SUMMARY OF PRODUCT CHARACTERISTICS UMBRA-40 TABLETS

1.0 NAME OF THE MEDICINAL PRODUCT:-

1.1 Product Name:-Umbra-40 Tablets

1.2 Generic Name:-Febuxostat Tablets 40mg.

1.3 Strength:-40mg

2.0 QUALITATIVE AND QUANTITAVE COMPOSITION:-

2.1 Each film-coated tablet contains:-

Febuxostat	40mg
Excipients	q.s.

Colour:-Titanium Dioxide BP

3.0 PHARMACEUTICAL FORM: - Film-Coated Tablets

4.0 CLINICAL PARTICULARS:-

4.1Therapeutic Indications:-Treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty Arthritis).

4.2 Posology and method of administration:-

Posology:-The recommended oral dose of Febuxostat once daily without regard to food. If serum uric acid is > 6 mg/dL (357 µmol/L) after 2-4 weeks, Febuxostat once daily may be considered. Febuxostat works sufficiently quickly to allow retesting of the serum uric acid after 2 weeks. The therapeutic target is to decrease and maintain serum uric acid below 6 mg/dL (357µmol/L).Gout flare prophylaxis of at least 6 months is recommended.

Elderly:-No dose adjustment is required in the elderly.

Renal impairment:-The efficacy and safety have not been fully evaluated in patients with severe renal impairment No dose adjustment is necessary in patients with mild or moderate renal impairment.

Hepatic impairment:-The efficacy and safety of Febuxostat has not been studied in patients with Severe hepatic impairment (Child Pugh Class C).The recommended dose in Patients with mild hepatic impairment is 40mg. Limited information is available in patients with moderate hepatic impairment.

Paediatric population:-The safety and the efficacy of Febuxostat in children aged below the age of 18 years have not been established. No data are available.

Method of administration:-Oral use

Febuxostat should be taken by mouth and can be taken with or without food.

4.3 Contraindications:-Febuxostat is contraindicated in patients being treated with azathioprine, Mercaptopurine or theophylline.

4.4 Special Warnings and Precautions for Use:-

Cardio-Vascular Disorders:-Treatment with Febuxostat in patients with ischaemic heart disease or Congestive heart failure is not recommended.

A numerical greater incidence of investigator-reported cardiovascular APTC events (defined endpoints from the Anti-Platelet Trialists' Collaboration (APTC) including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) was observed in the Febuxostat total group compared to the allopurinol group in the APEX and FACT studies (1.3 vs. 0.3 events per 100Patient Years (PYs)), but not in the CONFIRMS study. The incidence of investigator-reported cardiovascular APTC events in the combined Phase 3 studies (APEX, FACT and CONFIRMS studies) was 0.7 vs. 0.6 events per 100 PYs. In the long-term extension studies the incidences of investigator-reported APTC events were 1.2 and 0.6 events per 100 PYs for Febuxostat and allopurinol, respectively. No statistically significant differences were found and no causal relationship with Febuxostat was established. Identified risk factors among these patients were a medical history of atherosclerotic disease and/or myocardial infarction, or of congestive heart failure.

Medicinal Product Allergy/Hypersensitivity:-Rare reports of serious allergic/hypersensitivity reactions, including life-threatening Stevens - Johnson syndrome, Toxic epidermal necrolysis and acute anaphylactic reaction/shock, have been collected in the post-marketing experience. In most cases, these reactions occurred during the first month of therapy with Febuxostat. Some, but not all of these patients reported renal impairment and/or previous hypersensitivity to allopurinol. Severe hypersensitivity reactions, including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) were associated with fever, haematological, renal or hepatic involvement in some cases.
Patients should be advised of the signs and symptoms and monitored closely for symptoms of allergic/hypersensitivity reactions. Febuxostat treatment should be immediately stopped if serious allergic/hypersensitivity reactions, including Stevens - Johnson syndrome, occur since early withdrawal is associated with a better prognosis. If patient has developed allergic/hypersensitivity reactions including Stevens - Johnson syndrome and acute anaphylactic reaction/shock, Febuxostat must not be re-started in this patient at any time.

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:-In patients in whom the rate of urate formation is greatly increased (e.g. malignant disease and its treatment, Lesch-Nyhan syndrome) the absolute concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract. As there has been no experience with Febuxostat, its use in these populations is not recommended.

Mercaptopurine/azathioprine:-Febuxostat use is not recommended in patients concomitantly treated with mercaptopurine/azathioprine. Where the combination cannot be avoided patients should be closely monitored. A reduction of dosage of mercaptopurine or azathioprine is recommended in order to avoid possible haematological effects.

Organ Transplant Recipients:-As there has been no experience in organ transplant recipients, the use of Febuxostat in such patients is not recommended.

Theophylline:-Co-administration of Febuxostat 40 mg and theophylline 400mg single dose in healthy subjects showed absence of any pharmacokinetic interaction. Febuxostat 40mg can be used in patients concomitantly treated with theophylline without risk of increasing theophylline plasma levels.

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.

Febuxostat tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction.

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 drugs leading to toxicity. Drug interaction studies of febuxostat with drugs that are metabolized by XO have not been performed.

Drug interaction studies of febuxostat with cytotoxic chemotherapy have not been conducted. No data is available regarding the safety of febuxostat during cytotoxic therapy.

Rosiglitazone/CYP2C8 Substrates:-Febuxostat was shown to be a weak inhibitor of CYP2C8 in vitro. In a study in healthy subjects, co-administration of 120 mg febuxostat QD with a single 4 mg oral dose of rosiglitazone had no effect on the pharmacokinetics of rosiglitazone and its metabolite N-desmethyl rosiglitazone, indicating that febuxostat is not a CYP2C8 enzyme inhibitor in vivo.Thus,co-administration of febuxostat with rosiglitazone or other CYP2C8 substrates is not expected to require any dose adjustment for those Compounds.

Theophylline:-An interaction study in healthy subjects has been performed with febuxostat to evaluate whether the inhibition of XO may cause an increase in the theophylline circulating levels as reported with other XO inhibitors. The results of the study showed that the co-administration of febuxostat 40 mg QD with theophylline 400 mg single dose has no effect on the pharmacokinetics or safety of theophylline. Therefore no special caution is advised when febuxostat 40 mg and theophylline are given concomitantly.

Naproxen and other Inhibitors of Glucuronidation:-Febuxostat metabolism depends on Uridine Glucuronosyl Transferase (UGT) enzymes. Medicinal products that inhibit glucuronidation, such as NSAIDs and probenecid, could in theory affect the elimination of febuxostat. In healthy subjects concomitant use of febuxostat and naproxen 250mg twice daily was associated with an increase in febuxostat exposure (C_{max} 28%, AUC 41% and $t_{1/2}$ 26%). In clinical studies the use of naproxen or other NSAIDs/Cox-2 inhibitors was not related to any clinically significant increase in adverse events. 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/Indomethacin/Hydrochlorothiazide/Warfarin:- Febuxostat can be co-administered with colchicine or indomethacin with no dose adjustment of febuxostat or the co-administered active substance being necessary. No dose adjustment is necessary for febuxostat when administered with hydrochlorothiazide. No dose adjustment is necessary for warfarin when administered with febuxostat. Administration of febuxostat (40mg) with warfarin had no effect on the pharmacokinetics of warfarin in healthy subjects. INR and Factor VII activity were also not affected by the co- administration of febuxostat.

Desipramine/CYP2D6 Substrates:-Febuxostat was shown to be a weak inhibitor of CYP2D6 in vitro. In a study in healthy subjects, 40 mg Febuxostat resulted in a mean 22% increase in AUC of Desipramine, a CYP2D6 substrate indicating a potential weak inhibitory effect of febuxostat on the CYP2D6 enzyme in vivo. Thus, co-administration of febuxostat with other CYP2D6 substrates is not expected to require any dose adjustment for those compounds.

Antacids:-Concomitant ingestion of an antacid containing magnesium hydroxide and aluminium hydroxide has been shown to delay absorption of febuxostat (approximately 1 hour) and to cause a 32% decrease in C_{max}, but no significant change in AUC was observed. Therefore, febuxostat may be taken without regard to antacid use.

4.6 Pregnancy and Lactation:-

Pregnancy:-Data on a very limited number of exposed pregnancies have not indicated any adverse effects of febuxostat on pregnancy or on the health of the foetus/new born child. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development or parturition. The potential risk for human is unknown. Febuxostat should not be used during pregnancy.

Lactation:-It is unknown whether febuxostat is excreted in human breast milk. Animal studies have shown excretion of this active substance in breast milk and an impaired development of suckling pups. A risk to a suckling infant cannot be excluded. Febuxostat should not be used while breastfeeding.

Fertility:-In animals, reproduction studies up to 48 mg/kg/day showed no dose-dependent adverse Effects on fertility. The effect of Febuxostat on human fertility is unknown.

4.7 Effects on Ability to Drive and Use Machines:- 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 does not adversely affect performance

4.8 Undesirable Effects:-

Summary of the Safety Profile;-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 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.

Tabulated List of Adverse Reactions:-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.

Table1:-Adverse reactions in combined phase 3, long-term extension studies and post- marketing

Experience.

Blood and lymphatic system disorders	Rare Pancytopenia, thrombocytopenia
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, hyperlipidaemia, 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	Rare
disorders	Tinnitus
Cardiac disorders	Uncommon Atrial fibrillation, palpitations, ECG abnormal
Vascular disorders	Uncommon Hypertension, flushing, hot flush
Respiratory system disorders	Uncommon Dyspnoea, bronchitis, upper respiratory tract infection, cough
Gastrointestinal disorders	Common Diarrhoea**, nausea Uncommon Abdominal pain, abdominal distension, gastro-oesophageal reflux

	disease, vomiting, dry mouth, dyspepsia, constipation, frequent stools, flatulence, gastrointestinal discomfort Rare Pancreatitis, mouth ulceration
Hepato-biliary disorders	Common Liver function abnormalities** Uncommon Cholelithiasis Rare Hepatitis, jaundice*, liver injury*
Skin and subcutaneous tissue disorders	Common Rash Uncommon Dermatitis, urticaria, pruritus, skin discolouration, skin lesion, petechiae, rash macular, rash maculopapular, rash papular 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 morbilliform, alopecia, hyperhidrosis
Musculoskeletal and connective	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 disorder	Uncommon Erectile dysfunction

General disorders and administration	Common Oedema Uncommon Fatigue, chest pain, chest discomfort Rare Thirst
Investigations	Uncommon Blood amylase increase, platelet count decrease, WBC decrease, lymphocyte count decrease, blood creatine increase, blood creatinine increase, haemoglobin decrease, blood urea increase, blood triglycerides increase, blood cholesterol increase, haematocrit decrease, blood lactate dehydrogenase increased, blood potassium increase. Rare Blood glucose increase, activated partial thromboplastin time prolonged, red blood cell count decrease, blood alkaline phosphatase increase, blood creatine phosphokinase increase*

* Adverse reactions coming from post-marketing experience.
** Treatment-emergent non-infective diarrhoea and abnormal liver function tests in the Combined Phase 3 studies are more frequent in patients concomitantly treated with colchicine.
*** See section 5.1 for incidences of gout flares in the individual Phase 3 randomized controlled studies.

Description of Selected Adverse Reactions:-Rare serious hypersensitivity reactions to febuxostat, including Stevens - Johnson syndrome, Toxic epidermal necrolysis and anaphylactic reaction/shock, have occurred in the post-marketing experience. Stevens - Johnson syndrome and Toxic epidermal necrolysis are characterised by progressive skin rashes associated with blisters or mucosal lesions and eye irritation. Hypersensitivity reactions to febuxostat can be associated to the following symptoms: skin reactions characterised by infiltrated maculopapular eruption, generalised or exfoliative rashes, but also skin lesions, facial oedema, fever, Haematologic abnormalities such as thrombocytopenia and eosinophilia, and single or multiple organ involvement (liver and kidney including tubulointerstitial nephritis). Gout flares were commonly observed soon after the start of treatment and during the first months. Thereafter, the frequency of gout flare decreases in a time-dependent manner. Gout flare prophylaxis is recommended.

4.9 Overdose:-Patients with an overdose should be managed by symptomatic and supportive care.

5.0 PHARMACOLOGICAL PROPERTIES:-
5.1 Pharmacodynamics' Properties:- Uric acid is the end product of purine metabolism in humans and is

generated in the cascade of hypoxanthine → Xanthine → Uric acid. Both steps in the above transformations are catalyzed by xanthine oxidase (XO). Febuxostat is a 2-arylthiazole derivative that achieves its therapeutic effect of decreasing serum uric acid by selectively inhibiting XO. Febuxostat is a potent, non-purine selective inhibitor of XO (NP-SIXO) with an in vitro inhibition Ki value less than one 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, namely, guanine deaminase, hypoxanthine guanine phosphoribosyltransferase, orotate phosphoribosyltransferase, and orotidine monophosphate decarboxylase or purine nucleoside phosphorylase.

5.2 Pharmacokinetic Properties:-In healthy subjects, maximum plasma concentrations (C_{max}) and area under the plasma concentration time curve (AUC) of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg. For doses between 120 mg and 300 mg, a greater than dose proportional increase in AUC is observed for febuxostat. There is no appreciable accumulation when doses of 10 mg to 240 mg are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life ($t_{1/2}$) of approximately 5 to 8 hours.
Population pharmacokinetic/Pharmacodynamic analyses were conducted in 211 patients with hyperuricaemia and gout, treated with Febuxostat. In general, febuxostat pharmacokinetic parameters estimated by these analyses are consistent with those obtained from healthy subjects, indicating that healthy subjects are representative for pharmacokinetic/Pharmacodynamic assessment in the patient population with gout.

Absorption:-Febuxostat is rapidly (t_{max} of 1.0-1.5 h) and well absorbed (at least 84%). After single or multiple oral 80 and 120 mg once daily doses, C_{max} 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 C_{max} 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 may be taken without regard to food.

Distribution:-The apparent steady state volume of distribution (V_{ss}/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. *In vitro* studies with human liver microsomes showed that those oxidative metabolites were formed primarily by CYP1A1, CYP1A2, CYP2C8 or CYP2C9 and febuxostat glucuronide was formed mainly by UGT 1A1, 1A8, and 1A9.

Elimination:-Febuxostat is eliminated by both hepatic and renal pathways. Following an 40mg oral dose of ^{14}C-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%).

Renal Impairment:-Following multiple doses of 80 mg of Febuxostat in patients with mild, moderate or severe renal impairment, the C_{max} of febuxostat did not change, relative to subjects with normal renal function. The mean total AUC of febuxostat increased by approximately 1.8-fold from 7.5 µg·h/mL in the normal renal function group to 13.2 µg.h/mL in the severe renal dysfunction group. The C_{max} and AUC of active metabolites increased up to 2- and 4-fold, respectively. However, no dose adjustment is necessary in patients with mild or moderate renal impairment.

Hepatic Impairment:-Following multiple doses of 80 mg Febuxostat in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, the C_{max} and AUC of febuxostat and its metabolites did not change significantly compared to subjects with normal hepatic function. No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C).

Age.

There were no significant changes observed in AUC of febuxostat or its metabolites following multiple oral doses of Febuxostat in elderly as compared to younger healthy subjects.

Gender

Following multiple oral doses of Febuxostat C, the C_{max} and AUC were 24% and 12% higher in females than in males, respectively. However, weight-corrected C_{max} and AUC were similar between the genders. No dose adjustment is needed based on gender.

5.3 Preclinical Safety Data:-Effects in non-clinical studies were generally observed at exposures in excess of the maximum human exposure.

Carcinogenesis, Mutagenesis, Impairment of Fertility:-In male rats, a statistically significant increase in urinary bladder tumours (transitional cell papilloma and carcinoma) was found only in association with xanthine calculi in the high dose group, at approximately 11 times human exposure. There was no significant increase in any other tumour type in either male or female mice or rats. These findings are considered a consequence of species specific purine metabolism and urine composition and of no relevance to clinical use. A standard battery of test for genotoxicity did not reveal any biologically relevant genotoxic effects for febuxostat.

Febuxostat at oral doses up to 48 mg/kg/day was found to have no effect on fertility and reproductive performance of male and female rats.

There was no evidence of impaired fertility, teratogenic effects, or harm to the foetus due to febuxostat. There was high dose maternal toxicity accompanied by a reduction in weaning index and reduced development of offspring in rats at approximately 4.3 times human exposure. Teratology studies, performed in pregnant rats at approximately 4.3 times and pregnant rabbits at approximately 13 times human exposure did not reveal any teratogenic effects.

6.0 PHARMACEUTICAL PARTICULARS:-

6.1 List of Excipients:-

UMBRA-40 TABLETS
Starch BP
Microcrystalline Cellulose Powder-102 BP
Lactose Mono BP
Iso-Propyl Alcohol BP
P.V.P.K.-30 BP
Talcum BP
Magnesium Stearate BP
Sodium Starch Glycolate BP
Aerosil BP
White Coat (FC4S) IHS
Isopropyl Alcohol BP
Methylene Dihydrochloride BP
Colour Titanium Dioxide BP

6.2 Shelf Life: - 36 months.

6.3 Special Precautions for Storage: - Store in a cool, dry place, Protected from light below 30°C.

6.4 Nature and Contents of Container:-Alu/Alu Pack of 3X10 tablets/Carton.

6.5 Marketing Authorization Holder:

Leotetra Healthcare Limited

Plot-5, Naibawa Layout Zaria Rd, Kano.

6.6 Manufactured By:-

Trugen Pharmaceutical's Pvt. Ltd.

(WHO-GMP&ISO9001:2015CertifiedCompany)

Vill.-Tejjupur, Near Chodiala Rly. Station , Roorkee,

Distt-Haridwar, Uttarkahnd-247661

Trugen Pharmaceuticals Pvt. Ltd. APPROVED BY-QA Roorkee

6.7 Date of Revision of Text: - March. 2025.

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