BAXLUVIR®
(Baloxavir Marboxil)

1. NAME OF THE PRODUCT
BAXLUVIR® (Baloxavir Marboxil) 20mg Tablet
BAXLUVIR® (Baloxavir Marboxil) 40mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
BAXLUVIR® 20mg Tablet
Each film coated tablet contains:
Baloxavir Marboxil…….20mg

BAXLUVIR® 40mg Tablet
Each film coated tablet contains:
Baloxavir Marboxil…….40mg

3. PHARMACEUTICAL FORM
Film coated tablet

Appearance:
BAXLUVIR® 20mg Tablet: White to off-white color, oval shaped film coated tablets, plain on one side and break line on other side.
BAXLUVIR® 40mg Tablet: White to off-white color, oval shaped film coated tablets, plain on both sides.

4. CLINICAL PARTICULARS
4.1. THERAPEUTIC INDICATIONS:
Treatment of influenza: BAXLUVIR® is indicated for the treatment of uncomplicated influenza in patients aged 3 weeks and above.
Post-exposure prophylaxis of influenza: BAXLUVIR® is indicated for post-exposure prophylaxis of influenza in individuals aged aged 3 weeks and above.
BAXLUVIR® should be used in accordance with official recommendations.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:
Treatment of influenza: A single dose of **BAXLUVIR®** should be taken as soon as possible within 48 hours of symptom onset.
Post-exposure prophylaxis of influenza: A single dose of **BAXLUVIR®** should be taken as soon as possible within 48 hours following close contact with an individual known or suspected to have influenza.
Adults, adolescents, children and infants (≥ 3 weeks of age): The recommended single oral dose of **BAXLUVIR®** is determined by body weight.

BAXLUVIR® dosing by patient weight (≥ 3 weeks of age):

Patient body weight	Recommended oral dose
< 20 kg	2 mg/kg
≥ 20 kg to < 80 kg	Single dose of 40 mg taken as 1x40mg tablet OR 2 x 20mg tablets
≥ 80 kg	Single dose of 80 mg taken as 2 x 40mg tablets

There are no clinical data on the use of a repeat dose of **BAXLUVIR®** for the treatment of uncomplicated influenza or for post-exposure prophylaxis in any one influenza season.

Special populations:
Elderly (≥ 65 years): No dosage adjustment is required.
Renal impairment: No dose adjustment is required in patients with renal impairment.
Hepatic impairment: No dose adjustment is required for patients with mild or moderate hepatic impairment (Child-Pugh class A or B). The safety and efficacy of baloxavir marboxil have not been established in patients with severe hepatic impairment (Child-Pugh class C).
Paediatric population: The safety and efficacy of **BAXLUVIR®** in preterm neonates and children aged <3 weeks have not been established. No data are available.

Method of administration:
- For oral use.
- The tablets should be taken with water.
- **BAXLUVIR®** may be taken with or without food.

BAXLUVIR® should not be taken with products that contain polyvalent cations such as laxatives, antacids or oral supplements containing iron, zinc, selenium, calcium or magnesium.

4.3. CONTRAINDICATIONS:
Hypersensitivity to the active substance or to any of the excipients.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Lactose intolerance: Baloxavir Marboxil contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium: This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:

Effects of other medicinal products on baloxavir marboxil or its active metabolite baloxavir: Products that contain polyvalent cations may decrease plasma concentrations of baloxavir. Baloxavir Marboxil should not be taken with products that contain polyvalent cations such as laxatives, antacids or oral supplements containing iron, zinc, selenium, calcium or magnesium.

Immune response to influenza virus: Interaction studies with influenza vaccines and baloxavir marboxil have not been conducted. In studies of naturally acquired influenza, treatment with Baloxavir Marboxil did not impair the humoral antibody response to influenza infection.

Paediatric population: Interaction studies have only been performed in adults.

4.6. FERTILITY, PREGNANCY AND LACTATION:

Fertility: No effects on male or female fertility were observed in animal studies performed with baloxavir marboxil

Pregnancy: There are no or limited data from the use of baloxavir marboxil in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of Baloxavir Marboxil during pregnancy.

Breast-feeding: It is unknown whether baloxavir marboxil or baloxavir are excreted in human milk. Baloxavir marboxil and its metabolites are secreted in the milk of lactating rats. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to abstain from baloxavir marboxil therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Baloxavir Marboxil has no or negligible influence on the ability to drive and use machines.

4.8. UNDESIRABLE EFFECTS:

Summary of the safety profile:

Hypersensitivity reactions have been observed in the postmarketing setting which include reports of anaphylaxis/anaphylactic reactions and less severe forms of hypersensitivity reactions including urticaria and angioedema of these adverse reactions only urticaria has been observed in clinical studies with an estimated frequency category of “uncommon”.

Adverse drug reactions are listed according to system organ classes in MedDRA and the corresponding frequency category estimation for each adverse drug reaction is based on the following convention: 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) and not known (cannot be estimated from the available data).

Immune system disorders:

Not known: Anaphylaxis, Anaphylactic reactions, Hypersensitivity

Skin and subcutaneous disorders:

Uncommon: Urticaria

Not known: Angioedema

Gastrointestinal disorders:

Common: Diarrhoea, Vomiting

4.9. OVERDOSE:

Data are insufficient to determine what symptoms may be anticipated as a result of an overdose.

Management: No known specific antidote exists for Baloxavir Marboxil. In the event of overdose, standard supportive medical care should be initiated based on the patient's signs and symptoms. Baloxavir is unlikely to be significantly removed by dialysis due to high serum protein binding.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Antivirals for systemic use, other anti-virals.

ATC code: J05AX25.

Mechanism of action: Baloxavir marboxil is a prodrug that is converted by hydrolysis to baloxavir, the active form that exerts anti-influenza activity. Baloxavir acts on the cap-dependent endonuclease (CEN), an influenza virus-specific enzyme in the polymerase acidic (PA) subunit of the viral RNA polymerase complex and thereby inhibits the transcription of influenza virus genomes resulting in inhibition of influenza virus replication.

5.2. PHARMACOKINETICS PROPERTIES:

Absorption: After oral administration, baloxavir marboxil is extensively converted to its active metabolite, baloxavir. The plasma concentration of baloxavir marboxil is very low or below the limit of quantitation (< 0.100ng/mL). Following a single oral administration of 80mg of baloxavir marboxil, the time to achieve peak plasma concentration (T_{max}) is approximately 4 hours in the fasted state. The absolute bioavailability of baloxavir after oral dosing with baloxavir marboxil has not been established.

Food effect: Administration of baloxavir marboxil under fasting conditions and with a meal (approximately 400 to 500 kcal including 150 kcal from fat) indicated

that the C_{max} and AUC of baloxavir were decreased by 48% and 36%, respectively, under fed conditions. T_{max} was unchanged in the presence of food. There were no clinically relevant differences in efficacy when baloxavir was taken with vs without food.

Distribution: In an *in-vitro* study, the binding of baloxavir to human serum proteins, primarily albumin, is 92.9% to 93.9%. The apparent volume of distribution of baloxavir during the terminal elimination phase (Vz/F) following a single oral administration of baloxavir marboxil is approximately 1180 liters in Caucasian subjects and 647 liters in Japanese subjects.

Biotransformation: Baloxavir is primarily metabolised by UGT1A3 to form a glucuronide with a minor contribution from CYP3A4 to form a sulfoxide.

Excretion: Following a single oral administration of 40mg of [$_{14}$C]-labeled baloxavir marboxil, the proportion of total radioactivity excreted in faeces was 80.1% of the administered dose, with the urine accounting for 14.7% (3.3% and 48.7% of the administered dose was excreted as baloxavir in urine and faeces respectively).

Elimination: The apparent terminal elimination half-life ($t_{1/2,z}$) of baloxavir after a single oral administration of baloxavir marboxil is 79.1 hours in Caucasian subjects.

5.3. PRECLINICAL SAFETY DATA:

Nonclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, acute and repeated dose toxicity.

Prolongation of PT and APTT were observed in rats at exposures at least equal to the human exposure based on $AUC_{0\text{-}24hr}$ under specific experimental conditions, i.e. when fasted and when the food was either autoclaved or radiation-treated, resulting in vitamin K limiting/deficient conditions. These effects were not observed in monkey studies up to 4 weeks duration at the highest tested dose equivalent to 8-times the human exposure based on $AUC_{0\text{-}24hr}$. They are considered to be of limited clinical relevance.

Carcinogenicity studies have not been performed with baloxavir marboxil.

The pro-drug baloxavir marboxil, and its active form, baloxavir, were not considered genotoxic as they tested negative in bacterial reverse mutation tests, micronucleus tests with cultured mammalian cells, and as baloxavir marboxil was negative in an *in vivo* rodent micronucleus test.

Baloxavir marboxil had no effects on fertility when given orally to male and female rats at doses providing exposure equivalent to 5-times the human exposure based on $AUC_{0\text{-}24hr}$.

Baloxavir marboxil did not cause malformations in rats or rabbits.

The oral embryo-foetal development study of baloxavir marboxil in rats with daily doses from gestation day 6 to 17 revealed no signs of maternal or foetal toxicity up to the highest tested dose providing exposure equivalent to 5-times the human exposure based on $AUC_{0\text{-}24hr}$.

In rabbits, a dose providing exposure equivalent to 14-times the human exposure based on $AUC_{0\text{-}24hr}$ following the MHRD caused maternal toxicity resulting in miscarriages and significant increase in incidence of foetuses with a skeletal variation (cervical rib). The skeletal variations were reabsorbed during the growing process of adjacent cervical vertebra. A dose providing exposure equivalent to 6- times the human exposure based on $AUC_{0\text{-}24hr}$ in rabbits was without adverse effects.
The pre- and postnatal study in rats did not show drug-related adverse findings in dams and pups up to the highest tested dose providing exposure equivalent to 5-times the human exposure based on $AUC_{0\text{-}24hr}$.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

BAXLUVIR® 20mg Tablet:

- Lactose Monohydrate
- Microcrystalline Cellulose
- Polyvinyl Pyrrolidone
- Crosscarmellose Sodium
- Sodium Stearyl Fumarate
- Hypromellose
- Polyethylene Glycol
- Talcum Powder
- Titanium Dioxide
- Sodium Lauryl Sulphate

BAXLUVIR® 40mg Tablet:

- Lactose Monohydrate
- Microcrystalline Cellulose
- Polyvinyl Pyrrolidone
- Crosscarmellose Sodium
- Sodium Stearyl Fumarate
- Hypromellose
- Polyethylene Glycol
- Talcum Powder
- Titanium Dioxide
- Sodium Lauryl Sulphate

6.2. INCOMPATIBILITIES:

Not applicable

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Do not store over 30°C and protect from heat and moisture.
Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:

BAXLUVIR® 20mg Tablet: Alu/Alu blister packing, pack size is 1 tablet.
BAXLUVIR® 40mg Tablet: Alu/Alu blister packing, pack size is 1 tablet.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

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

6.7. DRUG PRODUCT SPECIFICATIONS:

BAXLUVIR® 20mg Tablet: Innovator's Specs.
BAXLUVIR® 40mg Tablet: Innovator's Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharma.com
ML No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

BAXLUVIR® 20mg Tablet: 120198
BAXLUVIR® 40mg Tablet: 125486

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

BAXLUVIR® 20mg Tablet: 16th August, 2024
BAXLUVIR® 40mg Tablet: 24th March, 2025

10. DATE OF REVISION OF THE TEXT

بیکسلوور® ٹیبلٹ

(بیلوگزاور ماربوگزل)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو ۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں،

گرمی اور نمی سے محفوظ رکھیں ورنہ دوا خراب ہو جائیگی۔