New Drugs to Treat Idiopathic Pulmonary Fibrosis: Esbriet and Ofev

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Goal. The goal of this lesson is to provide information on idiopathic pulmonary fibrosis, and two recently approved drugs to treat it: nintedanib (Ofev®) and pirfenidone (Esbriet®).

Objectives. At the completion of this activity, the participant will be able to:

1. recognize signs and symptoms, and key features of idiopathic pulmonary fibrosis (IPF) including information on its prevalence and prognosis;
2. list pharmacologic and nonpharmacologic treatments used historically to treat IPF;
3. recognize the pharmacologic actions, clinical applications, dosage, and route of administration for the new drugs;
4. demonstrate an understanding of adverse effects and toxicity, warnings, precautions, contraindications, and significant drug-drug interactions reported for the new drugs; and
5. list important information to convey to patients and/or their caregivers.

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and ultimately fatal form of interstitial lung disease of unknown origin, characterized by destruction of the gas-exchanging regions of the lung. Although periods of transient stability may be observed, continued progression of pulmonary scarring by the disease is inevitable. With a median survival of three years after diagnosis, IPF carries a prognosis worse than many cancers. In contrast to many cancers, there is limited, and sometimes conflicting, evidence that any drug could alter the course of this devastating disease.

This lesson discusses important facts relative to IPF and provides a brief introduction to pharmacologic and nonpharmacologic measures used in its treatment, with focus on two newer therapies – nintedanib (Ofev®) and pirfenidone (Esbriet®). The lesson is not intended to extend beyond an overview of the topic. The reader is, therefore, urged to consult the full Prescribing Information leaflets (package inserts) of the products and other published reference sources for more detailed descriptions.

Background

Epidemiology. IPF (also called cryptogenic fibrosing alveolitis) is the most common of the idiopathic interstitial lung diseases. Its incidence in the United States is estimated to be seven to 17 per 100,000 persons per year, while prevalence appears to be between 20 to 60 per 100,000. The age at diagnosis of IPF is usually between 50 and 85 years. IPF is uncommon in persons less than 50 years of age; this population accounts for 2 to 15 percent of those diagnosed with this disorder. More men than women are reported with IPF, with a male:female ratio of approximately 1.5:1.

Pathogenesis. The pathogenesis of IPF remains obscure. Both genetic and environmental factors have been implicated as causes. Once considered to be a relentless inflammatory process, the lack of efficacy of anti-inflammatory drug therapy including high-dose corticosteroids has cast serious doubt on the role of chronic inflammation in development of fibrosis in the disease.

The label idiopathic requires exclusion of known causes of pulmonary fibrosis. Such causes include underlying connective tissue diseases in which respiratory symptoms can occasionally precede other systemic manifestations; domestic or environmental exposure such as organic and inorganic dusts; radiation therapy; and pro-fibrotic drugs such as amiodarone and nitrofurantoin, which in a genetically predisposed individual, can lead to activation of abnormal pathways, resulting in failed resolution of the wound-healing response. Genetic predisposition to IPF is supported by familial clustering, occurrence of lung fibrosis in genetic multisystem disorders, and differing susceptibilities in humans exposed to similar levels of fibrogenic agents.

Recurrent or persistent alveolar epithelial injury with dysregulated repair is currently believed...
to be the major mechanism leading to progressive pulmonary fibrosis. Mechanisms underlying the recruitment and proliferation of myofibroblasts and fibrosis progenitor cells, as well as their pathologic differentiation, remain elusive, but it is thought there are a large number of mediators involved. These include cytokines, chemokines, coagulant proteins, fibrogenic factors, oxidants, and regulators of apoptosis. Deposition of extracellular matrix components, including collagen, is likely integral to this fibrotic process. Age-related biological changes probably play an important role as well, given that IPF usually afflicts middle-aged to older persons. These processes may lead to premature aging of alveolar cells with exhaustion of precursor cells required for alveolar regeneration, thus resulting in abnormal repair via fibrosis. The role of mechanical stress such as recurrent friction forces on the periphery of the aging lung may be a major factor in development of pulmonary fibrosis.

A number of environmental exposures such as organic and inorganic dusts, drug therapies, other medical disorders, and microbial agents such as Epstein-Barr virus are also potential risk factors. As a conservative estimate, about two-thirds of IPF patients are smokers. Despite a large number of studies reporting these associations, the etiologic role of these agents in the pathogenesis of IPF remains unknown.

The potential role of gastroesophageal reflux disease (GERD) and microaspiration of gastric contents has gained interest as a potential instigator in the pathogenesis of IPF. GERD is highly prevalent in patients with IPF, commonly seen in up to 94 percent of cases, and appears to be more frequent in these persons compared with those who have other lung diseases including asthma. The use of acid-suppressive therapy has been associated with longer survival in patients with IPF and a slowing in the rate of decline in pulmonary function.

**Clinical Considerations.** A typical patient with IPF is older than 50 years and presents with a gradual onset of symptoms such as progressively worsening dyspnea and cough, with or without sputum, that limit physical activity and reduce the patient’s quality of life and independence. Other less common symptoms may include chest discomfort or constitutional features such as fatigue, low-grade fever, or weight loss. Some patients may present with abnormal radiologic findings or pulmonary function abnormalities in the absence of respiratory symptoms. Nearly all patients with IPF have bibasilar respiratory crackles that are described as “Velcro-like.” Approximately one-half of patients manifest digital clubbing. Physical signs of pulmonary hypertension and cor pulmonale may be observed in patients with advanced disease. Cyanosis is a late manifestation.

As noted earlier, median survival for patients with IPF is estimated to be approximately three years after diagnosis, with only about one-third of patients surviving after five years. While many persons with IPF experience gradual progression of their lung disease associated with increasing exertional dyspnea and functional limitation, the clinical course of individual patients is often unpredictable. Some may experience little or no clinical worsening over months to years. Others encounter unexpected acute deteriorations or exacerbations of symptoms related to progressive respiratory insufficiency and comorbidities that are often fatal.

**Diagnosing IPF.** A diagnosis of IPF is one of exclusion of other pathologies since many, including other idiopathic interstitial lung disease such as nonspecific interstitial pneumonitis, can mimic the above clinical presentation. Some conditions that resemble IPF include interstitial lung diseases related to connective tissue disorders such as rheumatoid arthritis, scleroderma, systemic lupus erythematosus, and progressive systemic sclerosis, and conditions triggered by environmental exposures such as chronic hypersensitivity pneumonitis. An accurate confirmation of the diagnosis relies on all available clinical, radiological, and histological data, and is important considering the prognosis. More importantly, no therapy, prior to approval of the two new drugs, has been shown to reverse, halt, or delay the progression of disease in IPF in large, well-conducted, double-blind, placebo-controlled, prospective clinical trials.

A number of staging systems have been proposed to enhance accuracy of prognosis, but none have yet gained wide clinical acceptance. In one study investigating the immediate cause of death in 42 patients with IPF, respiratory failure was to blame in 64 percent, cardiovascular events in 21 percent, and noncardiopulmonary events in 14 percent. Acute exacerbation of IPF was the most common immediate cause of death at 29 percent. Pneumonia, aspiration, and drug-induced pulmonary disease were identified as other causes of respiratory death.

**Treatment**

**Pharmacologic Agents.** Despite advancements achieved over the years in understanding the pathogenesis of IPF, pharmacological treatment options remain limited. Traditional therapy for IPF stemmed from historic trials and consisted of corticosteroids alone or in conjunction with azathioprine or cyclophosphamide in the belief that uncontrolled chronic inflammation was the predominant underlying mechanism that led to development of progressive parenchymal fibrosis. Today it is clear that treatment regimens predominantly aimed at reducing lung inflammation do not appear to be efficacious. Pharmacologic agents with antifibrotic properties such as colchicine have been used, but have not yielded clinically relevant benefit. Interferon gamma inhibits proliferation of lung fibroblasts that
down-regulate the transcription of transforming growth factor β1, but neither improves survival nor quality of life outcome measures. There is a decreased presence of glutathione, one of the major pulmonary antioxidants, in epithelial lining fluid in patients with IPF. Oral N-acetylcysteine (NAC) is a glutathione precursor and has been given to increase glutathione levels. Results of clinical trials evaluating NAC for efficacy are pending.

Other pharmacological agents studied for IPF include warfarin, but it has not demonstrated benefit. Similarly ineffective remedies include etanercept, imatinib, bosentan, macitentan, ambrisentan, and sildenafil.

A recent study showed that the use of gastric acid suppressive agents (e.g., proton pump inhibitors, etc.) in patients with IPF was associated with a slower rate of decline in pulmonary function and longer survival.

Supportive Care. Nonpharmacologic therapy can be beneficial to patients with IPF. As the disease progresses, supplemental oxygen improves dyspnea and exercise tolerance for those with resting hypoxemia or notable oxygen desaturation with exercise while breathing room air.

Other supportive measures include optimizing nutritional status and keeping up-to-date with immunizations. Studies note that sleep apnea is common in IPF. This should be considered and continuous positive airway pressure therapy offered when appropriate. Deconditioning is a common problem for patients with chronic diseases such as IPF and can exacerbate functional and psychosocial impairments. Pulmonary rehabilitation can improve symptoms, walk distance, and quality of life.

Lung Transplantation. Lung transplantation in persons with IPF is the closest available treatment to a cure for IPF. It prolongs life in patients with end-stage IPF, reportedly extending a five-year survival rate by 40 to 50 percent. The surgery poses significant risks. Infection due to the need for immunosuppression therapy, acute or chronic graft rejection, and airway stenosis are common causes of poor long-term survival. These problems and drug-related adverse events limit the usefulness of lung transplantation. The accepted cut-off age for lung transplantation is 65 years, with exceptions based on patient function and comorbidities. The presence of other medical conditions in older individuals who make up the majority of patients with IPF and the shortage of available donors greatly limit access to lung transplantation in patients with this disease.

Pulmonary Rehabilitation. Benefits of physical rehabilitation have not been widely studied; however, pulmonary rehabilitation is considered important in re-establishing and maintaining aerobic and physical fitness. Training involves breathing exercises, physical conditioning, and anxiety and depression management. Similar to the necessity of counseling patients to convey a strong understanding of their treatment options, pulmonary rehabilitation is most essential in helping patients manage their condition and maintain the highest quality of life possible.

Cough Suppression. Cough is a major symptom of IPF impacting the patient’s quality of life, and one of the most difficult to treat. Approximately one-half of the cases of chronic cough in IPF can be attributed to more common causes such as hyper-responsive airways, gastroesophageal reflux and rhinosinusitis. Management of cough should, therefore, include a careful evaluation of other causes of chronic cough. Common treatments with both opioid and non-opioid drugs often fail. Ironically, systemic steroids that have no significant impact on the course of IPF may be effective in mitigating cough in this disease.

Recently Approved Drugs
In 1868, a respiratory condition called “chronic pneumonitis” along with bulbous appearance of patient’s fingertips was noted in the medical literature. This was

### Table 1
Selected new drugs

<table>
<thead>
<tr>
<th>Generic (Trade Name)</th>
<th>Distributor</th>
<th>Dose*</th>
<th>Dosage Form</th>
<th>Most Common Side Effects</th>
<th>Medication Guide*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nintedanib (Ofev)</td>
<td>Boehringer Ingelheim Pharmaceuticals</td>
<td>150 mg two times daily</td>
<td>100 mg, 150 mg capsules</td>
<td>(≥5%): diarrhea, nausea, abdominal pain, vomiting, liver enzyme elevation, decreased appetite, headache, weight decrease, hypertension</td>
<td>No</td>
</tr>
<tr>
<td>Pirfenidone (Esbriet)</td>
<td>InterMune Pharmaceuticals</td>
<td>801 mg three times daily</td>
<td>267 mg capsules</td>
<td>(≥10%): nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, anorexia, gastroesophageal reflux disease, sinusitis, insomnia, weight decrease, arthralgia</td>
<td>No</td>
</tr>
</tbody>
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*Recommended dose for most patients  
*Availability at the time of publication of this lesson
probably the first recorded case of IPF. Now, nearly 150 years later, medical science is at last starting to make some progress in understanding and treating this devastating and lethal disease.

Two new drugs were approved for treatment of IPF in October, 2014 (Table 1). FDA granted fast track, priority review, orphan product, and breakthrough designations to both drugs. Both were also approved ahead of the date the Agency was scheduled to complete its review of each drug's application for approval. The two drugs differ in their basic pharmacology, but both reduce the decline in pulmonary function and preserve quality of life.

**Nintedanib (Ofev)**

**Mechanism of Action.** Nintedanib is a potential inhibitor of multiple receptor tyrosine kinases and non-receptor tyrosine kinases. It inhibits the following receptor kinases: platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, vascular endothelial growth factor receptor (VEGFR) 1-3, and Fms-like tyrosine kinase-3 (FLT3). Among these, FGFR, PDGFR, and VEGFR have been implicated in IPF pathogenesis. Nintedanib binds competitively to the adenosine triphosphate binding pocket of these receptors and blocks the intracellular signaling that is crucial for the proliferation, migration, and transformation of fibroblasts representing essential mechanisms of the IPF pathology.

**Efficacy and Safety.** Safety and effectiveness were established in three clinical trials of 1,231 patients with IPF. The annual rate of decline in forced vital capacity – the amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible – was significantly reduced in patients receiving Ofev (OH-fev), compared to patients receiving placebo. No overall differences in effectiveness were observed between subjects who were 65 years and over and younger subjects; no overall differences in safety were observed between subjects who were 65 years and over, or 75 years and over, and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Ofev is not recommended for patients who have moderate to severe liver defects. The drug can cause fetal harm if pregnancy occurs. Women should be apprised of the potential for fetal harm. Women should not become pregnant while taking the drug. Women of child-bearing age should use adequate contraception during, and for at least three months after the last dose of Ofev.

Diarrhea was the most frequent gastrointestinal adverse reaction reported in 62 percent versus 18 percent of patients treated with Ofev or placebo, respectively. In most cases, diarrhea was mild to moderate, and occurred within the first three months of treatment.

**Warnings, Precautions, and Contraindications.** The following warnings and precautions are listed:

- **Elevated liver enzymes:** AST, ALT, and bilirubin elevations have occurred with Ofev. Monitor AST, ALT, and bilirubin before and during treatment. Temporary dosage reduction or discontinuation may be required.

- **Gastrointestinal disorders:** Diarrhea, nausea, and vomiting have occurred with Ofev. Treat patients at first signs with adequate hydration and anti-diarrheal medications (e.g., loperamide) or anti-emetics. Discontinue Ofev if severe diarrhea, nausea, or vomiting persists despite symptomatic treatment.

- **Embryofetal toxicity:** Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant.

- **Arterial thromboembolic events.** Use caution when treating patients at higher cardiovascular risk including known coronary artery disease.

- **Risk of bleeding events:** Use Ofev in patients with known bleeding risk only if anticipated benefit outweighs the potential risk.

**Drug Interactions.** Nintedanib is a substrate of P-glycoprotein (P-gp) and, to a minor extent, CYP3A4. In drug-drug interaction studies, coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60 percent. Therefore, concomitant use of P-gp and CYP3A4 inhibitors (e.g., erythromycin) with Ofev may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of Ofev.

In other studies, coadministration with oral doses of a P-gp and the CYP3A4 inducer rifampicin decreased exposure to nintedanib by 50 percent. Therefore, concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John’s wort) with Ofev should be avoided as these drugs may decrease exposure to nintedanib.

Nintedanib is a VEGFR inhibitor, and, thus, may increase the risk of hemorrhage. Monitor patients on anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary.

**Administration, Dosing, and Availability.** The recommended dosage is 150 mg twice daily taken with food, administered approximately 12 hours apart. If a dose is missed, the next dose should be taken at the next scheduled time. Liver function tests should be undertaken prior to initiating treatment with Ofev, and dosage modification or temporary interruption is necessary due to adverse reactions or liver enzyme elevations. Ofev treatment may be resumed at the
Inform patients:
• to read the FDA-approved Patient Information leaflet;
• that they will need to undergo liver function testing periodically. Immediately report any symptoms of liver problems (e.g., skin or the whites of eyes turn yellow, urine turns dark or brown [tea colored], pain on the right side of stomach, bleeding or bruising more easily than normal, lethargy);
• that gastrointestinal disorders such as diarrhea, nausea, and vomiting are commonly reported. They should drink plenty of fluids and contact their doctor if these disorders do not go away or become worse;
• that pregnancy prevention is needed. Females of childbearing potential should avoid becoming pregnant while receiving treatment with Ofev. They should use adequate contraception during treatment and for at least three months after taking the last dose of Ofev, and should notify their doctor if they become pregnant during therapy with Ofev;
• to discontinue nursing while taking Ofev or discontinue Ofev while nursing;
• about the signs and symptoms of acute myocardial ischemia and other arterial thromboembolic events including hemorrhage and the urgency to seek immediate medical care for these conditions;
• to stop smoking prior to treatment with Ofev and avoid smoking when taking Ofev because smoking alters the efficacy profile of Ofev;
• to swallow Ofev capsules whole with liquid, and not to chew or crush the capsules due to their bitter taste;
• not to take a missed dose, but continue administration at the next regularly scheduled time. The recommended maximum daily dosage of 300 mg should not be exceeded;
• to keep prescription containers of Ofev in a cool place and tightly closed, and out of the reach of children.

* A complete list of information is available in the product’s Prescribing Information leaflet.

full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If a patient does not tolerate 100 mg twice daily, discontinue treatment with Ofev.

Ofev capsules should be taken with food and swallowed whole with liquid. The capsules should not be chewed or crushed because of a bitter taste. The effect of chewing or crushing of the capsule on the pharmacokinetics of nintedanib is not known.

Ofev is available in 100 mg and 150 mg soft capsules. They should be stored at 25°C (77°F), with excursions permitted to 15° to 30°C (59° to 86°F), and protected from exposure to high humidity and excessive heat. If repackaged, USP tight containers should be used.

**Patient Counseling.** Specific points for patient counseling for Ofev are summarized in Table 2.

### Pirfenidone (Esbriet)

**Mechanism of Action.** Pirfenidone has antifibrotic, anti-inflammatory, and antioxidant properties that act on multiple pathways that may be involved in the scarring of lung tissue. The mechanism of action of pirfenidone in the treatment of IPF, and the specific receptor(s), have not been established.

**Efficacy and Safety.** Pirfenidone’s safety and effectiveness were established in three clinical trials of 1,247 patients with IPF. The decline in forced vital capacity was significantly reduced in patients receiving pirfenidone compared to patients receiving placebo. No overall differences in safety or effectiveness were observed between older and younger patients. No dosage adjustment is required based upon age.

Esbriet (es-BREE-et) is not recommended for patients who have severe liver problems, end-stage kidney disease, or who require dialysis. The drug should be taken with food to minimize the potential for nausea and dizziness.

The most common gastrointestinal events that led to dosage reduction or interruption in pre-marketing studies were nausea, diarrhea, vomiting, and dyspepsia.

The incidence of gastrointestinal events was highest early in the course of treatment (with highest incidence occurring during the initial three months) and decreased over time.

**Warnings, Precautions, and Contraindications.** The following warnings and precautions are listed:

• *Elevated liver enzymes:* ALT, AST, and bilirubin elevations have occurred with Esbriet. Monitor ALT, AST, and bilirubin before and during treatment. Temporary dosage reduction or discontinuation may be required.

• *Photosensitivity and rash:* Photosensitivity and rash have been noted with Esbriet. Avoid exposure to sunlight and sunlamps. Wear sunscreen and protective clothing daily. Temporary dosage reduction or discontinuation may be required.

No contraindications are noted.

**Drug Interactions.** Pirfenidone is metabolized primarily (70 to 80 percent) via CYP1A2. Minor contributions from other CYP isoenzymes include CYP2C9, 2C19, 2D6, and 2E1.

Concomitant administration of Esbriet and fluvoxamine or other strong CYP1A2 inhibitors (e.g., enoxacin) is not recommended because it significantly increases exposure to pirfenidone. Fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of Esbriet and avoided during Esbriet treatment. If fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended.

Concomitant administration of Esbriet and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to Esbriet. If ciprofloxacin at the dos-
The concomitant use of Esbriet and a CYP1A2 inducer may decrease the exposure of pirfenidone and thus lead to loss of efficacy. Therefore, discontinue use of strong CYP1A2 inducers prior to Esbriet treatment and avoid the concomitant use of Esbriet and a strong CYP1A2 inducer.

Administration, Dosing, and Availability. The recommended daily maintenance dosage of Esbriet is 801 mg (three 267 mg capsules) three times a day with food, for a total dose of 2403 mg/day. Upon initiation of treatment, titrate to the full dosage of nine capsules per day over a 14-day period as follows: Days 1 through 7, one capsule three times a day; days 8 through 14, two capsules three times a day; days 15 onward, three capsules three times a day. Dosages above 2403 mg/day (nine capsules per day) are not recommended. Doses should be taken at the same time each day. As with Ofev, liver function tests should be conducted prior to initiating treatment with Esbriet.

Patients who miss 14 or more days of Esbriet therapy should re-initiate treatment by undergoing the initial two-week titration regimen up to the full maintenance dosage. For treatment interruption of fewer than 14 days, the dosage prior to the interruption can be resumed.

Esbriet is available as 267 mg hard-gelatin capsules. Capsules should be stored at 25°C (77°F), with excursions of 15° to 30°C (59° to 86°F) permitted. Bottles and cartons of blister packs should be kept tightly closed. The product should not be used if the seal over the bottle opening is broken or missing.

Patient Counseling. Specific points for patient counseling for Esbriet are summarized in Table 3.

Overview and Summary
IPF is a chronic and devastating disease characterized by progressive lung fibrosis of unknown cause. Until recently, there were no drugs indicated specifically for its treatment. With FDA approval of Esbriet and Ofev, there is renewed hope on the horizon. The drugs, compared with placebo, have been shown to slow disease progression in persons with IPF, rather than simply provide palliative care.

In addition, the medical literature now suggests that it may be possible to identify persons at risk for IPF at a stage before advanced fibrotic pathology can be detected. Evidence shows that pharmacotherapy can effectively treat early stages of the disease. Thus, it may soon be possible that medical therapy could also be used to reverse, halt, or delay, rather than to solely slow, the progression of end-stage fibrotic disease.
New Drugs to Treat Idiopathic Pulmonary Fibrosis: Esbriet and Ofev

1. Age at diagnosis of IPF is usually between:
   a. 30-40 years.  
   b. 40-55 years.  
   c. 45-80 years.  
   d. 50-85 years.

2. All of the following statements about IPF are true EXCEPT:
   a. the male:female ratio is 1.5:1.  
   b. anti-inflammatory drugs are very efficacious.  
   c. idiopathic in defining pulmonary fibrosis means the cause is unknown.  
   d. both genetic and environmental factors have been implicated as causes.

3. All of the following are potential risk factors for IPF EXCEPT:
   a. smoking.  
   b. Epstein-Barr virus.  
   c. acid-suppressive therapy.  
   d. organic dusts.

4. Approximately how many IPF patients show digital clubbing?
   a. One-fourth  
   b. One-half  
   c. Three-fourths  
   d. All

5. Which of the following drugs can increase glutathione levels in patients with IPF?
   a. Colchicine  
   b. Interferon gamma  
   c. N-acetylcysteine  
   d. Warfarin

6. The closest treatment to a cure for IPF is:
   a. oxygen.  
   b. lung transplantation.  
   c. proton pump inhibitor.  
   d. interferon gamma.

7. Pulmonary rehabilitation involves all of the following EXCEPT:
   a. breathing exercises.  
   b. physical conditioning.  
   c. depression management.  
   d. vaccine administration.

8. Nintedanib inhibits which of the following enzyme systems?
   a. Phosphodiesterase  
   b. Adenyl cyclase  
   c. Monoamine oxidase  
   d. Tyrosine kinase

9. Ofev is not recommended for patients with moderate to severe disease of the:
   a. liver.  
   b. kidney.  
   c. ovaries.  
   d. thyroid.

10. The most frequent gastrointestinal adverse reaction reported in clinical trials with nintedanib was:
    a. nausea.  
    b. diarrhea.  
    c. dyspepsia.  
    d. GERD.

11. The recommended dosage for Ofev is 150 mg:
    a. daily at bedtime.  
    b. twice daily, every 12 hours, with food.  
    c. three times daily with food.  
    d. three times daily on an empty stomach.

12. Which of the following drugs given concurrently with Ofev may increase exposure to nintedanib?
    a. Carbamazepine  
    b. Erythromycin  
    c. Phenytoin  
    d. St. John’s wort

13. Esbriet is titrated over 14 days to a total daily dose of:
    a. 150 mg.  
    b. 267 mg.  
    c. 801 mg.  
    d. 2403 mg.

14. Patients should be instructed to use sunblock while taking which of the following?
    a. Ofev only  
    b. Neither Ofev nor Esbriet  
    c. Esbriet only  
    d. Both Ofev and Esbriet

15. FDA granted fast track, priority review, orphan product, and breakthrough designations for which of the following?
    a. Ofev only  
    b. Neither Ofev nor Esbriet  
    c. Esbriet only  
    d. Both Ofev and Esbriet