Effective Date: Feb 11, 2023

DIPLOSOL®

(®SALICYLIC ESTER OF SALICYLIC ACID (SESA)

DIPLOSOL tablets contain the active ingredient SALICYLIC ACID ESTER OF SALICYLIC ACID (SESA), also known chemically as 2-(2-hydroxybenzoyl)oxybenzoic acid which is a white powder with a melting point of 147 to 148° C and has no odor and is tasteless. SESA is insoluble in acid gastric fluids (<0.1 mg/mL at pH 1.0), but readily soluble in the small intestine where it is partially hydrolyzed to two molecules of salicylic acid. A significant portion of the parent compound is absorbed unchanged and undergoes rapid esterase hydrolysis in the body: its half-life is about one hour. About 13% is excreted through the kidneys as a glucuronide conjugate of the parent compound, the remainder as salicylic acid and its metabolites. Endoscopic studies using SESA at acceptable therapeutics doses has shown no increased tendency toward gastric or duodenal irritation (**Lanza, Roth, Scheiman, Cryer, Porro**). Two studies onr using 51-Cr-tagged red blood cells in healthy volunteers and one using the modified benzadine test in OA and RA indicate that fecal blood loss associated with tablets containing the SESA in therapeutic doses (3,000 mg/day in divided doses did not exceed the normal (placebo) range **(Leonard).** SESA was proven to have no significant gastroduodenal lesions **(0%)** after two weeks compared to naproxen treated individuals where **37%** had signficiant gastroduodenal lesions **(Roth)**. In clinical studies in patients with rheumatoid arthritis and/or osteoarthritis, SESA was shown to improve patient satisfaction and control the signs and symptoms of disease activity **(Fazarine, Mables, Montrone, Deodhar, Bomardier, Atkinson, McPherson, Liyange, ON Re)**. One study compared SESA to diclofenac in rheumatoid arthritis and reported equal efficacy **(Bomardier).** One study showed use of SESA reduced the erythrocyte sedimention rate (ESR) in patients with rheumatoid arthritis **(April)**

DIPLOSAL tablets may be used in combination with or without biologics, disease modifying anti-rheumatic drugs agents (DMARDS) and/or corticosteroids. SESA in DIPLOSOL tablets is rapidly absorbed. It is detectable in the plasma as early as 30 minutes (**Dromgoole**). Peak plasma SESA levels levels are generally attained 1 to 5 hours after administration. With single doses up to 2000 mg, a linear relationship exists between amount of drug administered and the integrated area under the plasma drug concentration vs time curve (**Dromgoole**). The active moiety of SESA is salicylic acid, which is detectable in the plasma as early as 30 minutes after oral ingestion of a single dose. Generally, the peak plasma level of salicylic acid occurs between 4-7 hours (**Harrison, Dromgoole**).

The administration of SESA tablets either under fasting conditions or after meals yields quite similar serum SESA/SALICYLIC ACID concentration-time profiles. The bioavailability of the drug is not altered by the presence of food (**Harrison).**

As there is no gastrointestinal bleeding risk with SESA, no bioavailability study has been conducted to show any interference with the absorption of the salicylic acid ester of salicylic acid when SESA tablets were given in conjunction with an antacid containing both aluminum hydroxide and magnesium hydroxide.

SESA is rapidly metabolized by plasma and tissue esterases into its active moiety, salicylic acid and eliminated in the urine (**Goff , Nordqvist)**. As 98% of SESA is absorbed in the gastrointestinal tract, only 2% is found excreted unchanged in the stool (**Atkinson**). Salicylic acid's inactive metabolites are salicyluric acid, salicylglucuronide and gentisic acid which are excreted via the kidney route.

The plasma half-life of SESA is 1.8 to 2.0 hours **(Harrison)**. Repeated doses of SESA does not result in any further accumulation in the plasma. However when steady state of SESA's active moiety, salicylic acid, is achieved, small adjustments in daily dose may result in large increases in salicylate plasma levels **(Singelton**) .

CONTRAINDICATIONS

DIPLOSOL tablets are contraindicated in patients with known hypersensitivity to SESA. DIPLOSOL tablets should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other salicylic acid containing medications. There are no reported cases of fatal or anaphylactic-like reactions to SESA.

Cardiovascular and Cerebrovascular Effects

Clinical trials of SESA have not reported any increase risk of cardiovascular adverse events. A study of 30 months duration testing the safety and efficacy of SESA in patients with established coronary artery disease revealed no increased risk of cardiovascular nor cerebrovascular adverse events compared to placebo treated subjects (**Hauser).**

Gastrointestinal Effects-Risk of Ulceration, Bleeding, and Perforation.

Double blind controlled clinical trials of SESA in healthy volunteers for 2 or more weeks showed no higher rate of gastroduodenal lesions endoscopically as well as by using chromium 51 labeled red blood cells. **(Leonards, Lanza, Roth, Scheiman, Cryer, Porro)**.

Hematological effects

SESA has been safely tested in patients with Hemophilia A with no effect on platelet aggregation or on bleeding time (**Stevens, Sweeney).**

Hypertension

No reports of SESA causing or worsening pre-existing hypertension.

Congestive Heart Failure and Edema

No fluid retention and edema have been observed in patients taking SESA.

Hepatic Effects There is one report of elevated liver function tests in HIV patients who were administered SESA. All elevated liver function tests reverted to normal upon discontinuation of the SESA. **(Juluri)**

Renal Effects

Long-term administration of SESA has not resulted in renal papillary necrosis or other renal injury. No change in glomerular filtration rate (GFR) in subjects taking the salicylic ester of salicylic acid for 30 months. Reports of increase in microalbumnuria with SESA have been report, clinical significance of which is unknown **(Goldfine, Hauser).** One case report of nephrotic syndrome was reported in a patient taking SESA **(Valles).**

Advanced Renal Disease

No information is available from controlled clinical studies regarding the use of DIPLOSOL tablets in patients with advanced renal disease. Therefore, treatment with DIPLOSOL tablets is not recommended in these patients with advanced renal disease. If DIPLOSOL tablet therapy must be initiated, close monitoring of the patients re function is advisable.

Overdose

One case was reported of accidental ingestion of the SESA occurred in a dialysis patient. It resulted in mild but reversible salicylism symptoms (tinnitus/hearing loss)(**Kleinman).**

Anaphylactoid Reactions

As with all medications, DIPLOSOL theoretically can cause anaphylactoid reactions in patients without known prior exposure to DIPLOSOL tablets. DIPLOSOL tablets should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or NSAIDS. Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions

There is one case report of a Steven's Johnson type rash in a patient prescribed SESA. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy

In pregnancy, DIPLOSOL tablets should be avoided.

PRECAUTIONS

General

DIPLOSOL tablets cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

Opthalmological

No reports of blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported in patients taking SESA . If a patient develops such complaints while receiving DIPLOSOL tablets, the drug should be discontinued, and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Information for Patients

Patients should be informed of the following information before initiating therapy with DIPLOSOL and periodically during the course of ongoing therapy.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Laboratory Tests

If clinical signs and symptoms consistent with liver or renal disease develop or abnormal liver tests persist or worsen, DIPLOSOL tablets should be discontinued.

Drug Interactions

Aspirin

When DIPLOSOL tablets are administered with aspirin, there is no increase in the bleeding time. NSAIDs should not be given concomitantly with DIPLOSOL.

Warfarin-type anticoagulants

Short-term controlled studies haven shown that DIPLOSOL's active moiety, salicylic acid, can significantly increase the prothrombin time when administered to individuals on coumarin-type anticoagulants.

Teratogenic effects

Studies conducted in rats using SESA have demonstrated evidence of developmental fetal abnormalities using doses at 2/3rds the LD 50 (many times the doses used in the human) **(Eriksson)** However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women. DIPLOSOL should NOT be used in pregnancy.

Labor and Delivery

The effects of DIPLOSOL tablets on labor and delivery in pregnant women are unknown.

Nursing Mothers

It is known whether this drug is excreted in human milk and therefore DIPLOSOL should not be used by nursing mothers.

Pediatric Use

Safety and effectiveness of DIPLOSAL tablets in pediatric patients has not been established.

Geriatric Use

As with any medication, caution should be exercised in treating the elderly (65 years and older). The average age of a 30 month study was 63 years (Hauser) with no serious adverse event reported in SESA treated patients compared to placebo treated patients **(Hauser).**

Adverse Reactions

The most common adverse event noted with SESA is reversible tinnitus (ringing in the ears) and hearing loss, both of which are completely reversible with dose reduction or dose discontinuation.

Other reported effects of SESA

Statistically significant reduction in triglycerides, blood sugar, HbA1c and uric acid were reported with long term use of SESA (1 year to 30 months **(Goldfine, Hauser).**

DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of DIPLOSOL tablets and other treatment options before deciding to use DIPLOSOL tablets. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. After observing the response to initial therapy with DIPLOSOL tablets, the dose and frequency should be adjusted to suit an individual patient's needs. Monitoring of the plasma salicylate level is recommended once steady state is reached, normally not before day 5 of DIPLOSOL TREATMENT. Although there is no specific guidelines for a "therapeutic" plasma salicylate level, reports have shown keeping the plasma salicylate level between 150-250 micrograms/millilter may help with the pain associated with inflammatory conditions. There is no strong correlation between tinnitus/hearing loss and the plasma salicylate level.

Do not exceed 4000 mg total daily dose unless there is insufficient clinical response and no tinnitus or hearing loss and only under a physician or other health care providers guidance.

Rheumatoid arthritis and osteoarthritis

Suggested Dosage of DIPLOSOL

1500 mg- 4000 mg daily (500 mg tablets, one to two tablets three to four times daily).

Individual patients may show a good response to the lower dose as well as to a higher dose. Therefore, when treating patients with a dose greater than 4000 mg per day, the physician should observe sufficient increased clinical benefits to offset potential increased risk. The dose should be tailored to each patient, and may be lowered or raised depending on the severity of symptoms either at time of initiating drug therapy or as the patient responds or fails to respond.

The smallest dose of DIPLOSOL tablets that yields acceptable control should be employed.

In chronic conditions, a therapeutic response to therapy with DIPLOSOL tablets is sometimes seen in a few days to a week but most often is observed by two weeks. After a satisfactory response has been achieved, the patient's dose should be reviewed and adjusted as required.

HOW SUPPLIED

DIPLOSOL tablets are available in the following strength, colors and size:

500 mg (white, round, biconcave imprinted with DIPLOSOL)

Bottles of 100

Bottles of 500

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP] Rx only

Manufactured by:

Pharmops, Inc. Phillipsburg, New Jersey, USA for

J & D Pharmaceuticals LLC, Phillipsburg, New Jersey, USA

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