomnia	65 (10.4)	41 (6.6)
Respiratory, Thoracic and Mediastinal Disorders		
Pharyngolaryngeal Pain	38 (6.1)	36 (5.8)
Epistaxis	22 (3.5)	21 (3.4)
Respiratory Tract Congestion	21 (3.4)	12 (1.9)
Skin and Subcutaneous Tissue Disorders		
Rash	189 (30.3)	64 (10.3)
Photosensitivity Reaction	58 (9.3)	7 (1.1)
Pruritus	49 (7.9)	33 (5.3)
Erythema	25 (4.0)	16 (2.6)
Dry Skin	21 (3.4)	11 (1.8)
Vascular Disorders		
Hot Flush	25 (4.0)	14 (2.2)
Hypertension	20 (3.2)	17 (2.7)

[a] Includes abdominal pain, upper abdominal pain, abdominal distension, abdominal discomfort, and stomach discomfort.

Abnormal Hematologic and Clinical Chemistry Findings

In studies PIPF 004 and PIPF 006, haematology and urinalysis parameters were similar between patients taking pirfenidone and placebo. Serum chemistry parameters were also similar across the groups with the exception of gamma glutamyl transferase (GGT) and creatinine. A mean increase at 72 weeks from Baseline in GGT level of 7.6 U/L was observed in the pirfenidone group while no change was seen in the placebo group. A mean decrease at 72 weeks from Baseline of 5.6 µmol/L in serum creatinine was observed in the pirfenidone group, compared with a mean decrease of 1.1 µmol/L in the placebo group. Few patients experienced shifts from Grade 0, 1, or

2 to Grade 3 or 4 in laboratory tests in the studies and across treatment groups. There was an imbalance between pirfenidone and placebo groups for shifts in hyponatraemia, hypophosphataemia and lymphopaenia, which were more frequent in the pirfenidone group.

Marked laboratory abnormalities in pooled data from studies PIPF-004, PIPF-006, and PIPF-016 occurred infrequently (≤1% per treatment group) and with no greater frequency in the pirfenidone group than in the placebo group, with the following exceptions in liver tests, lymphocytes, and hyponatremia. Patients treated with pirfenidone 2403 mg/day had a higher incidence of elevations in ALT or AST ≥3 × ULN than placebo patients (3.7% vs. 0.8%, respectively). Elevations ≥10 × ULN in ALT or AST occurred in 0.3% of patients in the pirfenidone 2403 mg/day group and in 0.2% of patients in the placebo group. Grade 0 to 3 reductions in lymphocyte count were seen in

6 pirfenidone patients (1.0%) and in 1 placebo patient (0.2%). One pirfenidone patient (0.2%) had a post-Baseline Grade 4 lymphocyte abnormality at Week 4, which was resolved at Week 6, Grade 2 at Weeks 12, 24, and 36, and resolved thereafter. Lymphocyte abnormalities were not associated with AEs. Grade 0 to 3 sodium (hyponatremia) abnormalities were reported in 9 pirfenidone patients (1.5%) and 1 placebo patient (0.2%).

Demographic Factors

No effect was seen between adverse events and sex (male versus female), age (<65 versus ≥65 years), or Baseline IPF severity (FVC <70% predicted versus FVC 70% to 80% predicted versus FVC ≥80% predicted) within the pirfenidone group. No effect also was seen for race (white *versus* non-white); however, there were only 65 non-white patients in the three predominantly North American Phase III studies combined

Dose-Response Relationship (PIPF-004 and PIPF-006)

Study PIPF-004 included a group receiving a lower dose of pirfenidone (1197 mg/day) than the marketed dose of 2403 mg/day. Adverse drug reaction rates in the lower dose pirfenidone group were intermediate to the pirfenidone 2403 mg/day and placebo groups for a number of the more frequently occurring adverse drug reactions including nausea, dyspepsia, abdominal pain, decreased appetite, dizziness, headache, photosensitivity reaction and rash.

Adverse Drug Reactions in SP3

The safety analysis in the randomized, double-blind Phase III study (SP3) conducted in Japan included 109 patients who were treated with 1800 mg/day pirfenidone. This dose is comparable to the 2403 mg/day dose administered in studies PIPF-004 and PIPF-006 on a weight-normalized basis to account for the heavier body weight of the mostly North American patients in PIPF-004 and PIPF-006. In study SP3, 107 patients received placebo, and 55 patients received pirfenidone 1200 mg/day, for approximately 52 weeks. The adverse drug reaction profile for pirfenidone in the Japanese study, SP3, was generally similar to that observed with pirfenidone in studies PIPF-004 and PIPF-006 (primarily North American patients), with the exception of a higher incidence of photosensitivity reaction (51.4%) and a lower incidence of rash (9.2%) in patients on 1800 mg/day in the Japanese study. However, no photosensitivity reaction or rash was serious, severe, or life-threatening. The incidence of serious adverse drug reactions was 9.2% in the pirfenidone

1800 mg/day group and 5.6% in the placebo group.

Adverse Drug Reactions in Long-Term Studies

Study PIPF-012 was an uncontrolled, open-label extension, long-term, safety study which allowed patients who completed PIPF-004 and PIPF-006 to continue on pirfenidone treatment at 2403 mg/day or switch to pirfenidone 2403 mg/day from placebo treatment. A total of 603 patients were enrolled in Study PIPF-012. The mean duration of pirfenidone 2403 mg/day treatment in Study PIPF-012 was 27.5 weeks. The adverse drug reaction profile resulting from an interim analysis was similar to that observed in the Phase III trials and previous trials. No new safety signals or trends were observed.

Post-Market Adverse Drug Reactions

Because post-marketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In post-marketing experience in Japan many of the adverse reactions reported during post-approval use of pirfenidone (marketed as Pirespa) are consistent with the clinical trial experience with pirfenidone. These events include: abdominal discomfort, constipation, diarrhoea, dyspepsia, nausea, vomiting, ALT increased, AST increased, GGT increased, decreased appetite, dizziness, dysgeusia, somnolence, photosensitivity reaction, pruritus, rash.

The serious and unexpected adverse drug reactions include, but are not limited to, the following:

Blood and Lymphatic Disorders: Agranulocytosis, febrile neutropaenia, anaemia **Cardiac**

Disorders: Atrial fibrillation, palpitations, angina pectoris, ventricular tachycardia

Gastrointestinal Disorders: Gastric ulcer haemorrhage, gastritis, ileus

Metabolism and Nutrition Disorders: Dehydration, hyperkalaemia

General Disorders and Administration Site Condition: Pyrexia

Hepatobiliary Disorders: Bilirubin increased in combination with increases of ALT and AST, hepatic function abnormal, liver disorder, clinically relevant Drug-Induced Liver Injury (incidence estimated as rare, i.e. $\geq$ 1/10,000 to < 1/1000) including isolated reports with fatal outcome

Immune System: Angioedema

Infections and Infestations: Bronchopulmonary aspergillosis, pneumonia, pneumonia bacterial, urinary tract infection

Investigations: C-reactive protein increased, hepatic enzyme increased, platelet count decreased, blood urea increased, renal impairment

Respiratory, Thoracic and Mediastinal Disorders: Lung disorder, pneumonitis, pneumothorax

DRUG INTERACTIONS

Overview

Drug-Interactions with Inhibitors of CYP1A2 and Other CYP Isoenzymes

Fluvoxamine

TEVA-PIRFENIDONE is contraindicated in patients with concomitant use of fluvoxamine (a strong inhibitor of CYP1A2 with inhibitory effects on CYP2C9, 2C19, and 2D6). Fluvoxamine should be discontinued prior to the initiation of treatment with TEVA-PIRFENIDONE and avoided during pirfenidone therapy due to the potential for reduced clearance of pirfenidone (see CONTRAINDICATIONS).

Ciprofloxacin

Co-administration of pirfenidone and 750 mg of ciprofloxacin (a moderate and selective inhibitor of CYP1A2) increased the exposure to pirfenidone by 81%. If ciprofloxacin at the dose of 750 mg twice daily (a total daily dose of 1500 mg) cannot be avoided, the dose of TEVA-PIRFENIDONE should be reduced to 1602 mg daily (a dose of 534 mg, three times a day). TEVA-PIRFENIDONE should be used with caution when ciprofloxacin is used at a total daily dose of 250 to 1000 mg (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Strong and Selective Inhibitors of CYP1A2

In vitro-in vivo extrapolations indicate that strong and selective inhibitors of CYP1A2 have the potential to increase the exposure to pirfenidone by approximately 2 to 4-fold. If concomitant use of TEVA-PIRFENIDONE with a strong and selective inhibitor of CYP1A2 cannot be avoided, the dose of TEVA-PIRFENIDONE should be reduced to 801 mg daily (267 mg, three times a day). Patients should be closely monitored for emergence of adverse reactions associated with TEVA-PIRFENIDONE therapy. Discontinue TEVA-PIRFENIDONE if necessary (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Other CYP1A2 Inhibitors

Agents or combinations of agents that are moderate to strong inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of pirfenidone (i.e., CYP2C9, 2C19, 2D6, and 2E1) should be avoided during TEVA-PIRFENIDONE treatment. TEVA-PIRFENIDONE should be used with caution in patients treated with moderate inhibitors of CYP1A2 that do not inhibit other CYP isoenzymes.

Pirfenidone is primarily metabolized via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6, and 2E1.

Patients should discontinue and avoid use of strong inhibitors of CYP1A2 due to the potential for reduced clearance of pirfenidone (see Table 2).

Patients should discontinue and avoid use of strong inducers of CYP1A2 to avoid reduced exposure to pirfenidone (see Table 2).

Drug-Drug Interactions

In a Phase I study, the co-administration of pirfenidone and fluvoxamine (a strong inhibitor of CYP1A2 with inhibitory effects on other CYP isoenzymes [CYP2C9, 2C19, and 2D6]) resulted in an approximately 4-fold increase in exposure to pirfenidone in non-smokers.

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e. those identified as contraindicated)

Table 2: Established or Potential Drug-Drug Interactions

	Ref.	Effect	Clinical Comment
CYP1A2 Inhibitors			
CYP1A2, 2C9, 2C19, 2D6: Fluvoxamine	CT	↑4× $AUC_{0-\infty}$, ↑2× C_{max} Increased exposure (and reduced clearance)	Concomitant therapy is contraindicated (see WARNINGS AND PRECAUTIONS).
CYP1A2: Ciprofloxacin	CT	↑81% $AUC_{0-\infty}$, ↑23% C_{max} Increased exposure (and reduced clearance)	Concomitant therapy should be used with caution. Dose reductions may be needed (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).
CYP1A2: Methoxsalen Mexiletine Oral contraceptives	T	↑$AUC_{0-\infty}$, ↑C_{max} Potential for increased exposure (and reduced clearance)	Concomitant therapy should be used with caution.
Inhibitors of Other CYPs when Administered with CYP1A2 Inhibitors			
CYP2C9: Amiodarone Miconazole	T	↑$AUC_{0-\infty}$, ↑C_{max} Potential for increased exposure (and reduced clearance)	Concomitant therapy with these agents and moderate-strong CYP1A2 inhibitors (listed above) should be discontinued and avoided.

	Ref.	Effect	Clinical Comment
CYP2C19: Fluconazole Esomeprazole Moclobemide Omeprazole Voriconazole	T	↑$AUC_{0-\infty}$, ↑C_{max} Potential for increased exposure (and reduced clearance)	Concomitant therapy with these agents and moderate-strong CYP1A2 inhibitors (listed above) should be discontinued and avoided.
CYP2D6: Bupropion Fluoxetine Paroxetine Quinidine Cinacalcet Duloxetine Terbinafine	T	↑AUC0-∞, ↑Cmax Potential for increased exposure (and reduced clearance)	Concomitant therapy with these agents and moderate-strong CYP1A2 inhibitors (listed above) should be discontinued and avoided.
CYP Inducers			
CYP1A2: Phenytoin	T	↓$AUC_{0-\infty}$, ↓C_{max} Potential for reduced exposure	Concomitant therapy should be discontinued and avoided.
CYP2C9: Carbamazepine Rifampin	T	↓$AUC_{0-\infty}$, ↓C_{max} Potential for reduced exposure	Concomitant therapy should be discontinued and avoided.
CYP2C9, 2C19: Rifampin	T	↓$AUC_{0-\infty}$, ↓C_{max} Potential for reduced exposure	Concomitant therapy should be discontinued and avoided.
Legend: CT = Clinical Trial; T = Theoretical			

Drug-Food Interactions

Administration of pirfenidone capsules with food results in a large reduction in C_{max} (by approximately 50%) and a smaller reduction in AUC, compared to the fasted state. Following oral administration of a single dose of 801 mg to healthy older adult volunteers (50–66 years of age) in the fed state, the rate of pirfenidone absorption slowed, while the AUC in the fed state was approximately 80 to 85% of the AUC observed in the fasted state. Less nausea and dizziness were observed in fed when compared with fasted subjects.

Therefore, TEVA-PIRFENIDONE should be administered with food to reduce the incidence of dizziness or nausea (see DOSAGE AND ADMINISTRATION: Dosing Considerations).

A comparative bioavailability study was done to compare the tablet formulation to the capsule formulation (Study GP29830). The effect of food on pirfenidone exposure was consistent between the tablet and capsule formulations (see CLINICAL TRIALS).

Consumption of grapefruit juice is associated with inhibition of CYP1A2 and should be avoided during treatment with TEVA-PIRFENIDONE to prevent increased exposure to pirfenidone.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Cigarette Smoking and Inducers of CYP1A2: Cigarette smoking induces hepatic enzyme production, including CYP1A2, and thus may increase clearance of pirfenidone leading to reduced exposure. Patients should stop smoking before, and not smoke during TEVA-PIRFENIDONE therapy to avoid reduced exposure to pirfenidone. In a Phase I study the exposure to pirfenidone in smokers was significantly less than in non-smokers. Cigarette smoking should be avoided during TEVA-PIRFENIDONE therapy to prevent reduced exposure to pirfenidone.

Effects on Ability to Drive and Use Machines: TEVA-PIRFENIDONE may cause dizziness and fatigue, which could influence the ability to drive or use machines. Patients should be reminded to take TEVA-PIRFENIDONE with food to reduce the incidence of dizziness.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Treatment with TEVA-PIRFENIDONE should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of IPF.
- TEVA-PIRFENIDONE should be taken with food (see DRUG INTERACTIONS).
- TEVA-PIRFENIDONE should not be taken concomitantly with fluvoxamine (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).
- Reduction of the TEVA-PIRFENIDONE dose may be required for ciprofloxacin and strong but selective inhibitors of CYP1A2 (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Recommended Dose and Dosage Adjustment

Adults

The recommended daily dose of TEVA-PIRFENIDONE for patients with IPF is 801 mg three times a day with food, for a total dose of 2403 mg/day.

Upon initiating treatment, the dose should be titrated to the recommended daily dose of 2403 mg/day over a 14-day period to improve tolerability as follows:

Days 1 to 7: a dose of 267 mg administered, three times a day (801 mg/day) with food

Days 8 to 14: a dose of 534 mg administered, three times a day (1602 mg/day) with food Day 15 onward: a dose of 801 mg administered, three times a day (2403 mg/day) with food

Doses above 2403 mg/day are not recommended for any patient (see OVERDOSAGE).

Patients who miss 14 consecutive days or more of TEVA-PIRFENIDONE treatment should re-initiate therapy by undergoing the initial 2 week titration regimen up to the recommended daily dose.

If treatment is interrupted for less than 14 consecutive days, the dose can be resumed at the previous recommended daily dose without titration.

Dose Adjustments

Gastrointestinal Events: In patients who experience intolerance to therapy due to gastrointestinal side effects, patients should be reminded to take TEVA-PIRFENIDONE with food. If gastrointestinal events do not improve, or worsen in severity, dose reduction or discontinuation of TEVA-PIRFENIDONE may be warranted. The dose of TEVA-PIRFENIDONE may be reduced to 267 mg – 534 mg, two to three times a day with food with re-escalation to the recommended daily dose as tolerated.

Photosensitivity Reaction or Rash: Patients who experience a mild to moderate photosensitivity reaction or rash should be reminded to use a sunblock daily and to avoid exposure to the sun. The dose of TEVA-PIRFENIDONE may be reduced to 801 mg each day. If the rash persists after 7 days, TEVA-PIRFENIDONE should be discontinued for 15 days, with re-escalation to the recommended daily dose in the same manner as the dose escalation period.

Patients who experience severe photosensitivity reaction or rash should be instructed to discontinue TEVA-PIRFENIDONE promptly and to seek medical advice without delay (see WARNINGS AND PRECAUTIONS). Once the rash has resolved, TEVA-PIRFENIDONE may be re-introduced and re escalated up to the recommended daily dose at the discretion of the physician.

Ciprofloxacin: Co-administration of pirfenidone and 750 mg of ciprofloxacin (a moderate and selective inhibitor of CYP1A2) increased the exposure to pirfenidone by 81%. If ciprofloxacin at the dose of 750 mg twice daily (a total daily dose of 1500 mg) cannot be avoided, the dose of TEVA-PIRFENIDONE should be reduced to 1602 mg daily (a dose of 534 mg, three times a day). TEVA-PIRFENIDONE should be used with caution when ciprofloxacin is used at a total daily dose of 250 to 1000 mg (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Elderly: No dose adjustment is necessary in patients 65 years and older.

Pediatric: Pirfenidone has not been studied in pediatric patients, and is not recommended for use in this patient population.

Hepatic Impairment: No dose adjustment is necessary in patients with mild to moderate hepatic

impairment (i.e., Child-Pugh Class A and B). However, since plasma levels of pirfenidone may be increased in individuals with moderate hepatic impairment (around 60% increase in Child-Pugh Class B), patients should be monitored closely for signs of toxicity especially if they are concomitantly taking a known CYP1A2 inhibitor (see DRUG INTERACTIONS). TEVA-PIRFENIDONE should not be used in patients with severe hepatic impairment or end-stage liver disease (see CONTRAINDICATIONS). Liver chemistry tests (ALT, AST, bilirubin) should be monitored before and during treatment with TEVA-PIRFENIDONE. Dose adjustments, including discontinuation, may be necessary in the event of elevations in ALT, AST, and/or bilirubin (see WARNINGS AND PRECAUTIONS, and see below for dose adjustments).

Recommendations in Case of ALT, AST, Bilirubin Elevations

For patients with confirmed elevations in ALT, AST or bilirubin during treatment, dose adjustments, including discontinuation, may be necessary. Confounding medicinal products should be discontinued promptly, other causes excluded and close monitoring of the patient is advised.

If a patient exhibits a Grade 2 ALT and/or AST elevation to >3 to <5 × ULN without hyperbilirubinaemia after starting treatment with TEVA-PIRFENIDONE at the recommended dose of 2403 mg/day, or any time after starting therapy, confounding medicinal products should be discontinued, other causes excluded, and the patient monitored closely. As clinically appropriate, TEVA-PIRFENIDONE can be continued at the recommended dose of 2403 mg/day, reduced or temporarily discontinued. Once ALT and AST levels have resolved, TEVA-PIRFENIDONE may be re-escalated to the recommended daily dose and continued, if tolerated and the patient should be monitored closely.

If a patient exhibits any ALT and/or AST elevation to >3 to <5 x ULN accompanied by clinical signs or symptoms indicative of liver injury or accompanied by hyperbilirubinaemia (excluding patients with known predominantly unconjugated hyperbilirubinaemia, e.g., Gilbert's syndrome), TEVA-PIRFENIDONE should be discontinued promptly. The patient should be monitored closely until resolution of elevated ALT, AST, bilirubin, and symptoms. The patient should NOT be re-challenged with TEVA-PIRFENIDONE.

If a patient exhibits ALT and/or AST elevation to ≥5 × ULN regardless of the level of serum bilirubin, TEVA-PIRFENIDONE should be discontinued promptly and the patient monitored closely until resolution of elevated ALT, AST, and bilirubin. The patient should NOT be re-challenged with TEVA-PIRFENIDONE.

Renal Impairment: No dose adjustment is necessary in patients with mild to moderate renal impairment. TEVA-PIRFENIDONE should not be used in patients with severe renal impairment or end-stage renal disease requiring dialysis (CrCl <30mL/min, per Cockcroft-Gault equation) (see CONTRAINDICATIONS).

Missed Dose

If a dose is missed, the next dose should be taken as originally planned. Double doses should not

be taken to make up for forgotten doses. If doses are missed for more than 14 days, TEVA-PIRFENIDONE treatment should be re-initiated by undergoing the initial 2 week titration regimen up to the recommended daily dose.

Administration

TEVA-PIRFENIDONE is to be swallowed whole with water and taken with food to reduce the possibility of nausea or dizziness.

OVERDOSAGE

In studies PIPF-004 and PIPF-006, an overdose was defined as any study drug exposure of greater than 15 capsules (>4005 mg) in any given day or greater than 5 capsules (>1335 mg) in any single dose. No patients met the definition of overdose in these studies. There is therefore, limited clinical experience with overdose. Multiple doses of pirfenidone up to a total dose of 4806 mg/day were administered as six 267 mg capsules three times daily to healthy adult volunteers over a 12-day dose escalation period. Adverse reactions were generally consistent with the most frequently reported adverse reactions for pirfenidone.

There is no specific antidote. In the event of a suspected overdose, supportive medical care should be provided including monitoring of vital signs and close observation of the clinical status of the patient.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanisms of action of pirfenidone have not been fully established. However, existing data suggest that pirfenidone exerts anti-fibrotic and anti-inflammatory properties in a variety of *in vitro* systems and animal models of pulmonary fibrosis (e.g., bleomycin- and transplant-induced fibrosis).

IPF is a chronic fibrotic and inflammatory pulmonary disease affected by the synthesis and release of pro-inflammatory cytokines including tumour necrosis factor-alpha (TNF-α) and interleukin-1-beta (IL-1β). Pirfenidone attenuates fibroblast proliferation, production of fibrosis- associated proteins and cytokines, and the increased biosynthesis and accumulation of extracellular matrix in response to cytokine growth factors such as transforming growth factor-beta (TGF-β) and platelet-derived growth factor (PDGF). Pirfenidone has been shown to reduce the accumulation of inflammatory cells in response to various stimuli.

Pharmacodynamics

An observed dose-response relationship favouring a dose of 2403 mg/day pirfenidone compared

with 1197 mg/day pirfenidone was observed in a Phase III randomized, double-blind, placebo-controlled study (PIPF-004). A PK-PD evaluation of a subset of these patients showed a weak positive relationship between pirfenidone plasma exposure and the primary endpoint of FVC change.

A double-blind, randomized, placebo- and active-controlled parallel arm study was performed to determine the impact of two doses of pirfenidone capsules (2403 mg/day & 4005 mg/day) on QT interval in healthy human volunteers (40/treatment arm). ECG assessments were performed at baseline and on day 10 of treatment. There was no evidence of a treatment-related effect on the QTc interval at either of the tested doses. Statistically significant increases in heart rate were observed, with maximum increases of 3.8 bpm (90% CI 1.7, 5.9) in the pirfenidone 2403 mg/day group and 4.9 bpm (90% CI 2.5, 7.4) in the pirfenidone 4005 mg/day group.

Pharmacokinetics

Table 3: Arithmetic Mean (Range) Pirfenidone Pharmacokinetic Parameters in Patients with IPF

	N	C_{max} (µg/mL)	AUC[a] (mg•h/L)	T_{max} (h)
IPF patients (PIPF-004)	57	14.7 (6.48–33.6)	180 (85.6–544)	not measured

a: AUC_{0-24} estimates reflect three doses of 801 mg administered over the 24 hour period at steady-state

Absorption: The absolute bioavailability of pirfenidone has not been determined in humans.

Administration of pirfenidone capsules with food results in a large reduction in C_{max} (by around 50%) and a smaller reduction of AUC, compared to the fasted state. Following oral administration of a single dose of 801 mg to healthy older adult volunteers (50 to 66 years of age) in the fed state, the rate of pirfenidone absorption slowed, while the AUC in the fed state was approximately 80 to 85% of the AUC observed in the fasted state.

A comparative bioavailability study was done to compare the tablet formulation to the capsule formulation (Study GP29830). Bioequivalence was demonstrated in both fasting and fed states when comparing the 801 mg tablet to three 267 mg capsules. The effect of food on pirfenidone exposure was consistent between the tablet and capsule formulations (see CLINICAL TRIALS).

Following oral administration of a single dose of 801 mg of pirfenidone either as 3 x 267 mg capsules or 1 x 801 mg tablet in healthy adult volunteers, reduced incidences of adverse events (in particular nausea and dizziness) were observed in fed subjects when compared to the fasted group in a controlled setting (studies PIPF-005 and GP29830). Therefore, TEVA-PIRFENIDONE should be administered with food to reduce the incidence of dizziness or nausea (see DOSAGE AND ADMINISTRATION: Dosing Considerations).

Distribution: Pirfenidone binds to human plasma proteins, primarily to albumin. The overall mean binding ranged from 50% to 58% at concentrations observed in clinical studies

(1 to 100 µg/mL). Mean apparent oral steady-state volume of distribution is approximately 70 L, indicating that pirfenidone distribution to tissues is modest.

Metabolism: Pirfenidone is primarily metabolized via CYP1A2 (approximately 70–80%) with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6, and 2E1. *In vitro* and *in vivo* studies to date have not detected any activity of the major metabolite, 5-carboxy-pirfenidone.

The clearance of oral pirfenidone appears modestly saturable. In a multiple-dose, dose-ranging study in healthy older adults administered doses ranging from 267 mg to 1335 mg three times a day, the mean clearance decreased by approximately 25% above a dose of 801 mg three times a day. The concentration-dependence of pirfenidone clearance did not appear to translate into a lack of dose proportionality in the Phase III trial and is not likely to be clinically relevant.

Excretion: Following single dose administration of pirfenidone in healthy older adults, the mean apparent terminal elimination half-life was approximately 2.4 hours. Approximately 80% of an orally administered dose of pirfenidone is cleared in the urine within 24 hours of dosing. The majority of pirfenidone is excreted as the 5-carboxy-pirfenidone metabolite (>95% of that recovered), with less than 1% of pirfenidone excreted unchanged in urine.

Special Populations and Conditions

Population pharmacokinetic analyses were conducted, using data collected from four studies in healthy subjects or patients with renal impairment and one study in patients with IPF. Results showed no clinically relevant effects of age, gender or body size on the pharmacokinetics of pirfenidone.

Pediatrics: The safety and effectiveness of pirfenidone in pediatric patients have not been established.

Geriatrics: The independent effect of patient age on the PK of pirfenidone is relatively small (the predicted AUC for pirfenidone was approximately 23% higher in 80 year old compared to 50 year old patients) and unlikely to be clinically significant.

Gender: No clinically relevant effect of gender on the pharmacokinetics of pirfenidone has been observed. The C_{max} of pirfenidone in females was approximately 10% higher than in males.

Race: No clinically relevant effect of race on the pharmacokinetics of pirfenidone has been observed. The predicted AUC_{0-24} of pirfenidone was found to be 21% lower in Caucasian compared with African-American subjects. However, there were only a small number of non-Caucasian patients included in controlled clinical trials.

Body Size: No clinically relevant effect of body size on the pharmacokinetics of pirfenidone has been observed. Obese subjects were observed to have higher exposure than either normal or overweight subjects but the former were older and had worse renal function.

Hepatic Insufficiency: The pharmacokinetics of pirfenidone were compared in subjects with moderate hepatic impairment (Child-Pugh Class B) and normal hepatic function. Results showed that there was a mean increase of 60% in pirfenidone exposure after a single dose of 801 mg pirfenidone (3 × 267 mg capsule) in patients with moderate hepatic impairment.
Pirfenidone should be used with caution in patients with mild to moderate hepatic impairment and patients should be monitored closely for signs of toxicity especially if they are concomitantly taking a known CYP enzyme inhibitor (in particular a CYP1A2 inhibitor). TEVA-PIRFENIDONE is contraindicated in severe hepatic impairment and end stage liver disease (see CONTRAINDICATIONS).

Renal Insufficiency: No significant differences in the pharmacokinetics of pirfenidone were observed in subjects with mild renal impairment (CrCl of 51–80 mL/min; Cockcroft-Gault equation) to severe renal impairment (CrCl <30 mL/min) compared with subjects with normal renal function (CrCl >80 mL/min). However, the parent drug is predominantly metabolized to 5-carboxy-pirfenidone, and the pharmacokinetics of this metabolite are altered in subjects with moderate to severe renal impairment. The $AUC_{0-\infty}$ of 5-carboxy-pirfenidone was significantly higher in the moderate ($p = 0.009$) and severe ($p < 0.0001$) renal impairment groups than in the group with normal renal function; 100 (26.3) and 168 (67.4) mg•h/L compared to 28.7 (4.99) mg•h/L respectively. However, the predicted amount of metabolite accumulation at steady state is minimal as the terminal elimination half-life is only 1–2 hours in these subjects. Caution is required in patients with mild to moderate renal impairment who are receiving pirfenidone. TEVA-PIRFENIDONE is contraindicated in patients with severe renal impairment (CrCl <30mL/min) or end stage renal disease requiring dialysis (see WARNINGS AND PRECAUTIONS and CONTRAINDICATIONS).

Japanese Patients:
Study SP3: a phase III study conducted in Japanese patients, compared pirfenidone 1800 mg/day (tablets, a comparable dose to 2403 mg/day in the North American and European populations of PIPF-004/006 on a weight-normalized basis) with placebo (N = 110, N = 109, respectively). Treatment with pirfenidone 1800 mg/day statistically significantly reduced mean decline in vital capacity (VC) at Week 52 (the primary endpoint) compared with placebo (-0.09 ± 0.02 L versus -0.16 ± 0.02 L respectively, relative difference 43.8%, $p = 0.042$). There was also a statistically significant prolongation in progression free survival compared with placebo (HR: 0.64 [0.43–0.96], $p = 0.028$).

STORAGE AND STABILITY

Store at room temperature (15 - 30°C).

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions for TEVA-PIRFENIDONE.

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed via wastewater and disposal through household waste should be avoided. Use established "collection systems," if available in your location.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TEVA-PIRFENIDONE 267 mg is a yellow, biconvex, oval shaped film-coated tablet, debossed with "3610" on one side, and "TEVA" on the other side

TEVA-PIRFENIDONE 801 mg is a purple, biconvex, oval shaped film-coated tablet, debossed with "3611" on one side and "TEVA" on the other side.

Each tablet contains pirfenidone and the following non-medicinal ingredients:
Black iron oxide, colloidal silicon dioxide, croscarmellose sodium, iron oxide red (801 mg), iron oxide yellow, macrogol (polyethylene glycol), magnesium stearate, microcrystalline cellulose, polyvinyl alcohol-part hydrolyzed, povidone, talc, and titanium dioxide.

TEVA-PIRFENIDONE tablets are supplied in in the following packaging formats:

267 mg
Bottle with 90 tablets, and 270 tablets.

801 mg
Bottle with 90 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

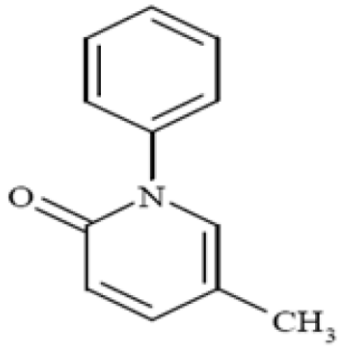
Drug Substance

Proper name: Pirfenidone

Chemical name: 5-Methyl-1-phenylpyridin-2(1*H*)-one

Molecular formula and molecular mass: $C_{12}H_{11}NO$, 185.2 g/mol

Structural formula:



Physicochemical properties:

Description: White or pale yellow, crystalline powder

Solubility: Freely soluble water, freely soluble in ethanol (96%) and very slightly soluble in heptane.

Melting point: Between 106 ºC – 112 ºC.

pKa 0.2

CLINICAL TRIALS

Bioequivalence Studies

An open label, randomized, single dose, two-treatment, two-period, two-sequence crossover, oral bioequivalence study of Teva-Pirfenidone tablets 801 mg (Teva Canada Limited) and ESBRIET® (pirfenidone) 801 mg tablets (Genentech USA Inc., a member of the Roche Group), was conducted in 54 healthy, adult Asian male and female subjects under fasting conditions. A summary of the bioavailability data from the 35 subjects who completed the study is presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Pirfenidone (1 x 801 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	74535.11 79721.53 (38.01)	72550.17 76997.78 (36.17)	102.7	98.8 - 106.8
AUC_I (ng.h/mL)	75527.33 81063.46 (39.20)	73520.39 78235.17 (37.26)	102.7	98.7 - 107.0
C_{max} (ng/mL)	15929.72 16234.95 (19.44)	15316.78 15641.88 (20.99)	104.0	97.3 - 111.1
T_{max}§ (h)	0.75 (0.33-2.33)	1.00 (0.33-3.00)		
$T_{½}$€ (h)	3.26 (32.90)	3.19 (29.66)		

* Teva-Pirfenidone Tablets, 801 mg, (Teva Canada Limited)

† ESBRIET® (pirfenidone) Tablets, 801 mg, (Genentech USA Inc. a member of the Roche Group), were purchased in the USA.

§ Expressed as median (range) only

€ Expressed as the arithmetic mean (CV%) only

Study Demographics and Trial Design

The clinical efficacy of pirfenidone capsules 267 mg has been studied in three Phase III, multicentre, randomized, double-blind, placebo-controlled studies in patients with IPF (PIPF-004, PIPF-006 and PIPF-016).

PIPF-004 and PIPF-006 compared treatment with pirfenidone 2403 mg/day to placebo. The studies were nearly identical in design, with few exceptions including an intermediate dose group (1197 mg/day) in PIPF-004. In both studies, treatment was administered three times daily for a minimum of 72 weeks. The final follow-up visit was held 3 to 4 weeks after the treatment completion visit. The primary endpoint in both studies was the change from Baseline to Week 72 in percent predicted Forced Vital Capacity (FVC).

PIPF-016 compared treatment with pirfenidone 2403 mg/day to placebo. Treatment was administered three times daily for 52 weeks. The primary endpoint was the change from Baseline to Week 52 in percent predicted FVC.

Table 4: Summary of Patient Demographics for Phase III Clinical Trials in Patients with IPF

Study #	Trial design	Dosage, route of administration and duration	Study patients (n) Pirfenidone/ Control	Mean age (Range)		Gender	
				Pirfenidone	Control	Pirfenidone	Control
PIPF-004	Randomized double-blind, placebo-controlled Phase III study to evaluate the efficacy and safety of pirfenidone in patients with IPF	2403 mg/day (three 267 mg capsules TID) pirfenidone vs. placebo, administered orally for 72 weeks.	174/174	65.7 years (45–80 years)	66.3 years (40–79 years)	32.2% female	26.4% female
PIPF-006	Randomized double-blind, placebo-controlled Phase III study to evaluate the efficacy and safety of pirfenidone in patients with IPF	2403 mg/day (three 267 mg capsules TID) pirfenidone vs. placebo, administered orally for 72 weeks.	171/173	66.8 years (45–80 years)	67.0 years (42–80 years)	28.1% female	28.3% female

Study #	Trial design	Dosage, route of administration and duration	Study patients (n) Pirfenidone/ Control	Mean age (Range)		Gender	
				Pirfenidone	Control	Pirfenidone	Control
PIPF-016	Randomized double-blind, placebo-controlled Phase III study to evaluate the efficacy and safety of pirfenidone in patients with IPF	2403 mg/day (three 267 mg capsules TID) pirfenidone vs. placebo, administered orally for 52 weeks.	278/277	68.4 years (47–80 years)	67.8 years (41–80 years)	20.1% female	23.1% female

Study Results

Forced Vital Capacity

In study PIPF-004, the decline in lung function, as measured by percent predicted FVC from Baseline at Week 72 of treatment, was significantly reduced in patients receiving pirfenidone (N = 174) compared with patients receiving placebo (N = 174; p = 0.001, rank ANCOVA). The absolute difference in the mean change in percent predicted FVC was 4.4% between treatment groups, representing a relative difference of 35.5%. Treatment with pirfenidone also significantly reduced the decline of percent predicted FVC from Baseline at Weeks 24 (p = 0.014), 36 (p < 0.001), 48 (p < 0.001), and 60 (p < 0.001). At Week 72, a decline from Baseline in percent predicted FVC of ≥10% (a threshold indicative of the risk of mortality in IPF) was seen in 20% of patients receiving pirfenidone compared to 35% receiving placebo (

Table 5).

In study PIPF-006, there was no statistically significant difference between treatment with pirfenidone (N = 171) and placebo (N = 173) in the reduction of the decline of percent predicted FVC from Baseline at Week 72 ($p = 0.501$, rank ANCOVA). However, treatment with pirfenidone reduced the decline in lung function, as measured by percent predicted FVC from Baseline at Weeks 24 ($p < 0.001$), 36 ($p = 0.011$), and 48 ($p = 0.005$). At Week 72, a decline in FVC of ≥10% was seen in 23% of patients receiving pirfenidone and 27% receiving placebo (

Table 5).

The primary endpoint analysis of the pooled population also showed a pirfenidone treatment effect on percent predicted FVC at week 72 ($p = 0.005$, rank ANCOVA). The absolute difference in the mean change in percent predicted FVC was 2.5% between two treatment groups, representing a relative difference of 22.8%. At Week 72, a decline from Baseline in percent predicted FVC of ≥10% was seen in 21.4% of patients receiving pirfenidone compared to 30.5% receiving placebo (

Table 5).

Table 5: Categorical Assessment of Change from Baseline to Week 72 in Percent Predicted FVC

	Number (% of Patients)					
	PIPF-004		PIPF-006		Pooled	
	Pirfenidone 2403 mg/d (n = 174)	Placebo (n = 174)	Pirfenidone 2403 mg/d (n = 171)	Placebo (n = 173)	Pirfenidone 2403 mg/d (n = 345)	Placebo (n = 347)
Decline of ≥10% or death or lung transplant	35 (20%)	60 (34%)	39 (23%)	46 (27%)	74 (21%)	106 (30%)
Decline of <10% but ≥0%	97 (56%)	90 (52%)	88 (52%)	89 (51%)	185 (54%)	179 (52%)
Improvement of >0%	42 (24%)	24 (14%)	44 (26%)	38 (22%)	86 (25%)	62 (18%)

In study PIPF 016, the decline of percent predicted FVC from Baseline at Week 52 of treatment, was significantly reduced in patients receiving pirfenidone (N = 278) compared with patients receiving placebo (N = 277; $p < 0.000001$, rank ANCOVA). Treatment with pirfenidone also significantly reduced the decline of percent predicted FVC from Baseline at Weeks 13 ($p < 0.000001$), 26 ($p < 0.000001$), and 39 ($p = 0.00002$).

Progression Free Survival (PFS)

In the analysis of PFS in study PIPF-004, treatment with pirfenidone significantly reduced the combined risk of death or disease progression by 36% compared to placebo (HR 0.64 [0.44–0.95]; $p = 0.023$). Disease progression was defined as ≥10% decline in percent predicted FVC or ≥15% decline in percent predicted diffusing capacity of the lungs for carbon monoxide (DL_{CO}).

The reduction in risk was primarily due to differences in disease progression due to decline in percent predicted FVC. In study PIPF-006, there was no difference in PFS between the two treatment arms (HR 0.84 [0.58–1.22]; $p = 0.355$). In the pooled analysis, treatment with pirfenidone 2403 mg/day resulted in a 26% reduction in the risk of death or progression of disease compared with placebo (HR 0.74 [95% CI, 0.57–0.96]; $p = 0.025$).

In the analysis of PFS in study PIPF-016, treatment with pirfenidone significantly reduced the combined risk of death or disease progression by 43% compared to placebo (HR 0.57 [0.43–0.77]; $p = 0.0001$). Disease progression was defined as death, ≥10% decline in percent predicted FVC or ≥ 50 meters decline in six minute walk test (6MWT) distance.

Six Minute Walk Test Distance

In study PIPF-004, there was no difference between patients receiving pirfenidone compared to placebo in change from baseline to Week 72 of distance walked during a six minute walk test (6MWT) by the prespecified rank ANCOVA ($p = 0.171$). The difference in the mean decline in the 6MWT distance between the treatment groups at Week 72 was 16.4 meters, representing a relative difference of 21.3%.

In study PIPF-006, the decline in 6MWT distance from baseline to Week 72 was significantly reduced compared with placebo in this study ($p < 0.001$, rank ANCOVA). The difference in the mean decline in the 6MWT distance between the treatment groups at Week 72 was 31.8 meters, representing a relative difference of 41.3%.

In study PIPF-016, the decline in 6MWT distance from baseline to Week 52 was significantly reduced compared with placebo ($p = 0.036$, rank ANCOVA). The difference in the mean decline in the 6MWT distance between the treatment groups was 26.7 meters, representing a relative difference of 44.2%.

Mortality

The overall survival was captured as an exploratory efficacy endpoint in pivotal studies. The cause of death was not adjudicated and the effect of pirfenidone on all-cause mortality is inconclusive.

In a pooled analysis of survival in PIPF-004 and PIPF 006 the mortality rate with pirfenidone 2403 mg/day group was 7.8% compared with 9.8% with placebo (HR 0.77 [95% CI, 0.47–1.28]).

In Study PIPF-016, the mortality rate with pirfenidone 2403 mg/ day group was 4.0 % compared with 7.2% with placebo (HR 0.55 [95% CI, 0.26–1.15]).

Comparative Bioavailability Studies

Study GP29830 was a Phase I, open-label, randomized, four-treatment period, four-sequence, single dose, crossover comparative bioavailability study designed to determine the bioequivalence of pirfenidone tablets (1 x 801 mg) to pirfenidone capsules (3 x 267 mg) under both fasted and fed conditions in 44 healthy male (64%) and female (36%) subjects from 20 to 54 years of age. The results from 43 subjects are presented below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILAIBLITY DATA
Fasting Conditions

PIRFENIDONE (1 x 801 mg for Tablet; 3 x 267 mg for Capsules) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Tablet*	Capsules†	% Ratio of Geometric Least Square Means	90% Confidence Interval
AUCT (ng • hr/mL)	49200 52200 (35.4)	49500 52300 (34.1)	99.63	96.66-102.69
AUCI (ng • hr/mL)	49400 52400 (35.9)	49700 52600 (34.5)	99.61	96.64-102.68
C_{max} (ng/mL)	12600 13400 (39.6)	12500 13000 (34.5)	101.26	94.41-108.60
T_{max}§ (h)	1.00 (0.25, 3.00)	0.75 (0.25, 2.00)	--	--
$T_{1/2}$ 2 (h)	2.77 (20.6)	2.77 (21.3)	--	--

*Test product, pirfenidone 801 mg tablets (Hoffmann-La Roche Limited), n=42

† Reference product, pirfenidone 267 mg capsules, manufacturer: F.Hoffmann-La Roche, country of purchase: USA, n=42

AUC_T = area under the plasma concentration versus time curve from time zero to the time of the last quantifiable concentration up to 24 hours post dosing

AUC_I = area under the plasma concentration versus time curve from time zero to infinity

§ Expressed as the median (range)

2 Expressed as the arithmetic mean (CV%)

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILAIBLITY DATA
Fed Conditions (High Fat Meal)

PIRFENIDONE (1 x 801 mg for Tablet; 3 x 267 mg for Capsules) From measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Tablet*	Capsules†	% Ratio of Geometric Least Square Means	90% Confidence Interval
AUCT (ng • hr/mL)	40600 43100 (35.8)	39500 42000 (36.6)	103.06	99.55-106.69
AUCI (ng • hr/mL)	40900 43400 (36.5)	39800 42400 (37.3)	103.05	99.54-106.69
C_{max} (ng/mL)	7640 7910 (26.0)	6560 6760 (24.8)	116.61	108.26-125.60
T_{max}§ (h)	2.05 (1.00, 6.00)	3.00 (0.50, 6.00)	--	--
T½[2] (h)	2.74 (21.1)	2.75 (21.3)	--	--

*Test product, pirfenidone 801 mg tablets (Hoffmann-La Roche Limited), n=43
† Reference product, pirfenidone 267 mg capsules, manufacturer: F.Hoffmann-La Roche, country of purchase: USA, n=43
AUC_T = area under the plasma concentration versus time curve from time zero to the time of the last quantifiable concentration up to 24 hours post dosing
AUC_I = area under the plasma concentration versus time curve from time zero to infinity
§ Expressed as the median (range)
[2] Expressed as the arithmetic mean (CV%)

DETAILED PHARMACOLOGY

Animal Pharmacology

The findings from a range of *in vitro* and *in vivo* primary pharmacodynamic studies suggested the anti-fibrotic and anti-inflammatory properties of pirfenidone. Bleomycin-induced pulmonary fibrosis has become an established model for human IPF and studies with pirfenidone in this model using mice, hamsters and rats demonstrated its activity in inhibiting the development and progression of fibrosis at exposures lower than that associated with the recommended human dose. *In vitro* and *in vivo* studies to date have not detected any activity of the major human

metabolite, 5-caboxy-pirfenidone.

At concentrations higher than the C_{max} seen in humans, pirfenidone may cause transient CNS depressant effects. Inhibitory effects on gastric emptying and small intestinal transport were observed in rats. An additional pharmacological effect was an arrhythmogenic effects in mice, rats and dogs.

Pirfenidone decreased "general activity and behavior" and "the central nervous system" in mice at an oral dose of 100 mg/kg or above. Pirfenidone had effects on "the respiratory and cardiovascular systems" in anesthetized rats at an intraduodenal dose of 30 mg/kg or above. Studies in mice and rats caused transient general activity and behavior effects (marked sedation and abnormal posture at oral doses of 100 mg/kg or above; at 300 mg/kg staggering gait, ptosis and a decrease in the body temperature), decreased the spontaneous motor activity and the body temperature at an oral dose of 100 mg/kg or above. At 300 mg/kg, significant potentiating effects of anesthesia, anticonvulsive effects (electroshock or PTZ-induced convulsions) and analgesic effects were observed and significantly reduced the blood pressure and significantly increased the respiratory volume and arterial blood flow in anesthetized rats at an intraduodenal dose of 30 mg/kg or above. At 100 mg/kg or above, pirfenidone caused a decrease in the respiratory rate, an increase in the heart rate, and occurrence of a premature beat.

In anesthetized rats, pirfenidone caused a transient increase in heart rate immediately after administration at 100 mg/kg. 300 mg/kg of pirfenidone caused a decrease in blood pressure and increase in heart rate lasting approximately 30 minutes. Pirfenidone caused premature ventricular contracts (PVC) and atrioventricular block at 100 mg/kg or above. Continuous PVC was also observed at 300 mg/kg.

Studies in anesthetized dogs demonstrated that an intraduodenal administration of pirfenidone at 100 mg/kg or more causes a decrease in blood pressure and an increase in heart rate.

Human Pharmacology

Pirfenidone was converted to 5-hydroxymethyl-pirfenidone and 5-carboxy-pirfenidone by NADPH-fortified human liver microsomes. The result of experiments with human recombinant CYP enzymes implicated several CYP enzymes such as CYP1A2, 2C9, 2C19, 2D6, and 2E1 in the metabolism of pirfenidone. However, the results of the antibody inhibition experiments and correlation analysis suggest that CYP1A2 is the major CYP enzyme responsible for the conversion of pirfenidone to 5-hydroxymethyl-pirfenidone and 5-carboxy-pirfenidone in human liver microsomes. The overall results indicate CYP1A2 as the major CYP involved in the metabolism, however, results from experiments with human recombinant CYP enzymes and correlation analysis indicate that other CYP enzymes participate in the overall metabolism of pirfenidone.

Pirfenidone was found not to significantly inhibit CYP or MAO enzymes. However under one experimental condition examined using human liver microsomes, pirfenidone caused direct inhibition of CYP1A2, CYP2A6, CYP2D6 and CYP2E1, as approximately 34%, 27%, 21% and

27% inhibition was observed at 1000 μM. As well, CYP enzymes are not influenced by 5-carboxy-pirfenidone and only mildly influenced by pirfenidone (at 250 μM).

TOXICOLOGY

With the exception of phototoxicity, nonclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and toxicity to reproduction. Phototoxicity and irritation were noted in guinea pigs and mice after oral administration of pirfenidone and with exposure to UVA light.

Acute Toxicity

In mice and rats the clinical signs observed at the maximum non-lethal doses included hypoactivity and abnormal gait. These clinical signs were observed in dogs in addition to vomiting, mydriasis and tremors. In a study with rats, the toxicity of pirfenidone was reduced when administered with food. Pirfenidone was more toxic to female rats and female dogs in which higher systemic exposures compared to males was observed.

Table 6: Acute Toxicity

Species	Route	Maximum Non-Lethal Dose (mg/kg)	Minimum Lethal Dose (mg/kg)
Mouse	Oral, gavage	1000	2000
Rat	Oral, gavage	500 (fasted); 1000 (fed)	1000 (fasted)
Dog	Oral, capsule	1000	Not determined

Chronic toxicity

In repeated dose studies, decreased body weight was observed in mice, rats and dogs administered oral pirfenidone. Increased liver weights were observed with hepatic centrilobular hypertrophy and increased CYP content in all species. In dogs, transient vomiting, abnormal gait, tremors, limb weakness, rigidity and hypoactivity were observed at doses 10-fold higher (C_{max}) than the clinical dose. The toxic signs observed in these studies were reversible after pirfenidone administration was stopped.

Table 7: Chronic Toxicity

Species	Route	Duration	Doses (mg/kg/day)	Results
Mouse, $B6C3F_1$	Oral, diet	13 weeks	0, 200, 600, 2000	↓ Body weight at the highest dose. ↑ Red blood cell indices, reticulocyte ratio and platelet count in males. ↓ Albumin (both sexes), A/Gratio (males), total protein (females) and cholesterol; ↑ BUN (males). Dose-related ↑ liver weight with centrilobular hepatocyte hypertrophy, and splenic extramedullary hematopoiesis in males at 2000 mg/kg/day. NOAEL: 600 mg/kg/day
Rat, F344	Oral, diet	13 weeks	0, 500, 1000, 1500	↓ Body weight and body weight gain, ↓ erythrocytes (RBC), haemoglobin, and hematocrit and ↑ MCV, platelets and reticulocytes in both sexes. ↑ Total protein, albumin, glucose, BUN, cholesterol, calcium, and inorganic phosphorous; ↓ A/G ratio, triglycerides and chloride. ↑ Liver, kidney, adrenal, and testes weights. Dose-dependent centrilobular hepatocyte hypertrophy, kidney tubular epithelial regeneration (males only), and adrenal gland zone fasciculata hypertrophy (males only at 1500 mg/kg/day).
Rat, SD	Oral, gavage	6 months	0, 20, 100, 500, 1000	Salivation, ↓ activity, and respiratory rate at 500 and 1000 mg/kg/day during the first 6 weeks of treatment. ↓ Food consumption and body weight gain in high-dose males. ↓ RBC, haemoglobin, and hematocrit in females, and ↑ MCV and MCH in males, together with ↓ prothrombin time in males and ↑ activated partial thromboplastin time in females. ↑ Total protein, albumin, A/Gratio, creatinine kinase, amylase, cholesterol, calcium, and inorganic phosphorous; ↓ creatinine, triglycerides, and chloride. ↑ Liver weight (both sexes) and centrilobular hypertrophy in 2/12 males at 1000 mg/kg/day. ↑ CYP content and selected isoenzymes at 500 and 1000 mg/kg/day. NOAEL: 100 mg/kg/day
Species	Route	Duration	Doses (mg/kg/day)	Results

Species	Route	Duration	Doses (mg/kg/day)	Results
Rat, SD	Intravenous	4 weeks	0, 500, 1000, 1625	Ten deaths by Day 4 of treatment (1 female at 1000 mg/kg/day and 9 females at 1625 mg/kg/day). ↑ Absolute liver and kidney weights and hepatic centrilobular hypertrophy at 1625 mg/kg/day. NOAEL: 500 mg/kg/day
Dog, Beagle	Oral, capsule	3 months	0, 20, 70, 200	Mucous in faeces, salivation, vomiting, abnormal gait, difficulty in standing, rigidity, limb weakness, head shakes, vocalization and hypoactivity at the higher doses. ↑ Platelet counts at 200 mg/kg/day. ↑ Alkaline phosphatase at 70 and 200 mg/kg/day. ↑ Liver weight and reversible hepatocellular hypertrophy at 200 mg/kg/day. ↑ Submaxillary gland weight and acinar hypertrophy at 200 mg/kg/day. ↑ CYP content and microsomal enzyme activities at all doses. NOAEL: 70 mg/kg/day
Dog, Beagle	Oral, capsule	9 months	0, 20, 70, 200	Mucous in faeces (all doses), salivation, vomiting, abnormal gait, difficulty standing, rigidity, limb weakness, head shakes, vocalization and hypoactivity at the higher doses. ↓ Body weight (females), ↑ platelet counts, ↑ alkaline phosphatase, ↑ liver weight with reversible hepatocellular hypertrophy, ↑ submaxillary gland weight and acinar hypertrophy at 200 mg/kg/day. ↑ CYP content and microsomal enzyme activities at all doses. NOAEL: 70 mg/kg/day
Dog, Beagle	Oral, capsule	9 months	0, 20, 70, 200 (given as b.i.d.)	Excessive salivation and reddening of the inner ear skin. And ↑ alkaline phosphatase at the higher doses. NOAEL: 200 mg/kg/day

A/G = albumin/globulin; MCV = mean corpuscular volume; MCH = mean corpuscular haemoglobin; BUN = blood urea nitrogen; RBC = red blood cells; SD = Sprague Dawley; NOAEL = no observed adverse effect level.

Reproductive Toxicity

Reproductive toxicology studies demonstrated no adverse effects of pirfenidone on male and female fertility or postnatal development of offspring in rats. Rats exhibited prolongation of the estrus cycle and an increased incidence of irregular cycles at higher doses (≥450 mg/kg/day).

Prolonged gestation and reduced fetal viability were observed in rats at high doses (≥1000 mg/kg/day). The placental transfer of pirfenidone and/or its metabolites occurred in animals with the potential for their accumulation in amniotic fluid. Dose-related increases in fetal incidences of soft tissue variations and skeletal variations were observed but were considered related to lower maternal food consumption and body weight. There was no evidence of teratogenicity in rats or rabbits at doses up to 4-fold higher than the clinical dose. Pirfenidone and/or its metabolites were also excreted in milk in lactating rats.

Table 8: Reproductive Toxicity

Species and Strain	Route	Duration	Doses (mg/kg/day)	Results
Rat, SD	Oral, diet	50–69 days: Premating (28 days M and 14 days F) to Gestation Day 20	0, 450, 900	↓ Body weight and food consumption at both dose levels. ↓ Gravid uterine weights and foetal body weights. NOAEL (fertility and foetal development): 900 mg/kg/day.
Rat, SD	Oral, gavage	50–69 days: Premating (28 days M and 14 days F) to Gestation Day 17	0, 50, 150, 450, 1000	Transient hypoactivity, ptosis, limb weakness, abnormal gait, and hypopnea (both sexes) at 150, 450, and 1000 mg/kg/day. Dose-related prolongation of estrus cycle and high incidence of irregular cycles at 450 and 1000 mg/kg/day. NOAEL (reproductive toxicity, males): 1000 mg/kg/day NOAEL (reproductive toxicity, females): 150 mg/kg/day NOAEL (foetal development): 1000 mg/kg/day
Rabbit, Japanese white	Oral, gavage	Gestation Days 6 to 18	0, 30, 100, 300	Transient accelerated respiration, prone position, dilation of auricular blood vessels, sluggish startle reaction, ear drop, scant feces, salivation, and ptosis at 100 and 300 mg/kg/day. ↓ Food consumption and ↓ body weight gain. One animal at 100 mg/kg/day delivered prematurely on Day 28 and two animals aborted (Day 24 and Day 26) and another died (Day 27) at 300 mg/kg/day. NOAEL (reproductive toxicity): 30 mg/kg/day NOAEL (foetal development): 300 mg/kg/day
Rat, SD	Oral, gavage	Gestation Day 7 to Lactation Day 20	0, 100, 300, 1000	F_0: ↓ activity, respiratory inhibition, salivation, and lacrimation at all doses. Prolongation of gestation period at 1000 mg/kg/day (22.7 days versus 22.2 days in

Species and Strain	Route	Duration	Doses (mg/kg/day)	Results
		(postpartum)		control) and decreased foetal viability. F_1: ↓ Body weights during pre-weaning period at 300 and 1000 mg/kg/day. F_2: no effect on litter size.

Genotoxicity and Photogenotoxicity

Pirfenidone showed no genotoxic potential in standard *in vitro* and *in vivo* genotoxicity assays. However, under UV exposure, pirfenidone was positive in a photoclastogenic assay in Chinese hamster lung cells but was not mutagenic in the Ames test. The metabolite 5-carboxy- pirfenidone was not photomutagenic or photoclastogenic in similar assays.

Table 9: Genotoxicity and Photogenotoxicity

Type of Study	Test System	Method of admin.	Doses	Results
Ames	*S. typhimurium*, *E. coli*	*In vitro*	100–5000 µg/plate	Negative
Chromosome Aberration	Chinese hamster ovary cells	*In vitro*	1000–2800 µg/mL (no activation) 500–1400 µg/mL (with activation)	Negative
Chromosome Aberration	Chinese hamster lung cells	*In vitro*	231–1850 µg/mL (with and without activation) 116–925 µg/mL (without activation, 48 hr exposure)	Negative
Bone marrow micronucleus	Mouse, ICR	Oral, gavage (single dose)	200, 400, 800 mg/kg	Negative
Liver UDS	Rat, F344	Oral, gavage (single dose)	1000, 2000 mg/kg	Negative
Ames	*S typhimurium* strains TA102 and TA98, *E coli* strain WP2/pKM101	*In vitro*	39.1–5000 µg/plate (without activation, with UV exposure)	Negative
Chromosome Aberration	Chinese hamster lung cells	*In vitro*	560–1900 µg/mL (without activation, in the absence of UV exposure)	Negative
Chromosome Aberration	Chinese hamster lung cells	*In vitro*	1–120 µg/mL (without activation, with UV exposure)	Positive

UDS = Unscheduled DNA synthesis

Carcinogenicity

In long term studies, an increased incidence of liver tumours (hepatocellular adenoma) was observed in mice (≥800 mg/kg/day) and rats (≥750 mg/kg/day). At a pirfenidone dose of 1500

mg/kg/day (4-fold higher than the clinical dose), a statistically significant increase in uterine adenocarcinoma was observed in female rats. The results of mechanistic studies indicated that the occurrence of uterine tumours may be related to a chronic dopamine-mediated sex hormone imbalance involving a species specific endocrine mechanism in the rat which is not present in humans. The relevance of these findings to humans is unknown.

Table 10: Carcinogenicity

Species and Strain	Route	Duration	Doses (mg/kg/day)	Results
Mouse, $B6C3F_1$	Oral, diet	104 weeks	0, 800, 2000, 5000	↑ Liver tumours at all doses (both sexes): considered to be a rodent species-specific non-genotoxic effect due to hepatic CYP induction.
Rat, F344	Oral, diet	104 weeks	0, 375, 750, 1500	↑ Liver tumours at all doses (both sexes): considered to be rodent species-specific non-genotoxic effect due to hepatic CYP induction. ↑ uterine tumours at 1500 mg/kg/day: considered to be rodent species-specific due to chronic dopamine-mediated sex hormone imbalance.

Phototoxicity

Pirfenidone was phototoxic in guinea pigs and mice inducing transient erythema at doses 4-fold higher than the clinical dose (based on C_{max}). Sunscreens with SPF 50+ prevented pirfenidone induced phototoxicity in guinea pigs.

Table 11: Phototoxicity and Photosensitivity

Species and Strain	Route	Duration	Doses (mg/kg/day)	Results
Guinea pig, Hartley	Oral, gavage/ topical	1 day/ 2 weeks	0, 40, 160 (oral); 0%, 1%, 5% (topical)	No phototoxicity or photosensitivity
Guinea pig, Hartley	Oral, gavage	3 days	0, 2.5, 10, 40, 160	Reversible phototoxic effects.
Guinea pig, Hartley	Oral, gavage	Single dose	0, 160	Severity of phototoxic lesions ↓ over time after UV exposure and was minimal at 6 hours post-dose.
Guinea pig, Hartley	Oral, gavage	Single dose	0, 160	Severity of phototoxic lesions ↓ with ↑ grade of sunscreen. SPF 50 cream and SPF 50 lotion decreased the total toxicity score by 100% and 74%, respectively.
Mouse, HR-1 Hairless	Oral, gavage	28 days	0, 500	Local toxicity of skin: mild acanthosis and mild single cell necrosis in the epidermis of the auricle and the dorsal skin. These changes were not apparent after a 1-month recovery period.

UV = ultraviolet; SPF = sun protection factor

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PART III: CONSUMER INFORMATION

PrTEVA-PIRFENIDONE
pirfenidone tablets

This leaflet is part III of a three-part "Product Monograph" published when TEVA-PIRFENIDONE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TEVA-PIRFENIDONE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
TEVA-PIRFENIDONE is used for the treatment of idiopathic pulmonary fibrosis (IPF) in adults.

What it does:
How TEVA-PIRFENIDONE works is not yet fully understood. It may reduce inflammation and fibrosis in your lungs. It may slow down worsening of your IPF.

When it should not be used:
- If you are allergic to pirfenidone or any of the other ingredients in this medicine.
- If you have previously experienced angioedema with pirfenidone, including symptoms such as swelling of the face, lips and/or tongue which may be associated with difficulty breathing or wheezing.
- If you have severe or end-stage liver disease.
- If you have severe or end-stage kidney disease or you require dialysis.
- If you are taking:
  - fluvoxamine to treat depression and obsessive compulsive disorder (OCD)
- Tell your doctor or pharmacist if you are taking fluvoxamine. A different medication should be prescribed for you before you begin taking TEVA-PIRFENIDONE.

What the medicinal ingredient is:
Pirfenidone

What the nonmedicinal ingredients are:
Black iron oxide, colloidal silicon dioxide, croscarmellose sodium, iron oxide red (801 mg), iron oxide yellow, macrogol (polyethylene glycol), magnesium stearate, microcrystalline cellulose, polyvinyl alcohol-part hydrolyzed, povidone, talc, and titanium dioxide

What dosage forms it comes in:
TEVA-PIRFENIDONE 267 mg is a **yellow**, biconvex, oval shaped film-coated tablet, debossed with "3610" on one side, and "TEVA" on the other side

TEVA-PIRFENIDONE 801 mg is a **purple,** biconvex, oval shaped film-coated tablet, debossed with "3611" on one side and "TEVA" on the other side

WARNINGS AND PRECAUTIONS

BEFORE you use TEVA-PIRFENIDONE talk to your doctor or pharmacist if you:
- Are taking fluvoxamine. Do not take TEVA-PIRFENIDONE with fluvoxamine.
- Are taking ciprofloxacin. A dose adjustment may be required if you take ciprofloxacin with TEVA-PIRFENIDONE.
- Are taking any other medications, obtained with or without a prescription, drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.
- Are normally exposed to direct or indirect sunlight.
- Have liver or kidney problems or disease.
- Are pregnant or planning to become pregnant. It is not known whether taking TEVA-PIRFENIDONE may be harmful to an unborn baby.
- Are breastfeeding or planning to do so. It is not known if TEVA-PIRFENIDONE passes into breast milk.

Driving and using machines:
Before you perform tasks which may require you to be alert and coordinated, wait until you know how you will respond to TEVA-PIRFENIDONE. Dizziness and tiredness can occur when you take TEVA-PIRFENIDONE. Taking TEVA-PIRFENIDONE with food may decrease dizziness. Be careful when driving or using machines.

Increased sensitivity to sunlight:
You may become more sensitive to sunlight when taking TEVA-PIRFENIDONE.
You should:
- Avoid (not take) other medicines which may make you more sensitive to sunlight. Ask your pharmacist if you are not sure.
- Avoid or minimize exposure to direct or indirect sunlight, including through windows and from sunlamps.
- Wear an effective sunblock daily (at least SPF 50, against UVA and UVB).
- Wear clothing that protects against sun exposure such as a wide-brimmed hat and long sleeves.
- Seek shade.

TEVA-PIRFENIDONE can cause weight loss. Your doctor will monitor your weight while you are taking this medicine.

Do not drink grapefruit juice during the time that you are taking TEVA-PIRFENIDONE. Grapefruit juice may prevent TEVA-PIRFENIDONE from working properly.

Do not smoke before and during treatment with TEVA-PIRFENIDONE. Cigarette smoking may reduce the effect of TEVA-PIRFENIDONE.

INTERACTIONS WITH THIS MEDICATION

Severe Drug Interactions can occur if TEVA-PIRFENIDONE is taken in combination with some other medications. In particular, do not take TEVA-PIRFENIDONE with **fluvoxamine.**

If you currently take fluvoxamine, a different medication should be prescribed for you before you begin taking TEVA-PIRFENIDONE.

Be sure to tell your doctor or pharmacist about **all** the medicines you take (including medicines obtained without a prescription, drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines), especially the medicines listed below.

- Amiodarone, mexiletine or quinidine to treat abnormal heart rhythm
- Bupropion, duloxetine, fluoxetine, moclobemide, or paroxetine to treat depression and/or anxiety
- Carbamazepine or phenytoin to treat seizure
- Cinacalcet to treat parathyroid condition
- Ciprofloxacin to treat bacterial infection
- Esomeprazole or omeprazole to treat heartburn
- Fluconazole, miconazole, terbinafine, or voriconazole to treat fungal infections
- Methoxsalen to treat skin conditions such as psoriasis
- Oral contraceptives (the Pill for birth control)
- Rifampin, a type of antibiotic, to treat bacterial infection

Ask your doctor or pharmacist for advice before taking any medications while you are taking TEVA-PIRFENIDONE.

PROPER USE OF THIS MEDICATION

TEVA-PIRFENIDONE should only be prescribed and monitored by physicians with the appropriate training and experience in the diagnosis and treatment of IPF.

Always take TEVA-PIRFENIDONE exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Swallow the tablets:

- Whole
- With a drink of water
- With food or during or after a meal to reduce the risk of side effects such as persistent stomach problems and dizziness (see **Serious Side Effects, How Often They Happen and What to Do About Them**)

Usual adult dose:

TEVA-PIRFENIDONE is usually prescribed in increasing doses as follows:

- 267 mg tablets are **yellow** in colour.
- 801 mg tablets are **purple** in colour.
  - **Days 1 to 7:** Take 1 **yellow** tablet three times a day with food (a total of 3 tablets a day or 801 mg a day)
  - **Days 8 to 14:** Take 2 **yellow** tablets three times a day with food (a total of 6 tablets a day or 1602 mg a day)
  - **Day 15 and onwards:** Take 3 **yellow** tablets three times a day with food **OR** take 1 **purple** tablet three times a day with food (a total of 2403 mg a day).

Your doctor may reduce your dose if you have:

- skin reactions to sunlight or sun lamps.
- significant changes to your liver enzymes.
- stomach problems.

If your stomach problems do not get better, your doctor may stop treatment with TEVA-PIRFENIDONE.

If you have not taken TEVA-PIRFENIDONE for 14 days or more in a row:

- your doctor will restart your treatment with the lowest dose.
- the dose will be gradually increased over 2 weeks to the usual dose.

Overdose:

If you think you have taken too much TEVA-PIRFENIDONE, contact your health care professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If a dose is missed, the next dose should be taken as originally planned. Double doses should not be taken to make up for forgotten doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- **Increased Sensitivity to Sunlight:** skin reactions after going out in the sun or using sunlamps, sunburn
- Skin problems such as **rash**, itchy skin, skin redness, dry skin
- Tiredness, feeling weak or feeling low in energy
- Indigestion, heartburn, acid reflux, loss of appetite, anorexia, changes in taste, bloating, abdominal pain and discomfort
- Infections of the throat or the airways going into the lungs and/or sinusitis, influenza and/or common cold
- Difficulty sleeping, feeling sleepy
- Headache
- Muscle pain, aching joints/joint pains
- Weight loss

If any of these affects you severely, tell your doctor or pharmacist.

TEVA-PIRFENIDONE may cause liver problems and other abnormal blood test results. To check whether your liver is working properly and your other blood levels you will need blood tests. Blood tests should be done before you start taking TEVA-PIRFENIDONE, at monthly intervals for the first 6 months and then every three months while you are taking this medicine. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Common	**Increased Sensitivity to Sunlight:** skin reaction/**rash** to sunlight, blistering and/or marked peeling of the skin	✓		
	Diarrhoea	✓		
	Fatigue	✓		
	Persistent Stomach Problems: such as nausea, vomiting	✓		
Common	**Dizziness**		✓	
Uncommon	**Liver Problems (abnormal blood test results related to your liver):** yellow skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite			✓
	Angioedema: swelling of the face, lips and/or tongue, difficulty breathing or wheezing			✓
Rare	**Allergic Reaction: rash,** hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Unknown	**Chest pain (angina),** slow, fast or irregular heart beats			✓

This is not a complete list of side effects. For any unexpected effects while taking TEVA-PIRFENIDONE contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of the reach and sight of children.
Store at room temperature (15 – 30ºC).

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph prepared for health professionals can be found by contacting Teva Canada Limited at:
Phone: 1-800-268-4127 ext. 3;
Email: druginfo@tevacanada.com; or
Fax: 1-416-335-4472

This leaflet was prepared by:
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Last revised: May 17, 2021