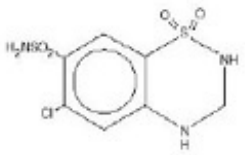
HYDROCHLOROTHIAZIDE- hydrochlorothiazide tablet
Oxford Pharmaceuticals, LLC

HYDROCHLOROTHIAZIDE TABLETS, USP
Rx Only

DESCRIPTION

Hydrochlorothiazide is a diuretic and antihypertensive. It is the 3,4-dihydro derivative of chlorothiazide. Its chemical name is 6-chloro-3,4-dihyrdo-2*H*-1,2,4-benzothiadiazine-7-sulfonamide1,1-dioxide, and its structural formula is



$C_7H_8ClN_3O_4S_2$ M.W. 297.73

Hydrochlorothiazide is a white, or practically white, crystalline powder, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

Each tablet, for oral administration, contains 25 mg or 50 mg hydrochlorothiazide. In addition. each tablet contains the following inactive ingredients: Anhydrous Lactose, Pregelatinized Starch from Corn, Magnesium Stearate, Microcrystalline Cellulose, and FD&C Yellow #6.

CLINICAL PHARMACOLOGY

The mechanism of the antihypertensive effect of thiazides is unknown. Hydrochlorothiazide does not usually affect normal blood pressure.

Hydrochlorothiazide affects the distal renal tubular mechanism of electrolyte reabsorption. At maximal therapeutic dosage all thiazides are approximately equal in their diuretic efficacy.

Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate.

After oral use diuresis begins within 2 hours. peaks in about 4 hours and lasts about 6 to 12 hours.

Pharmacokinetics and Metabolism

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half- life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

INDICATIONS AND USAGE

Hydrochlorothiazide tablets are indicated as adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy.

Hydrochlorothiazide has also been found useful in edema due to various forms of renal dysfunction such as the nephrotic syndrome, acute glomerulonephritis, and chronic renal failure.

Hydrochlorothiazide is indicated in the management of hypertension either as the sole therapeutic agent or to enhance the effectiveness of other antihypertensive drugs in the more severe forms of hypertension.

Use in Pregnancy

Routine use of diuretics during normal pregnancy is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy and there is no

satisfactory evidence that they are useful in the treatment of toxemia.

Edema during pregnancy may arise from pathologic causes or from the physiologic and mechanical consequences of pregnancy. Thiazides are indicated in pregnancy when edema is due to pathologic causes, just as they are in the absence of pregnancy (see **PRECAUTIONS, Pregnancy**). Dependent edema. in pregnancy, resulting from restriction of venous return by the gravid uterus, is properly treated through elevation of the lower extremities and use of support stockings. Use of diuretics to lower intravascular volume in this instance is Illogical and unnecessary. During normal pregnancy there is hypervolemia which is not harmful to the fetus or the mother in the absence of cardiovascular disease. However, it may be associated with edema. rarely generalized edema. If such edema causes discomfort, increased recumbency will often provide relief. Rarely this edema may cause extreme discomfort which is not relieved by rest. In these instances, a short course of diuretic therapy may provide relief and be appropriate.

CONTRAINDICATIONS

Anuria.

Hypersensitivity to this product or to other sulfonamide-derived drugs

WARNINGS

Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with Impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with diuretics (see **PRECAUTIONS, Drug Interactions**).

Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

PRECAUTIONS

General

All patients receiving diuretic therapy should be observed for evidence of fluid or electrolyte imbalance: namely, hyponatremia. hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte Imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., Increased ventricular irritability). Hypokalemia may be avoided or treated by

use of potassium sparing diuretics or potassium supplements such as foods with a high potassium content. Although any chloride deficit Is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life threatening. ln actual salt depletion. appropriate replacement is the therapy of choice.

Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazides.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out test for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients

Non-melanoma Skin Cancer: Instruct patients taking hydrochlorothiazide to protect skin from the sun and undergo regular skin cancer screening.

Laboratory Tests
Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be done at appropriate intervals.

Drug Interactions
When given concurrently the following drugs may interact with thiazide diuretics.

Alcohol, Barbiturates, or *Narcotics* -potentiation of orthostatic hypotension may occur.

Antidiabetic Drugs· (oral agents and insulin) - dosage adjustment of the antidiabetic drug may be required.

Other Antihypertensive Drugs - additive effect or potentiation.

Cholestyramine and Colestipol Resins - Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of cholestyramine and colestipol resins bind the hydrochlorothiazide and reduce its absorption in the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH - intensified electrolyte depletion, particularly hypokalemia.

Pressor Amines (e.g., Norepinephrine) - possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal Muscle Relaxants, Nondepolarizing (e.g., Tubocurarine) - possible increased responsiveness to the muscle relaxant.

Lithium - generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations

before use of such preparations with hydrochlorothiazide.

Nonsteroidal Anti-Inflammatory Drugs - In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when hydrochlorothiazide and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Drug/Laboratory Test Interactions
Thiazides should be discontinued before carrying out tests for parathyroid function (see **PRECAUTIONS, General**).

Carcinogenesis, Mutagenesis, Impairment of Fertility
Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential or hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium strains* TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were only obtained in the *In vitro* CHO Sister Chromatid Exchange (clastogenicity) and the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mg/ml, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception, and throughout gestation.

Pregnancy
Teratogenic Effects: Pregnancy Category B: Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg hydrochlorothiazide/kg, respectively, provided no evidence of harm to the fetus.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects: Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing Mothers
Thiazides are excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue hydrochlorothiazide, taking into account the importance of the drug to the mother.

Pediatric Use
There are no well controlled clinical trials in pediatric patients. Information on dosing in this age group is supported by evidence from empiric use in pediatric patients and published literature regarding the treatment of hypertension in such patients (see **DOSAGE AND ADMINISTRATION, Infants and Children**).

ADVERSE REACTIONS
The following adverse reactions have been reported and, within each category, are listed in order of

decreasing severity.

Body As A Whole: Weakness.
Cardiovascular: Hypotension including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics or antihypertensive drugs).
Digestive: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), diarrhea, vomiting. sialadenitis, cramping, constipation, gastric irritation, nausea, anorexia.
Hematologic: Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia.
Hypersensitivity: Anaphylactic reactions, necrotizing angiitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, photosensitivity, fever, urticaria, rash, purpura.
Metabolic: Electrolyte imbalance {see **PRECAUTIONS**), hyperglycemia, glycosuria, hyperuricemia.
Musculoskeletal: Muscle spasm.
Nervous System/Psychiatric: Vertigo, paresthesias, dizziness, headache, restlessness.
Renal: Renal failure, renal dysfunction, interstitial nephritis. (See **WARNINGS**.)
Skin: Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia.
Special Senses: Transient blurred vision, xanthopsia.
Urogenital: Impotence.

Postmarketing Experience
Non-melanoma Skin Cancer: Hydrochlorothiazide is associated with an increased risk of non-melanoma skin cancer. In a study conducted in the Sentinel System, increased risk was predominantly for squamous cell carcinoma (SCC) and in white patients taking large cumulative doses. The increased risk for SCC in the overall population was approximately 1 additional case per 16,000 patients per year, and for white patients taking a cumulative dose of ≥50,000 mg the risk increase was approximately 1 additional SCC case for every 6,700 patients per year.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

OVERDOSAGE

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

In the event of overdosage, symptomatic and supportive measures should be employed. Emesis should be induced or gastric lavage performed. Correct dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures. If required, give oxygen or artificial respiration for respiratory impairment. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

The oral LD_{50} of hydrochlorothiazide is greater than 10 g/kg in the mouse and rat.

DOSAGE AND ADMINISTRATION

Therapy should be individualized according to patient response. Use the smallest dosage necessary to achieve the required response.

Adults
For Edema- The usual adult dosage is 25 to 100 mg daily as a single or divided dose. Many patients with edema respond to intermittent therapy, i.e., administration on alternate days or on three to five days each week. With an intermittent schedule, excessive response and the resulting undesirable electrolyte imbalance are less likely to occur.

For Control of Hypertension - The usual initial dose in adults is 25 mg daily given as a single dose. The dose may be increased to 50 mg daily, given as a single or two divided doses. Doses above 50 mg are often associated with marked reductions in serum potassium (see also **PRECAUTIONS**).

Patients usually do not require doses in excess of 50 mg of hydrochlorothiazide daily when used concomitantly with other antihypertensive agents.

Infants and Children
For Diuresis and For Control of Hypertension - The usual pediatric dosage is 0.5 to 1 mg per pound (1 lo 2 mg/kg) per day in single or two divided doses, not to exceed 37.5 mg per day in infants up to 2 years of age or 100 mg per day in children 2 to 12 years of age. In infants less than 6 months of age, doses up to 1.5 mg per pound (3 mg/kg) per day in two divided doses may be required (see **PRECAUTIONS, Pediatric Use**).

HOW SUPPLIED
Hydrochlorothiazide Tablets, USP are supplied as follows:

25 mg - Peach, Round scored tablets, upper debossed with "361" above bisect and lower debossed "O". Available in bottles of:
100, NDC 69584-361-10
1000, NDC 69584-361-90
5000, NDC 69584-361-95

50 mg - Peach, Round scored tablets, upper debossed with "362" above bisect and lower debossed "O". Available in bottles of:
100, NDC 69584-362-10
1000, NDC 69584-362-90.

Store at: 20-25°C (68-77°F). [See USP Controlled Room Temperature].

Dispense in a well-closed container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

Manufactured by:
Oxford Pharmaceuticals, LLC
Birmingham, Alabama 35211

8200020
Revised: 08/2020 R00

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 69584-361-10

HYDROCHLOROTHIAZIDE TABLETS, USP

25 mg

Rx only

100 TABLETS

EACH TABLET CONTAINES:
Hydrochlorothiazide ..... 25 mg

USUAL DOSAGE: See package insert for full prescribing information.

STORE at 20° to 25°C (68° to 77°F)
[see USP Controlled Room Temperature).

DISPENSE in well-closed container as defined in the USP with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF REACH OF CHILDREN.

MANUFACTURED BY:
OXFORD PHARMACEUTICALS, LLC
BIRMINGHAM, ALABAMA 35211
8000080 Rev/ 06/2020 R00

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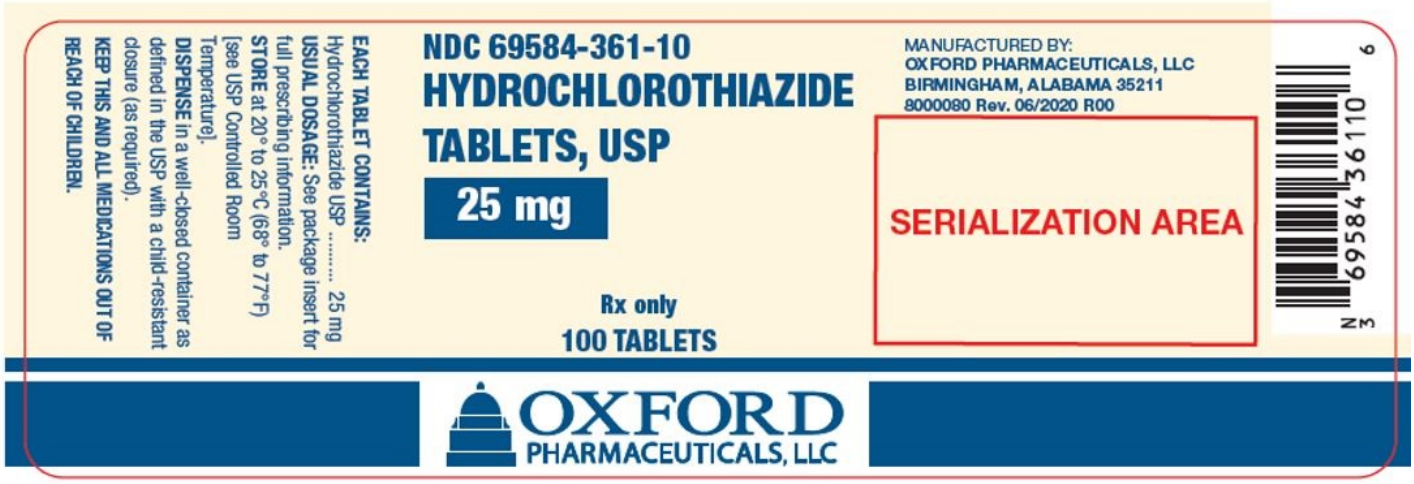
PHARMACEUTICALS, LLC



NDC 69584-362-10

HYDROCHLOROTHIAZIDE TABLETS, USP

50 mg

Rx only

100 TABLETS

EACH TABLET CONTAINES:
Hydrochlorothiazide ..... 50 mg

USUAL DOSAGE: See package insert for full prescribing information.

STORE at 20° to 25°C (68° to 77°F)
[see USP Controlled Room Temperature).

DISPENSE in well-closed container as defined in the USP with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF REACH OF CHILDREN.

MANUFACTURED BY:
OXFORD PHARMACEUTICALS, LLC
BIRMINGHAM, ALABAMA 35211
8000076 Rev/ 06/2020 R00

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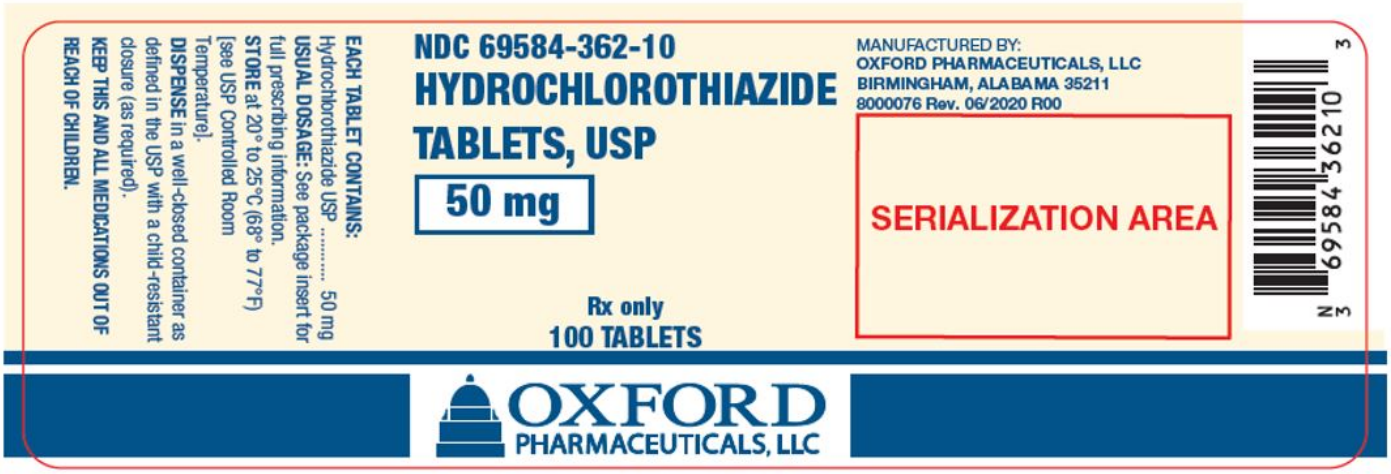

HYDROCHLOROTHIAZIDE

hydrochlorothiazide tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:69584-361
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
Hydrochlorothiazide (UNII: 0J48LPH2TH) (Hydrochlorothiazide - UNII:0J48LPH2TH)	Hydrochlorothiazide	25 mg

Inactive Ingredients	
Ingredient Name	**Strength**
Starch, Corn (UNII: O8232NY3SJ)	
Microcrystalline Cellulose 101 (UNII: 7T9FYH5QMK)	
Anhydrous Lactose (UNII: 3SY5LH9PMK)	
Magnesium Stearate (UNII: 70097M6I30)	
Fd&C Yellow No. 6 (UNII: H77VEI93A8)	

Product Characteristics			
Color	ORANGE (Peach)	**Score**	2 pieces
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	361;O
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69584-361-10	100 in 1 BOTTLE; Type 0: Not a Combination Product	09/25/2020	
2	NDC:69584-361-90	1000 in 1 BOTTLE; Type 0: Not a Combination Product	09/25/2020	
3	NDC:69584-361-95	5000 in 1 BOTTLE; Type 0: Not a Combination Product	09/25/2020	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA087059	09/25/2020	

HYDROCHLOROTHIAZIDE

hydrochlorothiazide tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:69584-362
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
Hydrochlorothiazide (UNII: 0J48LPH2TH) (Hydrochlorothiazide - UNII:0J48LPH2TH)	Hydrochlorothiazide	50 mg

Inactive Ingredients	
Ingredient Name	Strength
Starch, Corn (UNII: O8232NY3SJ)	
Microcrystalline Cellulose 101 (UNII: 7T9FYH5QMK)	
Anhydrous Lactose (UNII: 3SY5LH9PMK)	
Magnesium Stearate (UNII: 70097M6I30)	
Fd&C Yellow No. 6 (UNII: H77VEI93A8)	

Product Characteristics			
Color	ORANGE (Peach)	Score	2 pieces
Shape	ROUND	Size	8mm
Flavor		Imprint Code	362;O
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69584-362-10	100 in 1 BOTTLE; Type 0: Not a Combination Product	09/25/2020	
2	NDC:69584-362-90	1000 in 1 BOTTLE; Type 0: Not a Combination Product	09/25/2020	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA087068	09/25/2020	

Labeler - Oxford Pharmaceuticals, LLC (079638266)

Establishment

Name	Address	ID/FEI	Business Operations
Oxford Pharmaceuticals, LLC		079638266	manufacture(69584-361, 69584-362)

Revised: 8/2020 Oxford Pharmaceuticals, LLC