Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

GOTA-D 40/50

Febuxostat and Diacerein Tablets 40mg/50mg

2. Qualitative and quantitative composition

Each film coated tablet contains:

Febuxostat	40 mg
Diacerein BP	50 mg

Excipients of known effect: Lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film Coated Tablets.

White coloured, round shaped, biconvex, film-coated tablet.

4. Clinical particulars

4.1 Therapeutic indications

Febuxostat and Diacerein tablet is indicated in reducing acute gout flares, inflammation, and in reducing clinical symptoms in patients with refractory gout. Febuxostat and Diacerein tablet is indicated in adults.

4.2 Posology and method of administration Posology

Adults (aged over 18 years): The recommended oral dose of Febuxostat is 40 mg once or twice daily. If serum uric acid is > 6 mg/dL (357 µmol/L) after 2-4 weeks, Febuxostat 120 mg daily may be considered. Febuxostat works sufficiently quickly to allow retesting of the serum uric acid after 2 weeks.

As some patients may experience loose stools or diarrhea, the recommended starting dose of Diacerein is 50 mg once daily with evening meal for the first 2 to 4 weeks of treatment, after which the recommended daily dose is 50 mg

twice daily.

The treatment should be taken with food, one tablet with breakfast and the other tablet with evening meal.

Elderly and Renal impairment: In the elderly, and in moderate renal impairment, there is no need to change the dosage. In patients older than 65 years, caution should be exercised during use of this medicine; close supervision and monitoring of adverse reactions should be performed. In severe renal insufficiency (creatinine clearance below 30 ml/min), the daily dosage is to be halved.

Paediatric population: This product is not recommended to be used in children below the age of 18 years.

Method of administration

For oral use only. The tablets must be swallowed intact, without breaking or crushing, together with a glass of water.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Inflammatory organic bowel disease (ulcerative colitis, Crohn's disease). Intestinal obstruction or partial obstruction.
Abdominal pain syndromes of indeterminate etiology. Current and/or history of liver disease.

4.4 Special warnings and precautions for use Febuxostat:

Cardio-vascular disorders:

Treatment of chronic hyperuricaemia

Treatment with febuxostat in patients with ischaemic heart disease or congestive heart failure is not recommended.

Medicinal product allergy / hypersensitivity:

Rare serious allergic/hypersensitivity reactions, including life-threatening Stevens-Johnson Syndrome, Toxic epidermal necrolysis and acute anaphylactic reaction/shock, have been reported.

Acute gouty attacks (gout flare):

Febuxostat treatment should not be started until an acute attack of gout has

completely subsided. Gout flares may occur during initiation of treatment due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. At treatment initiation with febuxostat flare prophylaxis for at least 6 months with an NSAID or colchicine is recommended. If a gout flare occurs during febuxostat treatment, it should not be discontinued. The gout flare should be managed concurrently as appropriate for the individual patient. Continuous treatment with febuxostat decreases frequency and intensity of gout flares.

Xanthine deposition:

As there has been no experience with febuxostat, its use in patients with Lesch-Nyhan Syndrome is not recommended.

Mercaptopurine/azathioprine:

Febuxostat use is not recommended in patients concomitantly treated with mercaptopurine/ azathioprine as inhibition of xanthine oxidase by febuxostat may cause increased plasma concentrations of mercaptopurine/azathioprine that could result in severe toxicity.

Liver disorders:

During the combined phase 3 clinical studies, mild liver function test abnormalities were observed in patients treated with febuxostat (5.0 %). Liver function test is recommended prior to the initiation of therapy with febuxostat and periodically thereafter based on clinical judgment.

Thyroid disorders:

Increased TSH values (> 5.5 µIU/mL) were observed in patients on long-term treatment with febuxostat (5.5 %) in the long term open label extension studies. Caution is required when febuxostat is used in patients with alteration of thyroid function.

Diacerein:

Diarrhea:

Intake of diacerein frequently leads to diarrhea (see chapter 4.8) that can consequently lead to dehydration and hypokalemia. In patients receiving diuretics, caution should be exercised because dehydration and hypokalemia may occur. Particular caution should also be exercised in case of hypokalemia in patients treated with cardiac glycosides (digitoxin, digoxin). Concomitant intake of laxatives should be avoided.

Hepatotoxicity:

Elevated serum hepatic enzyme levels and symptomatic acute hepatic injury have been reported with diacerein in the post-marketing phase. Before treatment with diacerein is initiated, the doctor should question the patient about any possible comorbidities, and past or current liver disease and screen for major causes of active hepatic disease. A diagnosis of liver disease is a contraindication to diacerein use. Patients should be advised to limit their alcohol intake while on treatment with diacerein.

4.5 Interaction with other medicinal products and other forms of interaction Febuxostat:

Mercaptopurine/azathioprine:

On the basis of the mechanism of action of febuxostat on XO inhibition concomitant use is not recommended. Inhibition of XO by febuxostat may cause increased plasma concentrations of these medicinal products leading to toxicity.

Rosiglitazone/CYP2C8 substrates:

Co-administration of febuxostat with rosiglitazone or other CYP2C8 substrates is not expected to require any dose adjustment for those compounds.

Naproxen and other inhibitors of glucuronidation:

Febuxostat can be co-administered with naproxen with no dose adjustment of febuxostat or naproxen being necessary.

Inducers of glucuronidation:

Potent inducers of UGT enzymes might possibly lead to increased metabolism and decreased efficacy of febuxostat. Monitoring of serum uric acid is therefore recommended 1-2 weeks after start of treatment with a potent inducer of glucuronidation. Conversely, cessation of treatment of an inducer might lead to increased plasma levels of febuxostat.

Colchicine/indometacin/hydrochlorothiazide/warfarin:

Febuxostat can be co-administered with colchicine or with indomethacin or with hydrochlorothiazide or with warfarin with no dose adjustment of febuxostat or the co-administered active substance being necessary.

Diacerein:

Antacids (aluminum, calcium, and magnesium salts, oxides or hydroxides):
Decreased of digestive absorption of diacerein. Antacids should be taken separately from diacerein, allowing for an interval of greater than 2 hours if possible.
Diuretic and/or cardiac glycosides:
Intake of diacerein can lead to diarrhea and hypokalemia. Caution must be exercised in the concomitant administration of diuretics (high-ceiling loop and thiazides) and/or cardiac glycosides (digitoxin, digoxin), as the risk of arrhythmia is increased.

4.6 Pregnancy and lactation

Pregnancy

Clinically, there is currently no adequate data to assess a potential teratogenic or foetotoxic effect of this medicine when administered during pregnancy. Accordingly, the use of this medicine is not recommended during pregnancy.

Lactation

It is unknown whether febuxostat is excreted in human breast milk and the passage of the anthraquinone derivatives in breast milk in minimal proportions were highlighted in the literature. Therefore, it is not recommended to administer this medicine to women who is breast-feeding.

Fertility

The effect of this medicine on human fertility is unknown.

4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed. Somnolence, dizziness, paraesthesia and blurred vision have been reported with the use of febuxostat.
Patients should exercise caution before driving, using machinery or participating in dangerous activities until they are reasonably certain that Febuxostat and Diacerein Tablets does not adversely affect performance.

4.8 Undesirable effects

Febuxostat:

The most commonly reported adverse reactions in clinical trials (4,072 subjects treated at least with a dose from 10 mg to 300 mg) and post-marketing experience in gout patients are gout flares, liver function abnormalities, diarrhoea, nausea, headache, rash and oedema. These adverse reactions were mostly mild or moderate in severity. Rare serious hypersensitivity reactions to febuxostat, some of which were associated to systemic symptoms, have occurred in the post-marketing experience.

Common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000) adverse reactions occurring in patients treated with febuxostat are listed below. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Blood and lymphatic disorders

Rare: Pancytopenia, thrombocytopenia, agranulocytosis*

Immune system disorders

Rare: Anaphylactic reaction*, drug hypersensitivity*

Endocrine disorders

Uncommon: Blood thyroid stimulating hormone increased

Eye disorders

Rare: Blurred vision

Metabolism and nutrition disorders

Common: Gout flares

Uncommon: Diabetes mellitus, hyperlipidemia, decrease appetite, weight increase

Rare: Weight decrease, increase appetite, anorexia

Psychiatric disorders:

Uncommon: Libido decreased, insomnia

Rare: Nervousness

Nervous system

disorders *Common:*

Headache

Uncommon: Dizziness, paraesthesia, hemiparesis, somnolence, altered taste, hypoaesthesia, hyposmia

Ear and labyrinth disorders

Rare: Tinnitus

Cardiac disorders

Uncommon: Atrial fibrillation, palpitations, ECG abnormal

Vascular disorders

Uncommon: Hypertension, flushing, hot flush

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea, bronchitis, upper respiratory tract infection, cough

Gastro-intestinal disorders

Common: Diarrhoea, nausea

Uncommon: Abdominal pain, abdominal distension, gastrooesophageal reflux disease, vomiting, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort

Rare: Pancreatitis, mouth ulceration.

Hepatobiliary disorders

Common: Liver function abnormalities

Uncommon: Cholelithiasis

Rare: Hepatitis, jaundice, liver injury

Skin and subcutaneous tissue disorders

Common: Rash (including various types of rash reported with lower frequencies) *Uncommon:* Dermatitis, urticaria, pruritus, skin discolouration, skin lesion, petechiae, rash macular, rash maculopapular, rash popular

Rare: Toxic epidermal necrolysis, Stevens-Johnson Syndrome, angioedema, drug reaction with eosinophilia and systemic symptoms, generalized rash (serious), erythema, exfoliative rash, rash follicular, rash vesicular, rash pustular, rash pruritic, rash erythematous, rash morbillifom, alopecia, hyperhidrosis

Musculoskeletal and connective tissue disorders

Uncommon: Arthralgia, arthritis, myalgia, musculoskeletal pain, muscle weakness, muscle spasm, muscle tightness, bursitis

Rare: Rhabdomyolysis, joint stiffness, musculoskeletal stiffness

Renal and urinary disorders

Uncommon: Renal failure, nephrolithiasis, haematuria, pollakiuria, proteinuria

*Rare***:** Tubulointerstitial nephritis,

micturition urgency ***Reproductive system***

and breast disorders *Uncommon:* Erectile dysfunction

Diacerein:

Gastrointestinal disorders

Very common (> 1/10): diarrhea, abdominal pain.

Common (> 1/100 and < 1/10): frequent bowel movements, flatulence.

As a rule, these effects abate with continuing treatment. In some cases, diarrhea was severe with complications such as dehydration and disorders of fluid and electrolyte balance.

Pigmentation of the colorectal mucosa (melanosis coli) was rarely observed.

Hepatobiliary disorders

Uncommon (≥ 1/1000 and < 1/100): Cases of elevated hepatic enzymes in serum.

Skin and subcutaneous tissue disorders:

Common (> 1/100 and < 1/10): pruritus, rash, eczema.

Other:

Dark urine related to the structure of the molecule and without pathological value can be observed.

Cases of acute liver injury, including elevated serum hepatic enzymes and cases of hepatitis have been reported with diacerein. Most of them occurred during the first months of treatment. Patients should be monitored for signs and symptoms of hepatic injury.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions to report any suspected adverse reactions to the National Regulatory Authority.

4.9 Overdose

Patients with an overdose of febuxostat should be managed by symptomatic and supportive care. Profuse diarrhea may occur in the event of overdose of diacerein. Symptomatic treatment should then be instituted and electrolyte disorders and dehydration corrected if necessary.

5. Pharmacological properties

5.1 Pharmacodynamic properties:

Febuxostat: M04AA03, Antigout preparation, preparations inhibiting uric acid production. Febuxostat is a 2-arylthiazole derivative that achieves its therapeutic effect of decreasing serum uric acid by selectively inhibiting xanthine oxidase (XO). Febuxostat is a potent, non-purine selective inhibitor of XO (NP-SIXO) with an in vitro inhibition Ki value less than 1 nanomolar. Febuxostat has been shown to potently inhibit both the oxidized and reduced forms of XO. At therapeutic concentrations febuxostat does not inhibit other enzymes involved in purine or pyrimidine metabolism.

Diacerein: M01AX21, Other Anti-inflammatory and Antirheumatic agents, Non-Steroids. Diacerein is an anthraquinone derivative which has moderate anti-inflammatory activity. It is anti-inflammatory at high doses and devoid of any irritant effect on the stomach.

Action onset is slow, beginning towards day 30 of treatment and becoming significant after about 45 days. It has an additive effect in combination with NSAIDs. In vitro, diacerein has the following properties:

- inhibition of phagocytosis and macrophage migration
- inhibition of interleukin-1 synthesis
- reduction of collagenolytic activity

5.2 Pharmacokinetic properties Febuxostat:

Absorption: Febuxostat is rapidly (tmax of 1.0-1.5 h) and well absorbed (at least 84 %). After single or multiple oral 80 and 120 mg once daily doses, Cmax is approximately 2.8-3.2 µg/mL, and 5.0-5.3 µg/mL, respectively. Absolute bioavailability of the febuxostat tablet formulation has not been studied.

Following multiple oral 80 mg once daily doses or a single 120 mg dose with a high fat meal, there was a 49 % and 38 % decrease in Cmax and a 18 % and 16 % decrease in AUC, respectively. However, no clinically significant change in the percent decrease in serum uric acid concentration was observed where tested (80 mg multiple dose). Thus, Febuxostat tablets may be taken without regard to food.

Distribution: The apparent steady-state volume of distribution (Vss/F) of febuxostat ranges from 29 to 75 L after oral doses of 10-300 mg. The plasma

protein binding of febuxostat is approximately 99.2 %, (primarily to albumin), and is constant over the concentration range achieved with 80 and 120 mg doses. Plasma protein binding of the active metabolites ranges from about 82 % to 91 %.

Biotransformation: Febuxostat is extensively metabolized by conjugation via uridine diphosphate glucuronosyltransferase (UDPGT) enzyme system and oxidation via the cytochrome P450 (CYP) system. Four pharmacologically active hydroxyl metabolites have been identified, of which three occur in plasma of humans.

Elimination: Febuxostat is eliminated by both hepatic and renal pathways. Following an 80 mg oral dose of 14C-labeled febuxostat, approximately 49 % of the dose was recovered in the urine as unchanged febuxostat (3 %), the acyl glucuronide of the active substance (30 %), its known oxidative metabolites and their conjugates (13 %), and other unknown metabolites (3 %). In addition to the urinary excretion, approximately 45 % of the dose was recovered in the faeces as the unchanged febuxostat (12 %), the acyl glucuronide of the active substance (1 %), its known oxidative metabolites and their conjugates (25 %), and other unknown metabolites (7 %).

Diacerein:

Orally administered diacerein undergoes a hepatic first-pass effect and is totally deacetylated to rhein, the sulphoconjugated metabolite. After a single 50 mg dose, plasma diacerein concentrations peak arises at a mean 2.5 hours and the maximal concentration (Cmax) is of the order of 3 mg/l. Diacerein 50 mg intake with food increases the bioavailability (the area under the curve increases by nearly 25%) and delays absorption. For dose ranging from 50 to 200 mg of diacerin in single dose, the pharmacokinetic parameters are dose-independent. Protein binding is very strong (99%) and mainly consists in high-affinity binding to albumin. The elimination half-life (t1/2) of rhein is approximately 4.5 hours. The total quantity excreted in the urine is around 30%. 80% of the rhein excreted in urine is in sulpho- and glucuroconjugated form and 20% is excreted in unchanged form. Repeated administration of diacerein (50 mg twice daily) results in slight accumulation. In patients with severe kidney failure (creatinine clearance less than 30 ml/min), the area under the curve and elimination half-life are doubled and

urinary elimination halved.

6. Pharmaceutical particulars

6.1 List of excipients Core:

Lactose
Starch
Micro Crystalline Cellulose (112)
Sodium Starch Glycolate
Povidone K-30%
Purified Water
Magnesium Stearate
Talcum
Colloidal Silicon Dioxide

Coating:

Titanium Dioxide BP

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture.

6.5 Nature and contents of container

3 x 10 Alu/PVC blister pack

Febuxostat and Diacerein tablet – GOTA-D 40/50 is available in an Alu/PVC blister of 10 tablets. Such 03 blisters in a unit carton with package insert.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder

Conical Pharmaceuticals

13 FF, Raghuvir, Bapasitaram chowk, Nava Naroda, Ahmedabad-382346, Gujarat, India.

info@conicalpharmaceuticals.com

8. Marketing authorisation number

H2026/CTD11296/24677

9. Date of first authorization/renewal of the authorization

May 7, 2026

10. Date of revision of the text

May 7, 2026