Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
VABIOTIC 500mg

2. Qualitative and quantitative composition
Each capsule contains 500mg flucloxacillin

3. Pharmaceutical form
Oral capsule dosage form.

4. Clinical particulars
4.1 Therapeutic indications
Flucloxacillin is indicated for the treatment of infections due to penicillinase producing staphylococci and other grampositive organisms susceptible to this anti-infective. Flucloxacillin is also indicated for use as a prophylactic agent during major surgical procedures when appropriate; for example cardiothoracic and orthopaedic surgery.

4.2 Posology and method of administration
The dosage depends upon the severity and nature of the infection. The dosage may be increased if necessary. Maximum daily dose is 8 g per day
Adults (including elderly patients)
Oral - 250 mg four times a day.
In serious infections, the dosage may be doubled.
Osteomyelitis, endocarditis - Up to 8 g daily, in divided doses six to eight hourly. Surgical prophylaxis - 1 to 2 g IV at induction of anaesthesia followed by 500 mg six hourly IV, IM or orally for up to 72 hours.

Paediatric population
2-10 years: 125 mg four times daily.
Under 2 years: 62.5mg four times daily.
Premature infants, neonates, sucklings and infants Other pharmaceutical forms/strengths may be more appropriate for administration to this population.

Abnormal renal function:
In common with other penicillins, Flucloxacillin usage in patients with renal impairment does not usually require dosage reduction. However, in the presence of severe renal failure (creatinine clearance < 10 ml/min) a reduction in dose or an extension of dose interval should be considered. Flucloxacillin is not significantly removed by dialysis and hence no supplementary dosages need to be administered either during, or at the end of the dialysis period. The maximum recommended dose in adults is 1 g every 8 to 12 hours.

Hepatic impairment

Dose reduction in patients with reduced hepatic function is not necessary.

Method of administration
Oral: This medicine should be taken on an empty stomach. This means an hour before food or two hours after food.
Flucloxacillin capsules should be taken at least 1 hour before or 2 hours after meals. The capsules should be taken with a full glass of water (250 ml), to reduce the risk of oesophageal pain (see section 4.8). Patients should not lay down immediately after Flucloxacillin intake

4.3 Contraindications

Flucloxacillin is contraindicated in patients with a history of hypersensitivity to flucloxacillin or other beta-lactams or to any of the excipients of the product. Flucloxacillin is contraindicated in patients with a previous history of flucloxacillin-associated jaundice/hepatic dysfunction.

4.4 Special warnings and precautions for use

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthematous pustulosis (AGEP) (see section 4.8). In case of AGEP diagnosis, flucloxacillin should be discontinued and any subsequent administration of flucloxacillin contra-indicated.

The use of flucloxacillin (like other penicillins) in patients with renal impairment does not usually require dosage reduction. In the presence of severe renal failure (creatinine clearance less than 10ml/min), however, a reduction in dose or an extension of dose interval should be considered because of the risk of neurotoxicity. Flucloxacillin is not significantly removed by dialysis and so no supplementary dosages need to be administered either during or at the end of the dialysis period.

Hepatitis and cholestatic jaundice have been reported. These reactions are related neither to the dose nor to the route of administration. Flucloxacillin should be used with caution in patients with evidence of hepatic dysfunction, patients >50 years or patients with underlying disease all of whom are at increased risk of hepatic reactions. The onset of these hepatic effects may be delayed for up to two months posttreatment. In several cases, the course of the reactions has been protracted and lasted for some months. In very rare cases, a fatal outcome has been reported (see section 4.8). As for other penicillins contact with the skin should be avoided as sensitisation may occur. Patients with a known history of allergy are more likely to develop a hypersensitivity reaction. Prolonged use of an anti-infective agent may occasionally result in overgrowth of non-susceptible organisms.

Before initiating therapy with flucloxacillin, careful enquiry should be made concerning previous hypersensitivity reactions to β-lactams. Cross-sensitivity between penicillins and cephalosporins is well documented. Serious and occasionally fatal hypersensitivity reactions (anaphylaxis) have been reported in patients receiving β-lactam antibiotics. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral therapy. These reactions are more likely to occur in individuals with a history of β-lactam hypersensitivity.

If anaphylaxis occurs flucloxacillin should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions may require immediate emergency treatment with adrenaline (epinephrine). Ensure adequate airway and ventilation and give 100% oxygen. IV crystalloids, hydrocortisone, antihistamine and nebulised bronchodilators may also be required. Special caution is essential in the newborn because of the risk of hyperbilirubinaemia. Studies have shown that, at high dose following parenteral administration, flucloxacillin can displace bilirubin from plasma protein binding sites, and may therefore predispose to kernicterus in a jaundiced baby. In addition, special caution is essential in the newborn because of the potential for high serum levels of flucloxacillin due to a reduced rate of renal excretion. During prolonged treatments (e.g. osteomyelitis, endocarditis), regular monitoring of hepatic and renal functions is recommended.

Caution is advised when flucloxacillin is administered concomitantly with paracetamol due to the increased risk of high anion gap metabolic acidosis (HAGMA). Patients at high risk for HAGMA are in particular those with severe renal impairment, sepsis or malnutrition especially if the maximum daily doses of paracetamol are used.

After co-administration of flucloxacillin and paracetamol, a close monitoring is recommended in order to detect the appearance of acid-base disorders, namely HAGMA, including the search of urinary 5 oxoproline. If flucloxacillin is continued after cessation of paracetamol, it is advisable to ensure that there are no signals of HAGMA, as there is a possibility of flucloxacillin maintaining the clinical picture of HAGMA (see section 4.5). This medicinal product contains 46.5 mg sodium per gram, equivalent to 2.33% of the WHO recommended maximum daily intake of 2 g sodium for an adult. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Hypokalaemia (potentially life threatening) can occur with the use of flucloxacillin, especially in high doses. Hypokalaemia caused by flucloxacillin can be resistant to potassium supplementation. Regular measurements of potassium levels are recommended during the therapy

with higher doses of flucloxacillin. Attention for this risk is warranted also when combining flucloxacillin with hypokalemiainducing diuretics or when other risk factors for the development of hypokalemia are present (e.g. malnutrition, renal tubule disfunction).

Probenecid and sulfinpyrazone slow down the excretion of flucloxacillin by decreasing tubular secretion. Other drugs, such as piperacillin, which are excreted via renal tubular secretion, may interfere with flucloxacillin elimination.

Oral typhoid vaccine may be inactivated by flucloxacillin.

Flucloxacillin reduces the excretion of methotrexate which can cause methotrexate toxicity.

Flucloxacillin may reduce the response to sugammadex.

There are rare cases of altered international normalised ratio (INR) in patients taking warfarin and prescribed a course of flucloxacillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored during addition or withdrawal of flucloxacillin.

Bacteriostatic drugs may interfere with the bactericidal action of flucloxacillin.

4.6 Fertility, pregnancy, and lactation

Pregnancy: Animal studies with flucloxacillin have shown no teratogenic effects. The product has been in clinical use since 1970 and the limited number of reported cases of use in human pregnancy have shown no evidence of untoward effects. The decision to administer any drug during pregnancy should be taken with the utmost care. Therefore flucloxacillin should only be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment. Lactation: Trace quantities of flucloxacillin can be detected in breast milk. The possibility of hypersensitivity reactions must be considered in breast-feeding infants. Therefore flucloxacillin should only be administered to a breast-feeding mother when the potential benefits outweigh the potential risks associated with the treatment.

4.7 Effects on ability to drive and use machines.

Adverse effects on the ability to drive or operate machinery have not been observed.

4.8 Undesirable effects

The following convention has been utilised for the classification of undesirable effects:- Very common (≥1/10), common (≥1/100, <1/10),uncommon(≥1/1000,<1/100),rare(≥1/10,000,< 1/1000), very

rare(< 1/10,000),not known(cannot be estimated from the available data).
Unless otherwise stated, the frequency of the adverse events has been derived from more than 30 years of post-marketing reports.

System organ class	**Frequency**	**Undesirable Effects**
Blood and lymphatic system disorders	Very Rare	Neutropenia (including agranulocytosis) and thrombocytopenia. These are reversible when treatment is discontinued. Eosinophilia, Haemolytic anaemia.
Immune system disorders	Very Rare	Anaphylactic shock (exceptional with oral administration) (see Section 4.4 special Warnings and special precautions for use), angioneurotic oedema. If any hypersensitivity reaction occurs, the treatment should be discontinued. (See also Skin and subcutaneous tissue disorders).
Metabolism and nutrition disorders	Very Rare	Post marketing experience: very rare cases of high anion gap metabolic acidosis, when flucloxacillin is used concomitantly with paracetamol, generally in the presence of risk factors (see section 4.4.)
	Not known	Hypokalaemia.
Gastrointestinal disorders	Common	*Minor gastrointestinal disturbances.
	Very Rare	Pseudomembranous colitis. If pseudomembranous colitis develops, flucloxacillin treatment should be discontinued and appropriate therapy, e.g. oral vancomycin should be initiated.
	Not known	Oesophageal pain and related events **
Hepato-biliary disorders	Very Rare	Hepatitis and cholestatic jaundice. (See Section 4.4 Special Warnings and Special Precautions for Use). Changes in liver function laboratory test

		results (reversible when treatment is discontinued). These reactions are related neither to the dose nor to the route of administration. Hepatitis and cholestatic jaundice may be delayed for up to two months post-treatment; in several cases the course of the reactions has been protracted and lasted for some months. Hepatic events may be severe and in very rare circumstances a fatal outcome has been reported. Most reports of deaths have been in patients ≥ 50 years and in patients with serious underlying disease. There is evidence that the risk of flucloxacillin induced liver injury is increased in subjects carrying the HLAB*5701 allele. Despite this strong association, only 1 in 500-1000 carriers will develop liver injury. Consequently, the positive predictive value of testing the HLAB*5701 allele for liver injury is very low (0.12%) and routine screening for this allele is not recommended.
Skin and subcutaneous tissue disorders	Uncommon	*Rash, urticaria and purpura.
	Very Rare	Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. (See also Immune system disorders).
	Not known	AGEP – acute generalised exanthematous pustulosis (see section 4.4).
Musculoskeletal and connective tissue disorders	Very Rare	Arthralgia and myalgia sometimes develop more than 48 hours after the start of the treatment.
Renal and urinary disorders	Very Rare	Interstitial nephritis. This is reversible when treatment is discontinued.
General disorders and administration site conditions	Very Rare	Fever sometimes develops more than 48 hours after the start of the treatment.

*The incidence of these AEs was derived from clinical studies involving a total of approximately 929 adult and paediatric patients taking flucloxacillin.
** oesophagitis, burn oesophageal, throat irritation, oropharyngeal pain or oral pain.

4.9 Overdose

With high doses (mainly parenteral) neurotoxicity may develop. Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and should be treated symptomatically. Flucloxacillin is not removed from the circulation by haemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC code: J01CF05
Pharmacotherapeutic group: Beta-lactamase resistant penicillins
Properties: Flucloxacillin is a narrow-spectrum antibiotic of the group of isoxazolyl penicillins; it is not inactivated by staphylococcal β-lactamases.
Activity: Flucloxacillin, by its action on the synthesis of the bacterial wall, exerts a bactericidal effect on streptococci except those of group D (Enterococcus faecalis) and staphylococci. It is not active against methicillin-resistant staphylococci. There is evidence that the risk of flucloxacillin induced liver injury is increased in subjects carrying the HLA-B*5701 allele. Despite this strong association, only 1 in 500-1000 carriers will develop liver injury. Consequently, the positive predictive value of testing the HLA-B*5701 allele for liver injury is very low (0.12%) and routine screening for this allele is not recommended.
Breakpoints
MIC breakpoints for flucloxacillin are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) version 10.0.

rganism	MIC Breakpoints (mg/L)	
	usceptible ≤	esistant >
Staphylococcus spp.	ote[1]	ote[1]
Streptococcus groups A, C and G	ote[2]	ote[2]

[1]Most staphylococci are penicillinase producers and some are methicillin resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. Staphylococci that test susceptible to benzylpenicillin and cefoxitin can be reported susceptible to all penicillins. Staphylococci that test resistant to benzylpenicillin but susceptible to cefoxitin are susceptible to β-lactamase inhibitor combinations, the isoxazolylpenicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin) and nafcillin. For agents given orally, care to achieve sufficient exposure at the site of the infection should be exercised. Staphylococci that test resistant to cefoxitin are resistant to all penicillins.
[2]The susceptibility of streptococcus groups A, B, C and G to penicillins is inferred from the benzylpenicillin susceptibility with the exception of phenoxymethylpenicillin and isoxazolylpenicillins for streptococcus group B.

5.2 Pharmacokinetic properties

Absorption:

Flucloxacillin is stable in acid media and can therefore be administered either by the oral or parenteral route. The peak serum levels of flucloxacillin reached after one hour are as follows.

- After 250 mg by the oral route (in fasting subjects): Approximately 8.8 mg/l.
- After 500 mg by the oral route (in fasting subjects): Approximately 14.5mg/l.
- After 500 mg by the IM route: Approximately 16.5 mg/l.

The total quantity absorbed by the oral route represents approximately 79% of the quantity administered.

Distribution:

Flucloxacillin diffuses well into most tissue. Specifically, active concentrations of flucloxacillin have been recovered in bones: 11.6 mg/l (compact bone) and 15.6 mg/l (spongy bone), with a mean serum level of 8.9 mg/l.

Crossing the meningeal barrier: Flucloxacillin diffuses in only small proportion into the cerebrospinal fluid of subjects whose meninges are not inflamed.

Crossing into mother's milk: Flucloxacillin is excreted in small quantities in mother's milk.

Metabolism:

In normal subjects approximately 10% of the flucloxacillin administered is metabolised to penicilloic acid. The elimination half-life of flucloxacillin is in the order of 53 minutes.

Excretion:

Excretion occurs mainly through the kidney. Between 65.5% (oral route) and 76.1% (parenteral route) of the dose administered is recovered in unaltered active form in the urine within 8 hours. A small portion of the dose administered is excreted in the bile. The excretion of flucloxacillin is slowed in cases of renal failure.

Protein binding: The serum protein-binding rate is 95%.

5.3 Preclinical safety data

No further information of relevance to add.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose
Purified Talc
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage:

Store below 30°C.

Protect from light and moisture.

6.5 Nature and contents of container

Aluminum - Aluminum Blister Pack

10 Capsule are blister packed with Aluminum - Aluminum foil; such 3 blisters are packed in one cartonpack.
Pack size: 3 x 10 Capsules (i.e 30 Capsules) in one carton box along with packing leaflet.

6.6 Special precautions for disposal and other handling:
No special requirements.

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

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:
EASTLEIGH PHARMACEUTICAL COMPANY LIMITED
Address: P.O Box 167-00610 Nairobi, Kenya

Manufacturing site address:
MARS REMEDIES PVT LTD
Address: 635, GIDC Estate, Waghodia-391760, Vadodara, GUJARAT INDIA

8. Marketing authorization number
CTD9579

9. Date of first registration
11/11/2022

10. Date of revision of the text:
16/09/2023

11. Dosimetry:
Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:
Not Applicable