BAGEDA

TRADE NAME
Bageda

INTERNATIONAL NONPROPRIETARY NAME
Leflunomide

CHEMICAL NAME
5-Methyl-N-[4-(trifluoromethyl)phenyl]isoxazole-4-carboxamide

PHARMACEUTICAL FORM
Film coated tablets.

Description:
**Bageda 10 mg**
White to off-white, round, plain on both sides, biconvex film coated tablets.

**Bageda 20 mg**
Light yellow, round, plain on both sides, biconvex film coated tablets.

COMPOSITION
**Bageda 10 mg**
Film coated tablet contains
- Active ingredient: leflunomide 10 mg.
- Excipients: hydroxypropylcellulose, lactose monohydrate, lactose anhydrous, maize starch pregelatinised, povidone K30, magnesium stearate, sodium starch glycolate, silica colloidal anhydrous.
- Coating composition: Opadry® II White 85F18422 (polyvinyl alcohol partially hydrolyzed; titanium dioxide; macrogol, talc).

**Bageda 20 mg**
Film coated tablet contains
- Active ingredient: leflunomide 20 mg.
- Excipients: hydroxypropylcellulose, lactose monohydrate, lactose anhydrous, maize starch pregelatinised, povidone K30, magnesium stearate, sodium starch glycolate, silica colloidal anhydrous.
- Coating composition: Opadry® II Yellow 85F220095 (polyvinyl alcohol partially hydrolyzed, titanium dioxide, macrogol, talc, iron oxide yellow, tartrazine aluminum lake, sunset yellow FCF aluminum lake).

ATC CODE L04AA13

PHARMACOTHERAPEUTIC GROUP
Immunosuppressive agent.

PHARMACOLOGICAL PROPERTIES
**PHARMACODYNAMICS**
**Bageda** belongs to the class of the disease-modifying antirheumatic drugs. It has antiproliferative, immunomodulatory, immunosuppressive, and anti-inflammatory properties. The active metabolite of leflunomide, A771726, inhibits dihydroorotate dehydrogenase enzyme,
and it has an antiproliferative activity. Leflunomide reduces the symptoms and slow down the progression of the joint damage in active rheumatoid and psoriatic arthritis. The therapeutic effect usually starts after 4 to 6 weeks and may further improve up to 4 to 6 months.

**PHARMACOKINETICS**

**Absorption**

82% to 95% of the medicinal product is absorbed. Its absorption is not affected if it is taken with or without food. Time to peak plasma concentration of A771726 is variable: between 1 and 24 hours after single administration. Half-life is 2 weeks. Attainment of steady-state plasma concentration of the active metabolite requires approximately 2 months of daily maintenance doses. Therefore, a loading dose of 100 mg for first 3 days of therapy is used to facilitate the rapid attainment of steady-state plasma concentration of the active metabolite A771726. The pharmacokinetic parameters of A771726 are linear over the dose range of 5 mg to 25 mg. At a dose of 20 mg/day, average plasma concentration of A771726 is 35 μg/ml. At multiple dose, plasma level of the medicinal product is 33- to 35-fold compared to single dose.

**Distribution**

In plasma, A771726 is rapidly and extensively (almost 100%) bound to proteins (the unbound fraction of A771726 is 0.62%). Binding to plasma may be reduced in patients with rheumatoid arthritis and chronic renal insufficiency.

**Biotransformation**

Leflunomide is metabolised to one primary (A771726) and several minor metabolites including 4--trifluoromethylalanine.

Biotransformation of leflunomide to A771726 and subsequent metabolism of A771726 are controlled by several enzymes and occur in microsomal and cytosolic cellular fractions. Studies of interaction with cimetidine (non-specific cytochrome P450 inhibitor) has shown that in vivo CYP enzymes are involved in leflunomide metabolism only to a small extent.

**Elimination**

Elimination of A771726 is slow, and it is characterized by the clearance of 31 ml/hr. The elimination half-life is approximately 2 weeks. Leflunomide is excreted in faeces, due to biliary excretion, and in urine. The principal urinary metabolites are leflunomide glucuronides and derivatives of A771726. The principal faecal metabolite is A771726.

**Renal insufficiency**

The pharmacokinetics of A771726 in patients on continuous ambulatory peritoneal dialysis appeared to be similar to healthy volunteers.

**Hepatic insufficiency**

No data on the medicinal product pharmacokinetics in patients with hepatic insufficiency are available.

**Elderly**

Pharmacokinetic data in elderly patients (aged 65 and older) are consistent with the ones in the middle age group.

**THERAPEUTIC INDICATIONS**

The medicinal product is indicated for the treatment of adult patients with:
- active rheumatoid arthritis as a disease-modifying drug in order to reduce symptoms of the disease and inhibit structural joint damage;
- active psoriatic arthritis.

**POSOLOGY AND ADMINISTRATION**

**Bageda** should be indicated by the specialists experienced in the treatment of rheumatoid arthritis. The medicinal product is for oral administration, it is swallowed whole with a sufficient amount of liquid, without regard to food.

Therapy is started with an oral single loading dose of 100 mg for 3 days.
In rheumatoid arthritis, the recommended maintenance dose is leflunomide 10 mg to 20 mg once daily; in psoriatic arthritis, the recommended maintenance dose is leflunomide 20 mg once daily. The therapeutic effect usually starts after 4 to 6 weeks and may further improve up to 4 to 6 months.

No dosage adjustment is required in patients over the age of 65.

CONTRAINDICATIONS

The medicinal product is contraindicated:
- in patients under the age of 18;
- in patients with hypersensitivity to leflunomide or any other component of the medicinal product (with a history of Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme);
- in patients with hepatic insufficiency;
- in patients with severe immunodeficiency (e.g. AIDS);
- in patients with significantly impaired bone marrow hemopoiesis or significant anaemia, leucopenia, or thrombocytopenia due to any causes (except for rheumatoid or psoriatic arthritis);
- in patients with serious, uncontrolled infections;
- in patients with moderate to severe renal insufficiency (since insufficient clinical experience is available);
- in patients with severe hypoproteinaemia (e.g. with nephrotic syndrome);
- in pregnant women, or women of childbearing potential who do not use reliable contraception;
- during lactation period.

ADVERSE EFFECTS

Determination of the frequency of adverse effects: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), frequency is unknown (frequency cannot be estimated with the available data).

Infections: rare – severe infections, including opportunistic infections, and sepsis, which may be fatal. The incidence of possible infections may increase (in particular, the incidence of rhinitis, bronchitis, and pneumonia).

Cardiovascular system: common – mild increase in blood pressure; rare – severe increase in blood pressure.

Gastrointestinal tract, liver: common – diarrhoea, nausea, vomiting, anorexia, oral mucosal disorders (e.g. aphthous stomatitis, mouth ulceration), abdominal pains, elevation of hepatic transaminases activity (especially, ALT), GGT and ALP, hyperbilirubinaemia; rare – hepatitis, jaundice/cholestasis; very rare – severe liver injury such as hepatic insufficiency and acute hepatic necrosis, which may be fatal; pancreatitis.

Respiratory system and mediastinal disorders: very rare – interstitial lung disease (including interstitial pneumonitis), which may be fatal.

Metabolism and nutrition disorders: common – increase in phosphokinase level; uncommon – hypokalaemia, hyperlipidaemia, hypophosphataemia; rare – increase in lactate dehydrogenase level; with unknown frequency – hypouricaemia.

Nervous system: common – headache, dizziness, paraesthesia, peripheral neuropathy.


Skin & its derivatives: common – increased hair loss, eczema, dry skin; very rare – erythema multiforme.

Allergy: common – mild allergic reactions, rash (including maculopapular rash), pruritus; uncommon – urticaria; very rare – severe anaphylactic/anaphylactoid reactions, Stevens-Johnson syndrome, Lyell's syndrome; with unknown frequency – lupus erythematosus, pustular psoriasis.

Blood and lymphatic system: common – leucopenia (leucocytes > 2000/μl); uncommon – anaemia, mild thrombocytopenia (platelets < 100,000/μl); rare – eosinophilia, leucopenia
(leucocytes < 2000/μl), pancytopenia (probably by antiproliferative mechanism); very rare –
agranulocytosis.
Recent, concomitant or consecutive use of potentially myelotoxic agents may be associated with
a higher risk of haematological effects. The risk of malignancy, particularly lymphoproliferative
disorders, is increased while using some immunosuppressive agents. Reproductive system: with unknown frequency – reversible decrease in sperm concentration,
total sperm count and its motility.

SPECIAL WARNINGS
Bageda may be indicated to the patients only after sound medical judgement. Before starting
treatment with Bageda, it is necessary to remember that there may be increase in adverse
effects in patients who previously used other disease-modifying antirheumatic drugs
having hepato- and haematotoxic effects (e.g. methotrexate).
The active metabolite of leflunomide (A771726) has a long elimination half-life, usually 1 (one)
to 4 (four) weeks.
Due to the long elimination half-life of the active metabolite of leflunomide (A771726), serious
adverse effects might occur or remain (e.g. hepatotoxicity, haematotoxicity, or allergic
reactions), even if the treatment with leflunomide has been stopped. In this event the washout
procedure has to be followed. The procedure may be repeated as clinically necessary. If there are
suspected severe immunological/allergic reactions such as Stevens-Johnson syndrome or Lyell's
syndrome, the full washout procedure is obligatory.
Therefore, in such cases of toxicity and transfer to treatment with the other disease-modifying
drug (e.g. methotrexate), the washout procedure is required after the treatment with
leflunomide.
Liver reactions
Since the active metabolite of leflunomide (A771726) is protein bound and cleared via hepatic
metabolism and biliary secretion, plasma level of A771726 is expected to be increased in
patients with hypoproteinaemia. Bageda is contraindicated in patients with severe
hypoproteinaemia or impairment of liver function.
Rare cases of severe liver injury, including some fatal cases, have been reported during treatment
with leflunomide.
Most of the cases were observed within the first 6 (six) months of treatment. Although casual
relationship of these adverse effects with leflunomide is not established and most cases had
several additional suspicious factors, it is considered essential that monitoring treatment
recommendations are strictly adhered to.
ALT level should be checked before treatment with leflunomide, and then every 2 weeks during
the first 6 months of treatment; and it should be checked once every 6-8 weeks thereafter.
Depending on intensity and stability of ALT level elevation, there are following
recommendations on dosage adjustment and the drug discontinuation.
For the approved 2- to 3-fold excess of the upper limit of normal ALT level, dose reduction from
20 mg to 10 mg may allow to continue treatment with leflunomide provided that this indicator is
strictly controlled. In case 2- to 3-fold excess of the upper limit of normal ALT level remains or
there is an approved ALT level elevation of more than 3-fold the upper limit of normal level, the
use of leflunomide should be discontinued and the wash-out procedure should be initiated.
Due to the potential additive hepatotoxic effects, it is recommended to avoid alcohol
consumption during treatment with leflunomide.
Haematological reactions
A complete blood count, including differential white blood cell count and platelet count, should
be performed before treatment with leflunomide as well as every 2 weeks for the first 6 months
of treatment and every 6-8 weeks thereafter.
In patients with pre-existing anaemia, leucopenia, and/or thrombocytopenia as well as in patients with impaired bone marrow function or those at risk of such disorders, the risk of haematological disorders is increased. If such effects occur, the washout procedure should be performed to reduce plasma level of A771726.

In case of severe haematological reactions, including pancytopenia, the use of Bageda and any other concomitant myelosuppressive drug should be discontinued, and the washout procedure should be initiated.

**Combinations with other treatments**

There are no current data on the co-administration of leflunomide with antimalarial medications used in rheumatologic diseases (e.g. chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine and other immunosuppressive agents (except for methotrexate). The risk associated with combination therapy is unknown, in particular in long-term treatment. Since such therapy can lead to additive or even synergistic toxicity (e.g. hepatotoxicity), combination of this medicinal product with other disease-modifying drugs (e.g. methotrexate) is not advisable.

**Switching to other treatments**

Since leflunomide has a long persistence in the body, switching to another disease-modifying drug (e.g. methotrexate) without performing the appropriate washout procedure may raise the possibility of additive risks even for a long time after the switching (e.g. kinetic interaction, organ toxicity).

Similarly, recent treatment with hepatotoxic or haematotoxic medicinal products (e.g. methotrexate) may result in increased adverse effects; therefore, before the treatment with leflunomide, its benefit and risk aspects has to carefully be examined.

**Skin reactions**

In case of ulcerative stomatitis, leflunomide administration should be discontinued. Very rare cases of Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported in patients treated with leflunomide. In case of skin and/or mucosal reactions, administration of Bageda and any other concurrent drug should be discontinued, and the washout procedure should be performed immediately. A complete washout is essential. In such cases, rechallenge is contraindicated.

**Infections**

It is known that medicinal products with immunosuppressive properties – like leflunomide – may cause patients to be more susceptible to infections, including opportunistic infections (infections caused by fungi and microorganisms that are capable of inducing infections only if there is a decrease in immunity). The infectious diseases are usually severe and require early and intensive treatment. In case of the severe infection, it may be necessary to interrupt the leflunomide treatment and perform the washout procedure.

The patients with positive reaction to the tuberculin test require special care because of the tuberculosis reactivation risk.

**Respiratory reactions**

During therapy with leflunomide, rare cases of interstitial lung disease have been reported. Some symptoms such as cough and dyspnoea may cause discontinuation of the treatment with leflunomide.

**Blood pressure**

Blood pressure should be controlled before starting the leflunomide treatment and periodically thereafter.

**Interactions**

Caution is advised when leflunomide is given together with the drugs metabolised by CYP2C9 (such as phenytoin, warfarin, tolbutamide), except for NSAIDs (nonsteroidal anti-inflammatory drugs).

**Recommendations for men**
There are no data on the risk of fetal toxicity (that is related to the toxic effect of the medicinal product on the father's sperm) when leflunomide is used by men. Experimental studies in this regard have not been conducted. To minimize any possible risk, while planning for a baby, men should discontinue the use of leflunomide and take 8 g of colestyramine 3 times daily for 11 days or 50 g of powdered activated carbon 4 times daily for 11 days.

**EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**
In case of dizziness and other central nervous system disorders while administering Bageda, the patients should refrain from driving cars and using machines during the treatment.

**PREGNANCY AND LACTATION**
Leflunomide is contraindicated in pregnant women or women of childbearing potential who do not use effective contraception.

The patients should be advised that if there is a menstrual suppression or any other reason to suspect pregnancy, they should notify the physician immediately for pregnancy testing; if the pregnancy test is positive, the physician and patient should discuss the risk to the pregnancy. It is possible that the rapidly decreased blood level of the active metabolite, due to the drug elimination procedure described below, at the first menstrual suppression may reduce the risk to the foetus from leflunomide.

Women receiving leflunomide treatment and wishing to become pregnant, are recommended to observe one of the following procedures in order to be sure that the foetus is not exposed to the toxic concentrations of A771726 (target concentration is below 0.02 mg/l).

**Waiting period**
A771726 plasma level can be expected to be above 0.02 mg/l for a long period. Its plasma level may be expected to decrease below 0.02 mg/l in 2 years after discontinuing the treatment with leflunomide. After a two-year waiting period, A771726 plasma level is measured for the first time. Thereafter, A771726 plasma level should be determined after at least 14 days. If both plasma levels are below 0.02 mg/l, no teratogenic risk is to be expected.

**Washout procedure**
After the treatment with leflunomide is discontinued, 8 g of colestyramine is administered 3 times daily for a period of 11 days. Alternatively, 50 g of powdered activated carbon is administered 4 times daily for a period of 11 days.

Irrespective of the washout procedure chosen, verification by two separate tests at the interval of at least 14 days is required, then there should be a waiting period of one-and-a-half months between the first occurrence of a plasma level of below 0.02 mg/l and fertilization. Women of childbearing potential should be informed that after leflunomide treatment discontinuation, a waiting period of 2 years is required before they may try to get pregnant. If 2-year waiting period with reliable contraception is considered unreasonable, for prophylactic purposes, a washout procedure may be advisable.

Both colestyramine and activated carbon may influence the absorption of oestrogens and progestogens, therefore, reliable contraception in the form of oral contraceptives cannot provide an absolute guaranty during the washout period with colestyramine or activated carbon. Alternative contraceptive methods are recommended.

Animal studies have shown that leflunomide or its metabolites pass into the breast milk. Therefore, breast-feeding women should not administer leflunomide.

**PAEDIATRIC POPULATION**
Bageda is not recommended for use in patients under the age of 18 years since there are no data on efficacy and safety in this population.
INTERACTION WITH OTHER MEDICINAL PRODUCTS

Increased adverse effects may occur in case of recent or concomitant use of hepatotoxic (including alcohol) or haematotoxic and immunosuppressive drugs, or when leflunomide treatment is followed by such drugs without a washout procedure. In patients with rheumatoid arthritis, no pharmacokinetic interaction between leflunomide (10 to 20 mg daily) and methotrexate (10 to 25 mg weekly) was shown. It is recommended that patients receiving leflunomide are not treated with colestyramine or activated carbon as this leads to a rapid and significant decrease in the plasma level of A771726 (active metabolite of leflunomide). It is thought to be caused by disorders of A771726 enterohepatic recirculation and/or its gastrointestinal dialysis. If the patient has already administered NSAIDs and/or corticosteroids, their administration may be continued after starting treatment with leflunomide. The enzymes involved in the metabolism of leflunomide and its metabolites are not exactly known. In vivo study of its interaction with cimetidine (non-specific cytochrome P450 inhibitor) has shown a lack of a significant interaction. After concomitant administration of a single dose of leflunomide by the patients receiving multiple doses of rifampicin (non-specific cytochrome P450 inducer), A771726 peak levels were increased by approximately 40%, whereas AUC was not significantly changed. The mechanism of this effect is unclear. In vitro studies has shown that A771726 inhibits cytochrome P4502C9 (CYP2C9) activity. Clinical studies has shown no problems, while co-administrating leflunomide and NSAIDs metabolized by CYP2C9. Caution is advised when leflunomide is co-administered with other drugs metabolized by CYP2C9, other than NSAIDs, such as phenytoin, warfarin, and tolbutamide. Prothrombin time was reported to be increased, while co-administering leflunomide and warfarin. During the study supposing that leflunomide was co-administered with triphasic oral contraceptives containing 30 μg ethinyloestradiol by healthy female volunteers, no reduction in contraceptive activity of the pills was shown, and A771726 pharmacokinetics was entirely within the predicted ranges. There are no current data on the co-administration of leflunomide with antimalarial medications used in rheumatologic diseases (e.g. chloroquine and hydroxychloroquine), Au products (intramuscular or oral), D-penicillamine, azathioprine and other immunosuppressive agents (except for methotrexate). The risk associated with combination therapy is unknown, in particular in long-term treatment. Since such therapy can lead to additive or even synergistic toxicity (e.g. hepato- or haematoxicity), combination of this medicinal product with other disease-modifying drugs (e.g. methotrexate) is not advisable. Recent concomitant or consecutive use of potentially myelotoxic agents may be associated with a higher risk of haematological effects. The risk of infections as well as malignancy, particularly lymphoproliferative disorders, is increased with the use of immunosuppressive agents. Vaccination During treatment with leflunomide, no clinical data on the efficacy and safety of vaccinations are available. However, vaccination with live vaccines is not recommended. The long half-life of Bageda should be considered, when planning vaccination with a live vaccine after discontinuation of treatment with Bageda.

OVERDOSE

Symptoms. In patients taking leflunomide at a dose up to the five-fold recommended daily dose, chronic overdose was reported, as well as in adults and children acute overdose was reported. No adverse events were reported in most cases of overdose. The adverse effects were consistent with the safety profile for leflunomide. Most common adverse effects were: diarrhoea, abdominal pains, leucopenia, anaemia, and elevated liver enzymes. Management. In case of overdose or toxicity, colestyramine or activated carbon is recommended to accelerate the elimination.
These washout procedures may be repeated if clinically necessary. Studies using both hemodialysis and CAPD (chronic ambulatory peritoneal dialysis) indicate that A771726, the primary metabolite of leflunomide, is not dialysable.

**PACKAGING**
Film coated tablets.
10 tablets in a blister.
3 blisters with the enclosed leaflet in a carton box.

**STORAGE CONDITIONS**
Store in a protected from moisture place at temperature not exceeding 25°C.
Keep out of reach of children!

**SHELF LIFE**
3 years from the manufacture date.
Do not use after the expiry date.

**DISPENSING RULES**
Sold under prescription.

**MANUFACTURER**
The holder of trade mark and Marketing Authorization is
“DR SERTUS İLAÇ SANAYİ VE TİCARET LİMİTED ŞİRKETİ”, TURKEY.
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