DECLESAU (dergrafloxacin) tablets, for oral use
DECLESAU (dergrafloxacin) injection, solution for intravenous use

WARNING: TENDON EFFECTS and EXACERBATION OF MYASTHENIA GRAVIS

Fluoroquinolones, including DECLESAU, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in patients over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants [see Warnings and Precautions (5.1)].

Fluoroquinolones, including DECLESAU, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid using DECLESAU in patients with a known history of myasthenia gravis [see Warnings and Precautions (5.2)].

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of DECLESAU and other antibacterial drugs, DECLESAU should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

DECLESAU is indicated for the treatment of adults (≥18 years of age) with infections caused by susceptible isolates of the designated bacteria in the following conditions:

- Complicated skin and skin structure infections caused by methicillin-susceptible *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, or *Enterobacter cloacae* [see Clinical Studies (14.2)].

- Uncomplicated urinary tract infections (acute cystitis) caused by *Escherichia coli*, *Proteus mirabilis*, *Enterococcus faecalis*, or *Staphylococcus saprophyticus* [see Clinical Studies (14.3)].

4 CONTRAINDICATIONS

DECLESAU is contraindicated in patients with a history of hypersensitivity (e.g., anaphylaxis) to dergrafloxacin, any of the fluoroquinolone class of antimicrobial agents, or any of the product components [see Warnings and Precautions (5.3)].
5 WARNINGS AND PRECAUTIONS

5.1 Tendinopathy and Tendon Rupture

Fluoroquinolones, including DECLESAU, are associated with an increased risk of tendinitis and tendon rupture in all ages. Advise patients to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-fluoroquinolone antimicrobial drug. Discontinue DECLESAU if the patient experiences pain, swelling, inflammation or rupture of a tendon.

This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported.

The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in patients over 60 years of age, in those taking corticosteroid drugs, and in patients with kidney, heart, or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported.

5.2 Exacerbation of Myasthenia Gravis

Fluoroquinolones, including DECLESAU, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Postmarketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid DECLESAU in patients with a known history of myasthenia gravis.

5.3 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving fluoroquinolone therapy, including DECLESAU. These reactions often occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat, or facial edema/swelling), airway obstruction (including brochospsam, shortness of breath, and acute respiratory distress), dyspnea, urticaria, itching, and other serious skin reactions. Discontinue DECLESAU immediately at the first appearance of a skin rash or any other sign of hypersensitivity. Oxygen, intravenous steroids, and airway management, including intubation, should be administered as indicated.

5.4 Other Serious and Sometimes Fatal Reactions

Other serious and sometimes fatal reactions, some due to hypersensitivity and some due to uncertain etiology, have been reported in patients receiving therapy with fluoroquinolones, including DECLESAU. Discontinue DECLESAU immediately at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity and institute supportive measures.
Reactions may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following:

- fever, rash, or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome);
- vasculitis; arthralgia; myalgia; serum sickness;
- allergic pneumonitis;
- interstitial nephritis; acute renal insufficiency or failure;
- hepatitis; jaundice; acute hepatic necrosis or failure;
- anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

5.5 Central Nervous System Effects

Quinolones, including DECLESAU, may cause central nervous system (CNS) events, including: nervousness, agitation, insomnia, anxiety, nightmares or paranoia. Convulsions and increased intracranial pressure (including pseudotumor cerebri) have been reported in patients receiving quinolones. Quinolones may also cause CNS events including: dizziness, confusion, tremors, hallucinations, depression, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving DECLESAU, the drug should be discontinued and appropriate measures instituted. As with all quinolones, DECLESAU should be used with caution in patients with known or suspected CNS disorders (for example, severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold.

5.6 Clostridium difficile-associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including DECLESAU, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

5.7 Development of Drug Resistant Bacteria

Prescribing DECLESAU in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.
6 ADVERSE REACTIONS

The following serious and important adverse drug reactions are discussed in greater detail in other sections of labeling:

- Tendon effects [see Boxed Warning, Warnings and Precautions (5.1)]
- Exacerbation of myasthenia gravis [see Boxed Warning, Warnings and Precautions (5.2)]
- Hypersensitivity reactions [see Warnings and Precautions (5.3)]
- Other serious and sometimes fatal reactions [see Warnings and Precautions (5.4)]
- Central nervous system effects [see Warnings and Precautions (5.5)]
- *Clostridium difficile*-associated diarrhea [see Warnings and Precautions (5.6)]

The most common adverse reactions (≥3%) are abdominal pain (7%), nausea (6%), diarrhea (5%), and headache (4%).

Discontinuation of DECLESAU due to adverse drug reactions occurred in 3% of patients overall. The most common adverse drug reactions leading to discontinuation were nausea, vomiting, diarrhea, and headache.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to DECLESAU in 2954 patients in 15 pooled clinical trials. The population studied had a mean age of 48 years (approximately 77% of the population was < 65 years of age), 51% were male, 72% were Caucasian, 20% were Black. Ninety-one percent of the population received DECLESAU doses of 600 mg once daily. Treatment duration was usually 5-14 days, and the mean number of days on therapy was 7 days.

Adverse reactions occurring in ≥1% of DECLESAU-treated patients are shown below in Table 1.

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Adverse Reaction</th>
<th>% (N=2459)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Abdominal Pain</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>2</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Headache</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
<td>2</td>
</tr>
</tbody>
</table>
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

*Pregnancy Category C*

There are no adequate or well-controlled studies in pregnant women. DECLESau should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

Based on data with other fluoroquinolones and limited data with DECLESau, it can be presumed that dergrafloxacin will be excreted in human milk. Because of the potential for serious adverse reactions from DECLESau in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients and adolescents less than 18 years of age have not been established. Fluorouinolones, including dergrafloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species.

8.5 Geriatric Use

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as DECLESau. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported.

Caution should be used when prescribing DECLESau to elderly patients, especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue DECLESau and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur.

8.6 Renal Impairment

Clearance of dergrafloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in patients with impaired renal function (creatinine clearance < 50 mL/min), requiring dosage adjustment in such patients to avoid accumulation. Neither hemodialysis nor continuous ambulatory peritoneal dialysis (CAPD) is effective in removal of dergrafloxacin from the body, indicating that supplemental doses of DECLESau are not required following hemodialysis or CAPD.

8.7 Hepatic Impairment

Pharmacokinetic studies in hepatically impaired patients have not been conducted. Due to the limited extent of dergrafloxacin metabolism, the pharmacokinetics of dergrafloxacin are not expected to be affected by hepatic impairment.
14 CLINICAL STUDIES

14.1 Complicated Skin and Skin Structure Infections

A randomized, double-blind, active controlled clinical trial in patients with complicated skin and skin structure infections (cSSSI) compared the efficacy of sequential intravenous (IV)/oral (PO) DECLESAU 600 mg once daily for 7 to 14 days with an approved comparator for a mean of 10 ± 4.7 days. This study enrolled 365 patients, 295 of which were valid for the efficacy analysis. A total of 623 patients with cSSSI, 593 of whom were valid for efficacy analysis, were enrolled in a second randomized, open-label, active controlled, international study that compared DECLESAU 600 mg once daily for 10 days with an approved comparator. Surgical incision and drainage or debridement was performed in 52% of the DECLESAU-treated patients and 54% of the comparator-treated patients in these studies and formed an integral part of therapy for this indication. Success rates varied with the type of diagnosis ranging from 58% in patients with infected ulcers to 91% in patients with complicated erysipelas. These rates were similar to those seen with comparator drugs. The overall success rates in the evaluable patients and the clinical success by pathogen are shown in Tables 2 and 3.

Table 2. Overall Clinical Success Rates in Patients with Complicated Skin and Skin Structure Infections

<table>
<thead>
<tr>
<th>Study</th>
<th>DECLESAU n/N (%)</th>
<th>Comparator n/N (%)</th>
<th>95% Confidence Interval*</th>
</tr>
</thead>
<tbody>
<tr>
<td>North American</td>
<td>126/154 (80.8)</td>
<td>113/141 (80.1)</td>
<td>(-10.5%, 1.7%)</td>
</tr>
<tr>
<td>International</td>
<td>249/302 (81.5)</td>
<td>244/291 (83.8)</td>
<td>(-12.8%, 2.1%)</td>
</tr>
</tbody>
</table>

*of difference in success rates between DECLESAU and comparator (DECLESAU – comparator)

Table 3. Clinical Success Rates by Pathogen in Patients with Complicated Skin and Skin Structure Infections

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>DECLESAU n/N (%)</th>
<th>Comparator n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em> (methicillin-susceptible)</td>
<td>98/117 (83.8)</td>
<td>105/124 (84.7)</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>35/42 (83.3)</td>
<td>31/38 (81.5)</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>12/14 (85.7)</td>
<td>10/12 (83.3)</td>
</tr>
<tr>
<td><em>Enterobacter cloacae</em></td>
<td>9/12 (75)</td>
<td>11/15 (73.3)</td>
</tr>
</tbody>
</table>

14.2 Uncomplicated Urinary Tract Infections

DECLESAU was evaluated for the treatment of uncomplicated urinary tract infections (acute cystitis) in a randomized, double-blind, controlled clinical trial. A total of 894 patients were enrolled: 448 patients received DECLESAU 600 mg once daily for 10 days and 445 patients received an approved comparator. The primary efficacy variable was bacteriologic eradication of the baseline organism(s) with no new infection or superinfection at test-of-cure (TOC) visit (Day 4-11 post-therapy) (Table 4).

Table 4. Bacteriologic Eradication at Test-of-Cure

<table>
<thead>
<tr>
<th></th>
<th>Declesau n/N (%)</th>
<th>Comparator n/N (%)</th>
<th>Overall Difference [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable population</td>
<td>206/224 (91.9)</td>
<td>201/217 (92.6)</td>
<td>0.7 [-3.7%, 5.2%]</td>
</tr>
</tbody>
</table>
The clinical success rates at the TOC visit were similar between DECLESAU and the control treatment-evaluable patients: 91.1% (204/224) for DECLESAU-treated patients and 93.1% (202/217) for the control population. The 95% CI or the difference between rates (DECLESAU minus control group) was [-1.7%, 5.6%]. The bacteriologic eradication rates for specific pathogens are detailed below in Table 5.

Table 5. Bacteriologic Eradication Rates by Pathogen in Patients With an Uncomplicated Urinary Tract Infection following DECLESAU Treatment

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Bacteriologic Eradication Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>95/103 (92.2%)</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>31/35 (88.6%)</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>34/37 (91.9%)</td>
</tr>
<tr>
<td><em>Staphylococcus saprophyticus</em></td>
<td>29/32 (90.6%)</td>
</tr>
</tbody>
</table>