COMBOGESIC- acetaminophen and ibuprofen tablet, film coated
Hikma Pharmaceuticals USA Inc

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use COMBOGESIC safely and effectively. See full prescribing information for COMBOGESIC.

COMBOGESIC® (acetaminophen and ibuprofen) tablets, for oral use.
Initial U.S. Approval: 2023

WARNING: HEPATOTOXICITY, CARDIOVASCULAR RISK AND GASTROINTESTINAL RISK

***See full prescribing information for complete boxed warning*.**

- **COMBOGESIC contains acetaminophen, which has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with doses of acetaminophen that exceed 4,000 milligrams per day, and often involve more than one acetaminophen containing product (5.1).**
- **Nonsteroidal anti-inflammatory drugs (NSAIDS), like the ibuprofen in COMBOGESIC, cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use (5.2).**
- **COMBOGESIC tablets are contraindicated in the setting of coronary artery bypass graft (CABG) surgery (5.2).**
- **NSAIDS, like the ibuprofen in COMBOGESIC, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events (5.3).**

RECENT MAJOR CHANGES

Warnings and Precautions (5.9) **11/2024**

INDICATIONS AND USAGE

COMBOGESIC is a combination of acetaminophen and ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), and is indicated in adults for the short term management of mild to moderate acute pain (1).

DOSAGE AND ADMINISTRATION

- Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals (2).
- Do not administer with other acetaminophen-containing products (2).

Three tablets every 6 hours as needed for pain relief, up to a maximum of 12 tablets per day (2).

DOSAGE FORMS AND STRENGTHS

- Film-coated tablet containing 325 mg acetaminophen and 97.5 mg ibuprofen (3).

CONTRAINDICATIONS

COMBOGESIC is contraindicated in:

- patients with known hypersensitivity to acetaminophen, ibuprofen, other NSAIDs, or to any of the excipients in this product (4).
- patients with a history of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients (4).
- the setting of coronary artery bypass graft (CABG) surgery (4).

WARNINGS AND PRECAUTIONS

- Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (5.4).
- Heart Failure and Edema: Avoid use of COMBOGESIC in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure (5.5).
- Renal Toxicity: Long-term administration of NSAIDs, including the ibuprofen component of COMBOGESIC, has resulted in renal papillary necrosis and other renal injury (5.6).
- Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs (5.7).
- Exacerbation of Asthma Related to Aspirin Sensitivity: COMBOGESIC is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8).
- Serious Skin Reactions: Discontinue COMBOGESIC at first appearance of skin rash or other signs of hypersensitivity (5.9).
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Discontinue and evaluate clinically (5.10).
- Fetal Toxicity: Limit use of NSAID-containing products, including COMBOGESIC, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAID-containing products, including COMBOGESIC in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus (5.11).
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.12).

ADVERSE REACTIONS

The most common adverse reactions (greater than or equal to 2%) are nausea, vomiting, headache, dizziness, somnolence, post-procedural hemorrhage, and swelling of the face (6).

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

A number of known or potential interactions between COMBOGESIC and other drugs/drug classes exist. Please refer to the *Drug Interactions* section (7) for further information.

USE IN SPECIFIC POPULATIONS

- Infertility: NSAID-containing products, including COMBOGESIC, are associated with reversible infertility. Consider withdrawal of COMBOGESIC tablets in women who have difficulties conceiving. (8.3)
- Renal or hepatic impairment: Not recommended (5.1, 5.6, 8.6, 8.7).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: HEPATOTOXICITY, CARDIOVASCULAR RISK, AND GASTROINTESTINAL RISK

HEPATOTOXICITY

COMBOGESIC contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen-containing product *[see Warnings and Precautions (5.1)]*.

CARDIOVASCULAR RISK

COMBOGESIC contains ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID). NSAIDs cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction, and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use *[see Warnings and Precautions (5.2)]*.

COMBOGESIC is contraindicated for treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery *[see Warnings and Precautions (5.2)]*.

GASTROINTESTINAL RISK

NSAIDS cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

COMBOGESIC is indicated in adults for the short-term management of mild to moderate acute pain.

2 DOSAGE AND ADMINISTRATION

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)].*
- Do not exceed the recommended dose of COMBOGESIC in 24 hours *[see (2) below].*
- Do not co-administer COMBOGESIC with other acetaminophen- or NSAID-containing products *[see Warnings and Precautions (5.1, 5.2, 5.3)].*

The recommended dose of COMBOGESIC is 3 tablets every 6 hours as needed for pain relief, up to a maximum of 12 tablets per day.

3 DOSAGE FORMS AND STRENGTHS

Tablets: white, biconvex, capsule-shaped, film-coated tablets, debossed with the letters "CG" on one side and plain on the other side, each containing 325 mg acetaminophen and 97.5 mg ibuprofen.

4 CONTRAINDICATIONS

COMBOGESIC is contraindicated in:

- patients with a known hypersensitivity (e.g., anaphylactic reactions, serious skin reactions) to acetaminophen, ibuprofen, other NSAIDs, or to any of the excipients in this product *[see Warnings and Precautions (5.7, 5.8, 5.9)].*
- patients with a history of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDS *[see Warnings and Precautions (5.7 and 5.8)]*.
- the setting of coronary artery bypass graft (CABG) surgery *[see Warnings and Precautions (5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Acetaminophen

COMBOGESIC contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involved more than one acetaminophen-containing product. The excessive intake of acetaminophen may be intentional to cause self-harm or unintentional as patients attempt to obtain more pain relief or unknowingly take other acetaminophen-containing products.

The risk of acute liver failure is higher in individuals with underlying liver disease and in individuals who ingest alcohol while taking acetaminophen.

Instruct patients to look for acetaminophen or APAP on package labels and not to use more than one product that contains acetaminophen. Instruct patients to seek medical attention immediately upon ingestion of more than 4,000 milligrams of acetaminophen per day, even if they feel well.

Ibuprofen

Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including ibuprofen.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue COMBOGESIC immediately, and perform a clinical evaluation of the patient.

COMBOGESIC has not been studied in patients with impaired hepatic function. The use of COMBOGESIC in patients with hepatic impairment is not recommended.

5.2 Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI), and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as ibuprofen, increases the risk of serious gastrointestinal (GI) events *[see Warnings and Precautions (5.3)]*.

Status Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG *[see Contraindications (4)]*.

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of COMBOGESIC in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If COMBOGESIC is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

5.3 Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including the ibuprofen in COMBOGESIC tablets, can cause serious

gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. However, even short-term therapy is not without risk.

Risk Factors for Bleeding, Ulceration, and Perforation

Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy, concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless the benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternative therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulcerations and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate additional evaluation and treatment, and discontinue COMBOGESIC until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [*see Drug Interactions (7)*].

5.4 Hypertension

NSAIDs, including the ibuprofen in COMBOGESIC, can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

5.5 Heart Failure and Edema

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of ibuprofen may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) [*see Drug Interactions (7)*].

Avoid the use of COMBOGESIC in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If COMBOGESIC is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

5.6 Renal Toxicity and Hyperkalemia

Renal Toxicity

Long-term administration of NSAIDs, including the ibuprofen component of COMBOGESIC, has resulted in renal papillary necrosis and other renal injury.

Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

5.7 Anaphylaxis and Other Hypersensitivity Reactions

Acetaminophen

There have been postmarketing reports of hypersensitivity and anaphylaxis associated with the use of acetaminophen. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, pruritus, and vomiting. There were infrequent reports of life-threatening anaphylaxis requiring emergency medical attention. Instruct patients to discontinue COMBOGESIC immediately and seek emergency medical care if they experience these symptoms. Do not prescribe COMBOGESIC for patients with acetaminophen allergy *[see Contraindications (4)]*.

Ibuprofen

NSAIDs, including the ibuprofen in COMBOGESIC, has been associated with anaphylactic reactions in patients with and without known hypersensitivity to ibuprofen and in patients with aspirin-sensitive asthma. Instruct patients to discontinue COMBOGESIC immediately and seek emergency medical care if they experience these symptoms. Do not prescribe COMBOGESIC for patients with ibuprofen or NSAID allergy *[*see *Contraindications (4) and Warnings and Precautions (5.8)]*.

5.8 Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, COMBOGESIC is contraindicated in patients with this form of aspirin sensitivity [*see Contraindications (4)*]. When COMBOGESIC is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.9 Serious Skin Reactions

COMBOGESIC contains acetaminophen and ibuprofen. Acetaminophen or NSAIDs, including ibuprofen, may cause serious skin adverse events such as exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. NSAIDs can also cause fixed drug eruption (FDE). FDE may present as a more severe variant known as generalized bullous fixed drug eruption (GBFDE), which can be life-threatening. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions and to discontinue the use of COMBOGESIC at the first appearance of skin rash or any other sign of hypersensitivity. COMBOGESIC is contraindicated in patients with previous serious skin reactions to acetaminophen or NSAIDs [*see Contraindications (4)*].

5.10 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs, such as the ibuprofen in COMBOGESIC. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue COMBOGESIC and evaluate the patient immediately.

5.11 Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus

Avoid use of NSAID-containing products, including COMBOGESIC, in pregnant women at about 30 weeks gestation and later. NSAID-containing products, including COMBOGESIC, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment:

Use of NSAID-containing products, including COMBOGESIC, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is

often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some post-marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If, after careful consideration of alternative treatment options for pain management, NSAID- treatment is necessary between about 20 weeks and 30 weeks gestation, limit COMBOGESIC use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if COMBOGESIC treatment extends beyond 48 hours. Discontinue COMBOGESIC if oligohydramnios occurs and follow up according to clinical practice *[see Use in Specific Populations (8.1)].*

5.12 Hematologic Toxicity

Anemia has occurred in NSAID-treated patients. This may be due to occult or gross GI blood loss, fluid retention, or an incompletely described effect upon erythropoiesis. If a patient treated with COMBOGESIC has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including the ibuprofen in COMBOGESIC, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding [*see Drug Interactions (7)*].

5.13 Ophthalmological Effects

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported in patients receiving ibuprofen. If a patient develops such complaints while receiving COMBOGESIC, the drug should be discontinued, and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

5.14 Aseptic Meningitis

Aseptic meningitis with fever and coma has been observed on rare occasions in patients on ibuprofen therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease. If signs or symptoms of meningitis develop in a patient on COMBOGESIC, the possibility of its being related to ibuprofen should be considered.

5.15 Masking of Inflammation and Fever

The pharmacological activity of COMBOGESIC in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

5.16 Laboratory Monitoring

Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically [*see Warnings and Precautions (5.1, 5.3, 5.6)*].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions to ibuprofen or acetaminophen are described elsewhere in other sections of the labelling.

- Hepatotoxicity *[see Warnings and Precautions (5.1)]*
- Cardiovascular Thrombotic Events *[see Warnings and Precautions (5.2)]*
- Gastrointestinal Bleeding, Ulceration, and Perforation *[see Warnings and Precautions (5.3)]*
- Hypertension *[see Warnings and Precautions (5.4)]*
- Heart Failure and Edema *[see Warnings and Precautions (5.5)]*
- Renal Toxicity and Hyperkalemia *[see Warnings and Precautions (5.6)]*
- Anaphylaxis and Other Hypersensitivity Reactions *[see Warnings and Precautions (5.7)]*
- Serious Skin Reactions *[see Warnings and Precautions (5.9)]*
- Hematologic Toxicity *[see Warnings and Precautions (5.12)]*

The most common adverse reactions (incidence of ≥ 2% for patients receiving COMBOGESIC) are: nausea, vomiting, headache, dizziness, somnolence, post-procedural hemorrhage, and swelling of the face (Table 1).

6.1 Clinical Trials Experience

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

The clinical trials of COMBOGESIC have been conducted in patients with postoperative pain following dental and arthroscopic procedures, who received double-blind treatment every 6 hours for 24 or 48 hours.

Most commonly (≥2%) reported adverse reactions by organ system during double-blind treatment are listed in the table below. Adverse reactions are closely related to the extent (the level and length) of exposure. The incidences of overall and individual adverse reactions reported during the double-blind treatment period did not suggest an increase of risks associated with short-term (up to one or two days) use of the combination drug, COMBOGESIC in comparison to each individual component, acetaminophen or ibuprofen, and to placebo.

Table 1: Most commonly (≥2%) reported adverse reactions by organ system during double-blind treatment

	COMBOGESIC N=261	**Acetaminophen N=231**	**Ibuprofen N=231**	**Placebo N=199**
Total number of AEs	145	142	101	133
% of patients with ≥1 AE	30	38	29	37
Gastrointestinal disorders				
Nausea	15	19	12	23

Vomiting	7	10	3	10
Constipation	1	2	1	1
Dyspepsia	0.4	1	2	1
Injury, poisoning and procedural complications				
Post Procedural Hemorrhage	2	0.4	1	2
Nervous system disorders				
Headache	5	6	4	7
Dizziness	3	4	4	5
Somnolence	2	1	0	1
Skin and subcutaneous tissue disorders				
Swelling face	2	4	4	3
Pruritus	0.4	0.4	0.4	3

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of acetaminophen and ibuprofen. Because these 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.

Skin and Appendages: Exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and fixed drug eruption (FDE).

7 DRUG INTERACTIONS

Table 2: Clinically Significant Drug Interactions with COMBOGESIC

Drugs That Interfere with Hemostasis	
Clinical Impact:	• Ibuprofen and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of ibuprofen and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. • Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
	Monitor patients with concomitant use of COMBOGESIC with

Intervention:	anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding [*see Warnings and Precautions (5.12)*].
Aspirin	
Clinical Impact:	Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone [*see Warnings and Precautions (5.3)*].
Intervention:	Concomitant use of COMBOGESIC and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding [*see Warnings and Precautions (5.3)*]. COMBOGESIC is not a substitute for low dose aspirin for cardiovascular protection.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	
Clinical Impact:	• NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol). • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
Intervention:	• During concomitant use of COMBOGESIC and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of COMBOGESIC and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function [*see Warnings and Precautions (5.6)*]. • When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
Diuretics	
Clinical Impact:	Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of COMBOGESIC with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects [*see Warnings and Precautions (5.4 and 5.6)*].

Digoxin	
Clinical Impact:	The concomitant use of ibuprofen with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Intervention:	During concomitant use of COMBOGESIC and digoxin, monitor serum digoxin levels.
Lithium	
Clinical Impact:	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of COMBOGESIC and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
Intervention:	During concomitant use of COMBOGESIC and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of NSAIDS and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of COMBOGESIC and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	
Clinical Impact:	Concomitant use of ibuprofen with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy [*see Warnings and Precautions (5.3)*].
Intervention:	The concomitant use of ibuprofen with other NSAIDs or salicylates is not recommended.
Pemetrexed	
Clinical Impact:	Concomitant use of NSAIDS and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Intervention:	During concomitant use of COMBOGESIC and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Ibuprofen

Use of NSAID-containing products, including COMBOGESIC, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of COMBOGESIC use between about 20 and 30 weeks of gestation and avoid COMBOGESIC use at about 30 weeks of gestation and later in pregnancy (see *Clinical Considerations, Data*).

Premature Closure of Fetal Ductus Arteriosus:

Use of NSAID-containing products, including COMBOGESIC, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment:

Use of NSAID-containing products, including COMBOGESIC, at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimester of pregnancy are inconclusive.

In published animal reproduction studies, there were no clear developmental effects at doses up to 2.7-times the maximum human daily dose (MHDD) in the rabbit and 1.5-times in the MHDD rat when dosed throughout gestation. In contrast, an increase in membranous ventricular septal defects was reported in rats treated on Gestation Days 9 & 10 with 2.2-times the MHDD.

Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as ibuprofen, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

Acetaminophen

Prolonged experience with acetaminophen in pregnant women over several decades, based on published observational epidemiological studies and case reports, did not identify a drug associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes *(see Data)*. Reproductive and developmental studies in rats and mice from the published literature have identified adverse events at clinically relevant doses of acetaminophen. Fetotoxicity, increases in bone variations in the fetuses, and necrosis in the fetus liver and kidney have been noted in studies in rats. In mice treated with acetaminophen at doses within the clinical dosing range, cumulative adverse effects on reproduction were seen in a continuous breeding study. A reduction in number of

litters of the parental mating pair was observed as well as retarded growth and abnormal sperm in their offspring and reduced birth weight in the next generation.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAID-containing products, including COMBOGESIC, in women at about 30 weeks gestation and later in pregnancy, because NSAID-containing products, including COMBOGESIC, can cause premature closure of the fetal ductus arteriosus *(see Data)*.

Oligohydramnios/Neonatal Renal Impairment:

If, after consideration of alternative treatments for pain management, an NSAID-containing product, including COMBOGESIC, is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If COMBOGESIC treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue COMBOGESIC and follow up according to clinical practice *(see Data).*

Labor or Delivery

There are no studies on the effects of COMBOGESIC during labor or delivery. In animal studies, NSAIDs, including ibuprofen, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data

Human Data

Ibuprofen:

Premature Closure of Fetal Ductus Arteriosus

Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment

Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

Acetaminophen:

The results from a large population-based prospective cohort, including data from 26,424 women with live born singletons who were exposed to oral acetaminophen during the first trimester, indicate no increased risk for congenital malformations, compared to a control group of unexposed children. The rate of congenital malformations (4.3%) was similar to the rate in the general population. A population-based, case-control study from the National Birth Defects Prevention Study showed that 11,610 children with prenatal exposure to acetaminophen during the first trimester had no increased risk of major birth defects compared to 4,500 children in the control group. Other epidemiological data showed similar results. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including recall bias.

Animal Data

Ibuprofen:

In a published study, female rabbits given 7.5, 20, or 60 mg/kg ibuprofen (0.12, 0.33, or 0.99-times the maximum human daily dose of 1170 mg of ibuprofen based on a body surface area comparison) from Gestation Days 1 to 29, no clear treatment-related adverse developmental effects were noted. This dose was associated with significant maternal toxicity (stomach ulcers, gastric lesions). In the same publication, female rats were administered 7.5, 20, 60, 180 mg/kg ibuprofen (0.06, 0.17, 0.50, 1.5-times the maximum daily dose) did not result in clear adverse developmental effects. Maternal toxicity (gastrointestinal lesions) was noted at 20 mg/kg and above.

In a published study, rats were orally dosed with 300 mg/kg ibuprofen (2.5-times the maximum human daily dose of 1170 mg based on a body surface area comparison) during Gestation Days 9 and 10 (critical time points for heart development in rats). Ibuprofen treatment resulted in an increase in the incidence of membranous ventricular septal defects. This dose was associated with significant maternal toxicity including gastrointestinal toxicity. One incidence each of a membranous ventricular septal defect and gastroschisis was noted fetuses from rabbits treated with 500 mg/kg (8.3-times the maximum human daily dose) from Gestation Day 9 to 11.

Acetaminophen:

Studies in pregnant rats that received oral acetaminophen during organogenesis at doses up to 0.87-times the maximum human daily dose (MHDD = 3.9 grams/day, based on a body surface area comparison) showed evidence of fetotoxicity (reduced fetal weight and length) and a dose-related increase in bone variations (reduced ossification and rudimentary rib changes). Offspring had no evidence of external, visceral, or skeletal malformations.

When pregnant rats received oral acetaminophen throughout gestation at doses of 1.2-

times the MHDD (based on a body surface area comparison), areas of necrosis occurred in both the liver and kidney of pregnant rats and fetuses. These effects did not occur in animals that received oral acetaminophen at doses 0.3-times the MHDD, based on a body surface area comparison.

In a continuous breeding study, pregnant mice received 0.25, 0.5, or 1.0% acetaminophen via the diet (357, 715, or 1430 mg/kg/day). These doses are approximately 0.45, 0.89, and 1.8 times the MHDD, respectively, based on a body surface area comparison. A dose-related reduction in body weights of fourth and fifth litter offspring of the treated mating pair occurred during lactation and post-weaning at all doses. Animals in the high dose group had a reduced number of litters per mating pair, male offspring with an increased percentage of abnormal sperm, and reduced birth weights in the next generation pups.

8.2 Lactation

Risk Summary

The components of COMBOGESIC, ibuprofen and acetaminophen, are present in human milk. Limited published literature reports that, orally administered ibuprofen is present in human milk at relative infant doses of 0.06% to 0.6% of the maternal weight-adjusted daily dose. There are no reports of adverse effects of ibuprofen on the breastfed infant and no effects on milk production.

Limited published studies report that orally administered acetaminophen passes rapidly into human milk with similar levels in the milk and plasma. Average and maximum neonatal doses of 1% and 2%, respectively, of the weight-adjusted maternal dose are reported after a single oral administration of 1 gram acetaminophen. There is one well-documented report of a rash in a breast-fed infant that resolved when the mother stopped acetaminophen use and recurred when she resumed acetaminophen use.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for COMBOGESIC and any potential adverse effects on the breastfed infant from COMBOGESIC or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Infertility

Ibuprofen

Based on the mechanism of action, the use of prostaglandin mediated NSAID-containing products, including COMBOGESIC, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAID containing products, including COMBOGESIC in women who have difficulties conceiving or who are undergoing investigation of infertility.

Acetaminophen

Based on animal data, use of acetaminophen may cause reduced fertility in males and females of reproductive potential. It is not known whether these effects on fertility are reversible.

Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are approximately 1.2 times the MHDD and greater (based on a body surface area comparison) result in decreased testicular weights, reduced spermatogenesis, and reduced fertility. In female animals given the same doses, reduced implantation sites were reported. Additional published animal studies indicate that acetaminophen exposure in utero adversely impacts reproductive capacity of both male and female offspring at clinically relevant exposures *[see Nonclinical Toxicology (13.1)].*

8.4 Pediatric Use

The safety and effectiveness of COMBOGESIC in pediatric patients have not been established. COMBOGESIC is not approved for patients under 18 years of age.

8.5 Geriatric Use

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects [*see Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5, 5.6*)].

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Use in Renal Disease

COMBOGESIC has not been studied in patients with impaired renal function. The use of COMBOGESIC in patients with renal impairment is not recommended *[see Warnings and Precautions (5.6)]*.

8.7 Use in Hepatic Disease

COMBOGESIC has not been studied in patients with impaired hepatic function. The use of COMBOGESIC in patients with hepatic impairment is not recommended *[see Warnings and Precautions (5.1)]*.

10 OVERDOSAGE

COMBOGESIC is a combination product. The clinical presentation of overdose may include the signs and symptoms of acetaminophen toxicity, ibuprofen toxicity, or both.

Acetaminophen

The initial symptoms seen within the first 24 hours following an acetaminophen overdose are: anorexia, nausea, vomiting, malaise, pallor and diaphoresis. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and coagulation defects also may occur. Plasma acetaminophen levels >300 mcg/mL at 4

hours after oral ingestion were associated with hepatic damage in 90% of patients; minimal hepatic damage is anticipated if plasma levels at 4 hours are <150 mcg/mL or <37.5 mcg/mL at 12 hours after ingestion.

If an acetaminophen overdose is suspected, obtain a serum acetaminophen assay as soon as possible, but no sooner than 4 hours following oral ingestion. Obtain liver function studies initially and repeat at 24-hour intervals. Administer the antidote N-acetylcysteine (NAC) as early as possible. As a guide to treatment of acute ingestion, the acetaminophen level can be plotted against time since oral ingestion on a nomogram Rumack-Matthew). The lower toxic line on the nomogram is equivalent to 150 mcg/mL at 4 hours and 37.5 mcg/mL at 12 hours. If serum level is above the lower line, administer the entire course of NAC treatment. Withhold NAC therapy if the acetaminophen level is below the lower line.

Ibuprofen

Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare [*see Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.6, 5.14)*].

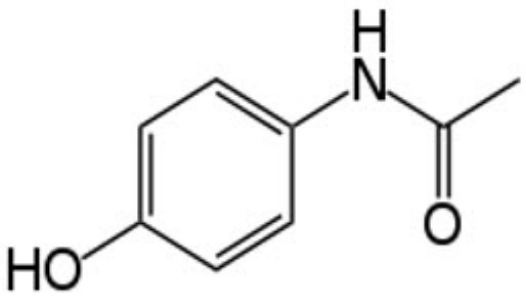
Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. It is advisable to contact a poison control center (1-800-222-1222) to determine the latest recommendations because strategies for the management of overdose are continually evolving.

If gastric decontamination may benefit the patient, e.g., short time since ingestion or a large overdosage (5 to 10 times the recommended dosage), consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or an osmotic cathartic in symptomatic patients if clinically appropriate.

11 DESCRIPTION

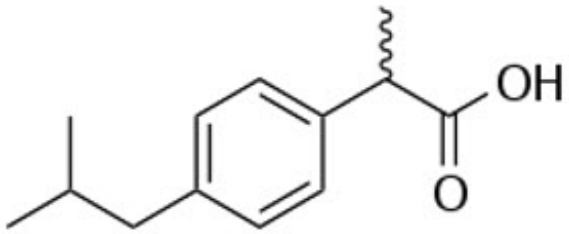
COMBOGESIC tablets are a combination of acetaminophen, an analgesic and antipyretic, and ibuprofen, a non-steroidal anti-inflammatory drug (NSAID).

The chemical name for acetaminophen is *N*-acetyl-*p*-aminophenol. The molecular formula is $C_8H_9NO_2$ and the structural formula is:



The molecular weight of acetaminophen is 151.17. Acetaminophen is a white, odorless, crystalline powder, possessing a slightly bitter taste. Acetaminophen is soluble in boiling water and 1N sodium hydroxide, and is freely soluble in alcohol.

The chemical name for ibuprofen is (±)-2-(p-isobutylphenyl) propionic acid. The molecular formula is $C_{13}H_{18}O_2$ and the structural formula is:



The molecular weight of ibuprofen is 206.29. Ibuprofen is a white powder with a melting point of 74-77°C and is very slightly soluble in water (<1 mg/mL) and readily soluble in organic solvents such as ethanol and acetone.

COMBOGESIC tablets contain 325 mg acetaminophen and 97.5 mg ibuprofen and are white in color. The inactive ingredients in the tablet are croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, maltodextrin, medium chain triglycerides, microcrystalline cellulose, polydextrose, povidone-30, sodium lauryl sulfate, talc, titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Analgesia

COMBOGESIC contains acetaminophen and ibuprofen.

Acetaminophen is a non-opiate, non-salicylate analgesic. The precise mechanism of the analgesic properties of acetaminophen is not established but is thought to primarily involve central actions. Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID). Its mechanism of action for analgesia, like that of other NSAIDs, is not completely understood, but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Ibuprofen is a potent inhibitor of prostaglandin synthesis in vitro. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because ibuprofen is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

12.2 Pharmacodynamics

Hematological Effects

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of

shorter duration, and reversible.

12.3 Pharmacokinetics

Absorption

Peak plasma concentration following the administration of three COMBOGESIC tablets occurs at approximately 45 minutes and 1 hour 15 minutes after administration for acetaminophen and ibuprofen, respectively, under fasting condition. In the same study, the peak plasma concentration (C_{max}) and the extent of absorption ($AUC_{0\text{-}inf}$) are 14.88 mcg/mL and 47.44 mcg.h/mL for acetaminophen and 25.58 mcg/mL and 95.62 mcg.h/mL for ibuprofen, respectively. The C_{max} and $AUC_{0\text{-}inf}$ values for both acetaminophen and ibuprofen increase dose proportionally to increases in COMBOGESIC doses from one, to two, to three tablets. A single-dose pharmacokinetic study of COMBOGESIC in volunteers showed no drug interactions between acetaminophen and ibuprofen.

Food effects

When COMBOGESIC was administered with food, the time to peak plasma concentration was delayed by approximately 30 minutes for acetaminophen and was approximately the same when compared to fasting conditions for ibuprofen. The peak plasma concentration of acetaminophen was reduced by approximately 30%, but the extent of absorption was not affected. Peak plasma concentration and the extent of absorption were not affected for ibuprofen.

Distribution

Acetaminophen appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 L/kg. A relatively small portion (~20%) of acetaminophen is bound to plasma protein.

Elimination

The half-life of acetaminophen is about 2 to 3 hours in adults. It is somewhat shorter in children and somewhat longer in neonates and in cirrhotic patients. Acetaminophen is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner.

Ibuprofen is rapidly metabolized and eliminated in the urine. The elimination half-life of ibuprofen is in the range of 1.9 to 2.2 hours.

Metabolism

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways:

a) conjugation with glucuronide;
b) conjugation with sulfate; and
c) oxidation via the cytochrome, P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 as additional pathways.

In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a

lesser extent, with sulfate. These glucuronide-, sulfate-, and glutathione-derived metabolites lack biologic activity. In premature infants, newborns, and young infants, the sulfate conjugate predominates.

Excretion

Less than 9% of acetaminophen is excreted unchanged in the urine.

The excretion of ibuprofen is virtually complete 24 hours after the last dose. Studies have shown that following ingestion of ibuprofen 45% to 79% of the dose was recovered in the urine within 24 hours as metabolite A (25%), (+)-2-[p-(2hydroxymethyl-propyl) phenyl]propionic acid and metabolite B (37%), (+)-2-[p-(2carboxypropyl)phenyl]propionic acid; the percentages of free and conjugated ibuprofen were approximately 1% and 14%, respectively.

Specific Populations

Pediatric Patients

The pharmacokinetics of COMBOGESIC has not been studied in pediatric patients below 18 years of age.

Hepatic Impairment

The pharmacokinetics of COMBOGESIC in patients with impaired hepatic function has not been studied *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.7)]*.

Renal Impairment

The pharmacokinetics of COMBOGESIC in patients with renal impairment has not been studied. *[see Warnings and Precautions (5.6) and Use in Specific Populations (8.6)].*

Drug Interaction Studies

Aspirin: When ibuprofen is administered with aspirin, its protein binding is reduced, although the clearance of free ibuprofen is not altered. The clinical significance of this interaction is not known *[see Drug Interactions (7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Studies to evaluate the potential effects of COMBOGESIC on carcinogenicity, mutagenicity, or impairment of fertility have not been conducted.

Carcinogenesis

Acetaminophen

Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing acetaminophen up to 6000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 0.8 times the maximum human daily dose (MHDD) of 3.9 grams/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats (0.7 times) or mice

(1.3-1.5 times the MHDD, based on a body surface area comparison).

Ibuprofen

Adequate long-term animal studies have not been conducted to evaluate the carcinogenic potential of ibuprofen.

Mutagenesis

Acetaminophen

Acetaminophen was not mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, acetaminophen tested positive in the in vitro mouse lymphoma assay and the in vitro chromosomal aberration assay using human lymphocytes. In the published literature, acetaminophen has been reported to be clastogenic when administered a dose of 1500 mg/kg/day to the rat model (3.7-times the MHDD, based on a body surface area comparison). In contrast, no clastogenicity was noted at a dose of 750 mg/kg/day (1.9-times the MHDD, based on a body surface area comparison), suggesting a threshold effect.

Ibuprofen

In published studies, ibuprofen was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames assay).

Impairment of Fertility

Acetaminophen

In studies of acetaminophen conducted by the National Toxicology Program, fertility assessments with acetaminophen have been completed in Swiss mice via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 1.8 times the MHDD of acetaminophen, based on a body surface area comparison. Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal sperm in mice consuming 1.8 times the MHDD (based on a body surface area comparison) and there was a reduction in the number of mating pairs producing a fifth litter at this dose, suggesting the potential for cumulative toxicity with chronic administration of acetaminophen near the upper limit of daily dosing.

Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface area comparison) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment.

In a published mouse study, oral administration of 50 mg/kg acetaminophen to pregnant mice from Gestation Day 7 to delivery (0.062 times the MHDD) reduced the number of primordial follicles in female offspring and reduced the percentage of full term pregnancies and number of pups born to these females exposed to acetaminophen in utero.

In a published study, pregnant rats oral administration of 350 mg/kg acetaminophen (0.87 times the MHDD) from Gestation Day 13 to 21 (dams), reduced the number of germ cells in the fetal ovary and decreased ovary weight and reduced number of pups per litter in F1 females as well as reduced ovary weights in F2 females.

Ibuprofen

In a published study, dietary administration of ibuprofen to male and female rats 8-weeks prior to and during mating at dose levels of 20 mg/kg (0.17-times the MHDD based on body surface area comparison) did not impact male or female fertility or litter size.

In other studies, adult mice were administered ibuprofen intraperitoneally at a dose of 5.6 mg/kg/day (0.023-times the MHDD based on a body surface area comparison) for 35 or 60 days in males and 35 days in females. There was no effect on sperm motility or viability in males, but decreased ovulation was reported in females.

14 CLINICAL STUDIES

In a Phase 3 efficacy study in 110 patients (aged from 16 to 55 years, approximately two-thirds female, and more than 80% Caucasian) with post-procedural pain following surgical extraction of impacted wisdom teeth, three tablets of COMBOGESIC provided greater pain reduction than placebo or comparable doses of acetaminophen or ibuprofen alone. The treatment differences were measured by the primary end point.

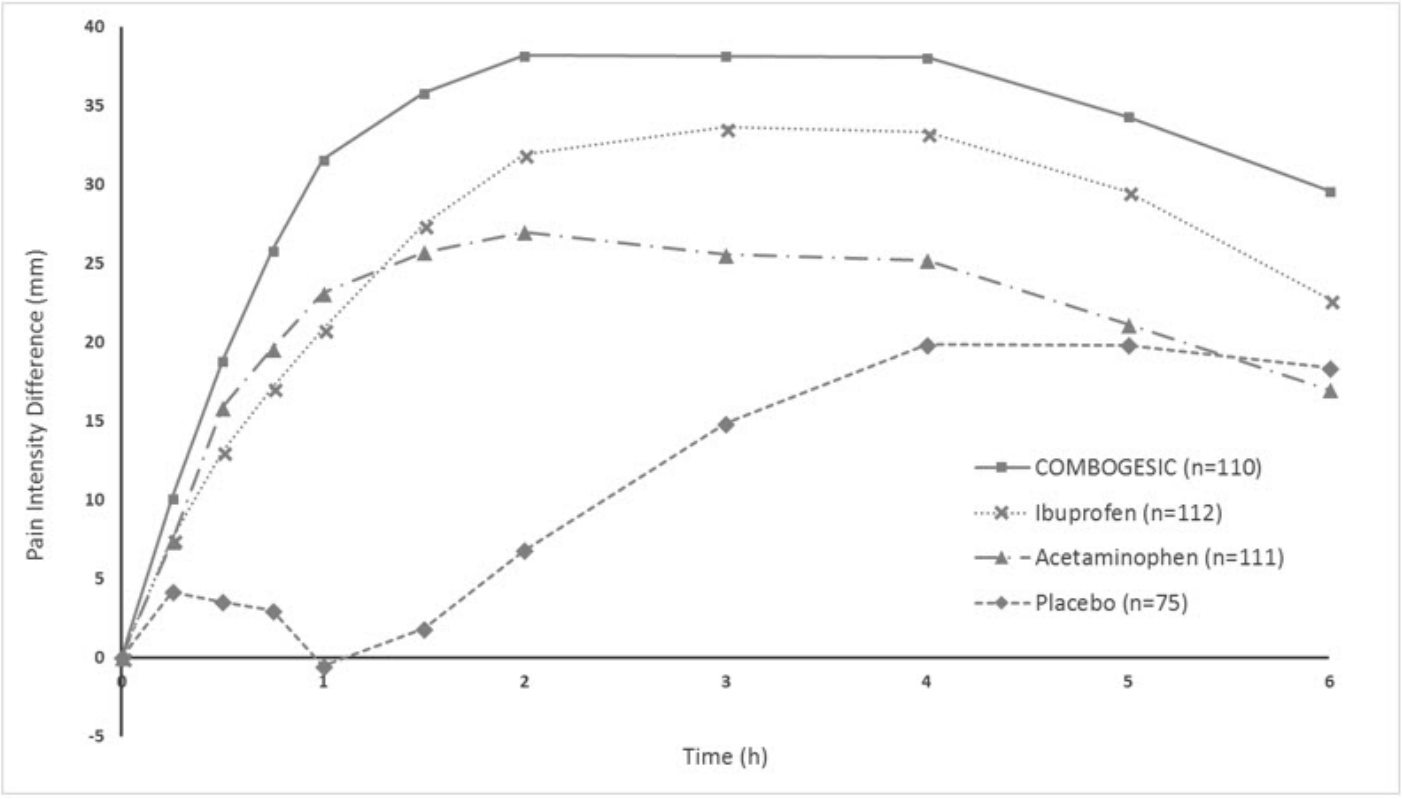
The treatment differences in the time-adjusted Summed Pain Intensity Difference over the first 48 hours (SPID 0-48), are statistically significant as summarized in the table below.

Table 3: Summary of Time-adjusted SPID (0-48 Hours) by Treatment Group

	Ibuprofen 97.5 mg ***N=112***	**Acetaminophen 325 mg** ***N=111***	**Placebo** ***N=75***	**COMBOGESIC** ***N=110***
Mean	23.18	17.71	14.86	31.56
SE	1.89	1.89	2.26	1.94
95% CI (Lower)	19.47	14.00	10.43	27.76
95% (Upper)	26.89	21.43	19.30	35.37
P-value COMBOGESIC	<0.001	<0.001	<0.001	-

The observed treatment differences over the first six hours are illustrated by the separation of pain curves as shown in Figure 1 below.

Figure 1: Pain Intensity Differences from baseline over the first dose interval of AFT-MX-6



16 HOW SUPPLIED/STORAGE AND HANDLING

COMBOGESIC tablets with acetaminophen 325 mg and ibuprofen 97.5 mg are white, biconvex, capsule-shaped film coated tablets, debossed with the letters "CG" on one side and plain on the other side and are available as follows:

NDC 0143-9432-27	1 bottle containing 250 tablets

Store at 20°C to 25°C (68°F to 77°F) with excursions permitted within USP controlled room temperature of 15°C to 30°C (59°F to 86°F). Protect from moisture and light.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Important Dosage and Administration Information:

- Clearly explain to patients the single-dose and 24-hour dose limit and the time interval between doses. Explain that exceeding these recommendations can result in hepatic toxicity and/or gastrointestinal bleeding, ulceration, and perforation *[See Dosage and Administration (2), Warnings and Precautions (5.1, 5.3)].*
- Inform patients that the concomitant use of COMBOGESIC with other NSAIDs, acetaminophen-containing products, or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of hepatic and gastrointestinal toxicity, and little or no increase in efficacy [see *Warnings and Precautions (5.1, 5.3), Drug Interactions (7)*]. Alert patients that these may be present in "over the counter" medications for treatment of colds, fever, or insomnia.

- Alert patients that NSAIDs and acetaminophen may be present in "over the counter" medications for treatment of colds, fever, or insomnia.

Hepatotoxicity: Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness and "flu-like" symptoms). Instruct patients to stop therapy and seek immediate medical assistance if these occur *[see Warnings and Precautions (5.1)]*.

Alcohol: Advise patients not to take COMBOGESIC concomitantly with alcohol-containing beverages *[see Warnings and Precautions (5.1)]*.

Cardiovascular Thrombotic Effects: Inform patients that COMBOGESIC, like other NSAID-containing medications, may cause serious CV side effects such as MI or stroke, which may result in hospitalization and even death. Advise patients to be alert for chest pain, shortness of breath, weakness, and slurring of speech, and to seek medical assistance when observing any sign or symptom indicative of CV effects *[see Warnings and Precautions (5.2)]*.

Gastrointestinal Bleeding, Ulceration, and Perforation: Inform patients that COMBOGESIC, like other NSAID-containing medications, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Advise patients to be alert for the signs and symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis, and to seek medical assistance should these symptoms occur *[see Warnings and Precautions (5.3)]*.

Heart Failure and Edema: Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur *[see Warnings and Precautions (5.5)]*.

Weight Gain and Edema: Advise patients to promptly report unexplained weight gain or edema to their physicians *[see Warnings and Precautions (5.5)]*.

Anaphylactic Reactions: Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur *[see Warnings and Precautions (5.7)]*.

Serious Skin Reactions, including DRESS: Advise patients to stop taking COMBOGESIC immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible *[see Warnings and Precautions (5.9, 5.10)].*

Female Fertility: Advise females of reproductive potential who desire pregnancy that NSAID containing products, including COMBOGESIC tablets, may be associated with a reversible delay in ovulation *[see Use in Specific Populations (8.3)].*

Fetal Toxicity: Inform pregnant women to avoid use of COMBOGESIC and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with COMBOGESIC is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours *[see Warnings and Precautions (5.11) and Use in Specific Populations (8.1)].*

Use of NSAIDS and Low-Dose Aspirin: Inform patients not to use low-dose aspirin concomitantly with COMBOGESIC until they talk to their healthcare provider *[see Drug*

Interactions (7)].

Manufactured by: Catalent Greenville Inc., 1240 Sugg Parkway, Greenville, NC 27834

Distributed by:
Hikma Pharmaceuticals USA Inc. Berkeley Heights, NJ 07922
Information and patents: https://www.combogesictablets.com

Medication Guide
COMBOGESIC (*kom-boh-JEE-zik*)
(acetaminophen and ibuprofen)
tablets

COMBOGESIC is a combination prescription medicine that contains acetaminophen **and** ibuprofen (a nonsteroidal anti-inflammatory drug [NSAID]).

What is the most important information I should know about COMBOGESIC?
COMBOGESIC may cause serious side effects, including:

- **Severe liver problems.** Acetaminophen, one of the ingredients in COMBOGESIC, has caused severe and life-threatening acute liver failure which caused the need for a liver transplant and has caused death.
  - Taking COMBOGESIC with other products that contain acetaminophen can lead to serious severe liver problems and death. **Do not take COMBOGESIC with other acetaminophen containing products.**
  - **You should not take more than 3 COMBOGESIC tablets in one dose or more than 12 COMBOGESIC tablets in one day.**
  - If you take too much COMBOGESIC or acetaminophen, call your healthcare provider or Poison Control Center at 1-800-222-1222, or go to the nearest hospital emergency room right away.
- **Increased risk of a heart attack or stroke that can lead to death**. This risk may happen early in treatment and may increase**:**
  - with increasing doses of medicines containing NSAIDs
  - with longer use of medicines containing NSAIDs

  Do not take COMBOGESIC right before or after a heart surgery called a "coronary artery bypass graft (CABG)."
  Avoid taking COMBOGESIC after a recent heart attack unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take COMBOGESIC after a recent heart attack.
- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
  - anytime during use
  - without warning symptoms
  - that may cause death

  The risk of getting an ulcer or bleeding increases with:
  - past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
  - taking medicines called "corticosteroids", "anticoagulants", "SSRIs", or "SNRIs"
  - increasing doses of NSAIDs
  - longer use of NSAIDs

- smoking
- drinking alcohol
- older age
- poor health
- advanced liver disease
- bleeding problems

COMBOGESIC should only be taken exactly as prescribed, at the lowest dose possible for your treatment, and for the shortest time needed.

What is COMBOGESIC?

COMBOGESIC is a combination prescription medicine that contains acetaminophen and ibuprofen (a non-steroidal anti-inflammatory drug [NSAID]) used in adults for the short-term management of mild to moderate acute pain.

It is not known if COMBOGESIC is safe and effective for use in children.

Do not take COMBOGESIC:

- If you are allergic to acetaminophen, ibuprofen, other NSAIDs, or to any of the ingredients in COMBOGESIC. See the end of this Medication Guide for a complete list of ingredients in COMBOGESIC.
- If you have had an asthma attack, hives, or other allergic reactions after taking aspirin or any other NSAIDs.
- Right before or after heart bypass surgery.

Before taking COMBOGESIC, tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems
- have high blood pressure
- have asthma
- have heart problems
- have bleeding problems
- have or have had ulcers
- drink alcohol
- are pregnant or plan to become pregnant. Taking COMBOGESIC at about 20 weeks of pregnancy or later may harm your unborn baby.
  - If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. **You should not take NSAIDs after about 30 weeks of pregnancy.**
  - NSAID containing products, including COMBOGESIC, may cause reversible fertility problems in females, which may temporarily affect your ability to become pregnant during treatment with COMBOGESIC. Talk to your healthcare provider if this is a concern for you.
- are breastfeeding or plan to breastfeed**.** Ibuprofen can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with COMBOGESIC.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. COMBOGESIC and some other medicines can interact with each other and cause serious side effects. **Do not start taking any new medicine without talking to**

your healthcare provider first.

How should I take COMBOGESIC?

- Take COMBOGESIC exactly as your healthcare provider tells you to take it.
- **You should not take more than 3 COMBOGESIC tablets in one dose or more than 12 COMBOGESIC tablets each day.**
- If you take too much COMBOGESIC, call your healthcare provider or Poison Control Center at 1-800-222-1222, or go to the nearest hospital emergency room right away.

What should I avoid while taking COMBOGESIC?

- You should avoid drinking alcohol during treatment with COMBOGESIC. Drinking alcohol during treatment with COMBOGESIC may increase your chances of having serious side effects.

What are the possible side effects of COMBOGESIC?
COMBOGESIC may cause serious side effects, including:
See "What is the most important information I should know about COMBOGESIC?"

- new or worse high blood pressure
- heart failure
- liver problems including liver failure
- kidney problems including kidney failure
- high potassium level in your blood (hyperkalemia)
- life-threatening allergic reactions
- life-threatening skin reactions
- low red blood cells (anemia)
- changes in your vision

Other side effects of COMBOGESIC include: nausea, vomiting, headache, dizziness, sleepiness, bleeding after medical procedures, swelling of the face.
Get emergency help right away if you get any of the following symptoms:

- shortness of breath or trouble breathing
- slurred speech
- chest pain
- swelling of the face or throat
- weakness in one part or side of your body

Stop taking COMBOGESIC and call your healthcare provider right away if you get any of the following symptoms:

- nausea
- vomit blood
- more tired or weaker than usual
- there is blood in your bowel movement or it is black and sticky like tar
- diarrhea
- itching
- unusual weight gain
- your skin or eyes look yellow
- skin rash or blisters with fever (including rash with hives, sores in your mouth or eyes, or your skin blisters and peels)

- indigestion or stomach pain
- swelling of the arms, legs, hands, and feet
- flu-like symptoms

These are not all the possible side effects of COMBOGESIC.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about NSAIDs

- Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

General information about the safe and effective use of COMBOGESIC.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use COMBOGESIC for a condition for which it was not prescribed. Do not give COMBOGESIC to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about COMBOGESIC that is written for health professionals.

What are the ingredients in COMBOGESIC?
Active ingredients: acetaminophen and ibuprofen
Inactive ingredients: croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, maltodextrin, medium chain triglycerides, microcrystalline cellulose, polydextrose, povidone-30, sodium lauryl sulfate, talc, titanium dioxide.
Manufactured by: Catalent Greenville Inc, 1240 Sugg Parkway, Greenville, NC 27834. Ph: +1-252-752-3800
Distributed by: Hikma Pharmaceuticals USA Inc. Berkeley Heights, NJ 07922. Ph: 1-877-845-0689
For more information, go to www.hikma.com or call: 908-673-1030

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued:11/2024

PRINCIPAL DISPLAY PANEL - 325 mg/97.5 mg Tablet Bottle Label

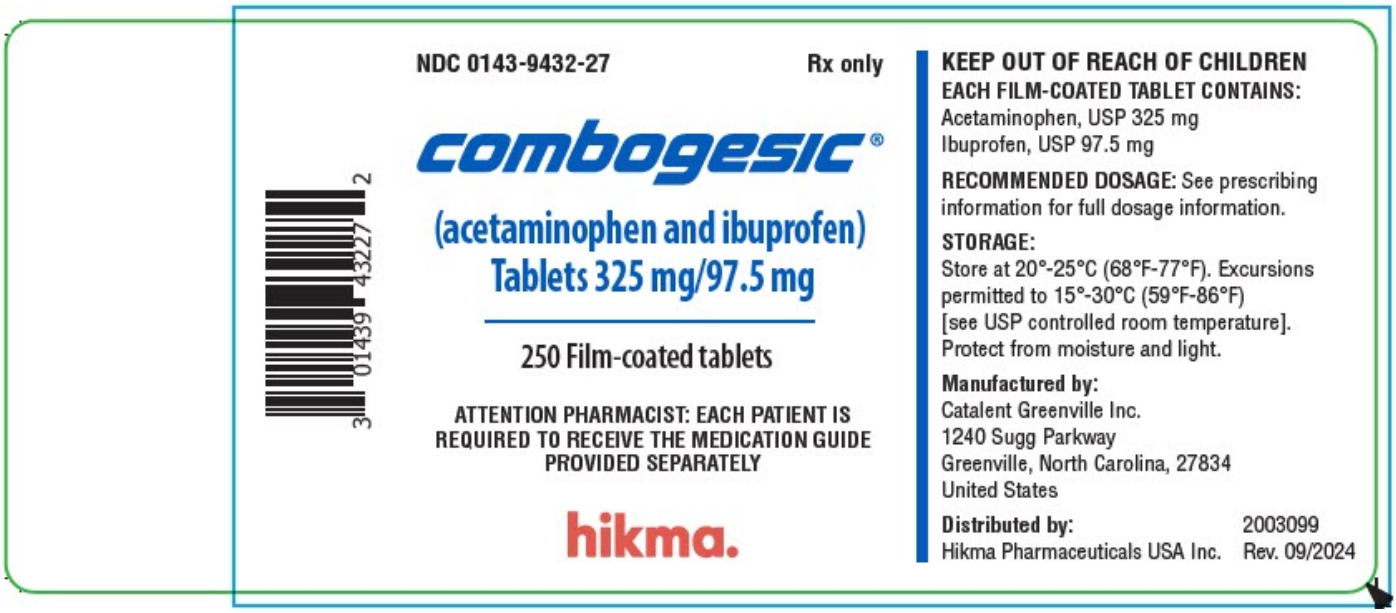
NDC 0143-9432-27
Rx only

combogesic®
(acetaminophen and ibuprofen)
Tablets 325 mg/97.5 mg

250 Film-coated tablets

ATTENTION PHARMACIST: EACH PATIENT IS
REQUIRED TO RECEIVE THE MEDICATION GUIDE
PROVIDED SEPARATELY

hikma.



COMBOGESIC

acetaminophen and ibuprofen tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0143-9432
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ACETAMINOPHEN (UNII: 362O9ITL9D) (ACETAMINOPHEN - UNII:362O9ITL9D)	ACETAMINOPHEN	325 mg
IBUPROFEN (UNII: WK2XYI10QM) (IBUPROFEN - UNII:WK2XYI10QM)	IBUPROFEN	97.5 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE K30 (UNII: U725QWY32X)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
HYPROMELLOSE 2910 (15 MPA.S) (UNII: 36SFW2JZ0W)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYDEXTROSE (UNII: VH2XOU12IE)	
TALC (UNII: 7SEV7J4R1U)	
MALTODEXTRIN (UNII: 7CVR7L4A2D)	
MEDIUM-CHAIN TRIGLYCERIDES (UNII: C9H2L21V7U)	

Product Characteristics			
Color	WHITE	**Score**	no score
Shape	OVAL (biconvex ,oval)	**Size**	18mm
Flavor		**Imprint Code**	CG
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0143-9432-27	250 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	01/06/2025	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA209471	01/06/2025	

Labeler - Hikma Pharmaceuticals USA Inc (001230762)

Registrant - AFT Pharmaceuticals US, Inc. (119336103)

Revised: 1/2025 Hikma Pharmaceuticals USA Inc