SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Flucloxacillin Orion 500 mg film-coated tablets
Flucloxacillin Orion 750 mg film-coated tablets
Flucloxacillin Orion 1 g film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains flucloxacillin sodium monohydrate equivalent to 500 mg, 750 mg or 1 g flucloxacillin.

Excipient with known effect:

Flucloxacillin Orion 500 mg contains sodium 28 mg per tablet.
Flucloxacillin Orion 750 mg contains sodium 42 mg per tablet.
Flucloxacillin Orion 1 g contains sodium 56 mg per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

500 mg tablet:
White to off-white, capsule shaped, film-coated biconvex tablets debossed with ‘Y’ on one side and ‘05’ with score line between ‘0’ and ‘5’ on the other side, 17.4 x 8.1 mm. The tablet can be divided into equal doses.

750 mg tablet:
White to off - white, capsule shaped, film - coated biconvex tablets debossed with ‘Y’ on one side and ‘06’ with score line between ‘0’ and ‘6’ on the other side, 20.4 x 8.4 mm. The tablet can be divided into equal doses.

1 g tablet:
White to off-white, elliptical shaped, film-coated biconvex tablets debossed with ‘T’ on one side and ‘63’ with score line between ‘6’ and ‘3’ on the other side, 9.8 x 21.3 mm. The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Flucloxacillin Orion is used when staphylococcal aetiology is suspected or has been confirmed in:
– Skin and soft tissue infections
– Bone/joint and lung infections, e.g. pneumonia, acute exacerbations of chronic bronchitis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Adults
Skin and soft tissue infections
750 mg–1 000 mg three times a day.

Bone and joint infections
1 000 mg–1 500 mg three times a day. If necessary (e.g. in cases of osteomyelitis and osteitis) the dose can be increased to 6 000 mg in 3–6 divided doses.

For chronic staphylococcal osteomyelitis: 1 500 mg three times a day for six months.

Lung infections
Following treatment with a parenteral preparation leading to an improvement in the condition, the infection can continue to be treated with 750 mg flucloxacillin three times a day.

Paediatric population

Lung infections and skin and soft tissue infections
30–50 mg/kg body weight per day.

Example dose:
40 kg: one 500 mg tablet three times a day
50 kg: as adults (750 mg–1 000 mg three times a day)

Bone and joint infections and severe lung, skin and soft tissue infections
The daily dose for children over 2 years old can be doubled, i.e. 60–100 mg/kg body weight per day.

Method of administration

Flucloxacillin Orion produces the best effect if taken between meals.

Flucloxacillin Orion tablets should be taken at least 1 hour before or 2 hours after meals.

The tablets 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 Orion intake.

Flucloxacillin Orion tablets have a saliva-resistant coating to protect the normal flora in the oral cavity and throat.

4.3 Contraindications

Hypersensitivity to flucloxacillin, penicillin or to any of the excipients listed in section 6.1.

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.

Cross-allergy between penicillins and cephalosporins may occur.

Older patients, patients with underlying hepatic disease and those receiving flucloxacillin for longer periods are at greater risk for flucloxacillin induced hepatitis and cholestatic jaundice. In these patients, hepatic events may be severe, and in very rare circumstances, deaths have been reported (see section 4.8). The onset may be delayed for up to 2 months after flucloxacillin treatment has been stopped.

Diarrhoea/pseudomembranous colitis caused by *Clostridium difficile* may occur. Patients with diarrhoea must therefore be closely monitored.

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).

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 hypokalemia-inducing diuretics or when other risk factors for the development of hypokalemia are present (e.g. malnutrition, renal tubule disfunction).

Excipients

500 mg tablet contains 28 mg sodium per tablet, equivalent to 1.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

750 mg tablet contains 42 mg sodium per tablet, equivalent to 2.1% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

1 g tablet contains 56 mg sodium per tablet, equivalent to 2.8% 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

There is a report describing toxic reaction to **methotrexate** when the patient was treated with furosemide and penicillin V; organic acids that may compete with the tubular secretion of methotrexate. Suspected interactions have also been reported for the combination of methotrexate with mezlocillin and amoxicillin.

There are reports of reduced efficacy of **warfarin** during concomitant oral treatment with flucloxacillin. The mechanism is unclear.

Probenecid delays renal excretion of flucloxacillin, which can lead to higher serum concentrations of flucloxacillin over a prolonged period.

Caution should be taken when flucloxacillin is used concomitantly with **paracetamol** as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risk factors. (see section 4.4.)

Flucloxacillin is a weak inducer of CYP3A4, which may lead to clinically relevant drug–drug interactions for some narrow therapeutic range drugs that are substrates of CYP3A4, eg **immunosuppressants (eg tacrolimus, everolimus and ciclosporin)**.

Flucloxacillin (CYP450 inducer) has been reported to significantly decrease plasma **voriconazole** concentrations. If concomitant administration of flucloxacillin with voriconazole cannot be avoided, monitor for potential loss of voriconazole effectiveness (e.g. by therapeutic drug monitoring); increasing the dose of voriconazole may be needed.

4.6 Fertility, pregnancy and lactation

Pregnancy
Clinical data indicates that flucloxacillin does not lead to an increased risk of foetal damage. Animal studies do not indicate congenital malformations. The use of flucloxacillin may be considered during pregnancy, if necessary, but caution should be administered.

Breast-feeding
Flucloxacillin is excreted in human milk, but at therapeutic doses effects on the breastfed infants are considered unlikely. Nevertheless, potential effects on gastrointestinal and mouth flora, as well as possibility of sensitisation of the infant should be considered. Flucloxacillin can be used during breast-feeding if the benefit to the mother outweighs the risk to the infant.

4.7 Effects on ability to drive and use machines

Flucloxacillin Orion has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most common undesirable effects are gastrointestinal, which occur in approximately 5% of treated patients.

Calculated frequencies of undesirable effects are ranked as follows: 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); not known (frequency cannot be estimated from the available data).

Infections and infestations	Rare	Pseudomembranous colitis
Blood and lymphatic system disorders	Uncommon	Eosinophilia
	Rare	Agranulocytosis, neutropenia
Immune system disorders	Rare	Anaphylactic reactions
Metabolism and nutrition disorders	Very rare	Post marketing experience: 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
Nervous system disorders	Not known	Dizziness
Gastrointestinal disorders	Common	Nausea, diarrhoea
	Not known	Abdominal pain, vomiting, oesophageal pain and related events [2)]
Hepatobiliary disorders	Rare	Liver injury[1)], hepatitis, cholestatic jaundice (see section 4.4)
	Common	Exanthema

Skin and subcutaneous tissue disorders	Uncommon	Urticaria
	Rare	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
	Very rare	Itching
	Not known	AGEP - acute generalized exanthematous pustulosis (see section 4.4)

Fungal overgrowth in oral cavity and genitals may occur.

[1)] Liver injury
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 500–1 000 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.
[2)] Oesophagitis, burn oesophageal, throat irritation, oropharyngeal pain or oral pain

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Toxicity
Large doses are usually well tolerated. Acute reactions mainly arise when there is hypersensitivity.

Symptoms
Toxic reactions; nausea, vomiting, diarrhoea, electrolyte disorders, impaired consciousness, muscular twitching, myoclonia, convulsions, coma, haemolytic reactions, renal failure and acidosis. In exceptional instances, anaphylactic shock can occur within 20–40 minutes.

Management
If justified, gastric lavage, charcoal. Symptomatic treatment. In severe cases, haemoperfusion or haemodialysis.

Treatment for anaphylactic reaction: Epinephrine (adrenaline) 0.1–0.5 mg slow intravenous, hydrocortisone 200 mg intravenous, possibly promethazine 25 mg intravenous, fluids, acidosis correction.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, beta-lactamase-resistant penicillins.
ATC code: J01CF05.

Mechanism of action
Flucloxacillin belongs to the group isoxazolyl penicillins, which exhibit activity against beta-lactamase-producing staphylococci. Flucloxacillin works by inhibiting bacterial cell wall synthesis and has a bactericidal effect.

Pharmacokinetic/pharmacodynamic relationship
The antibacterial effect of flucloxacillin is best correlated to the time when the concentration of antibiotics exceeds MIC.

Mechanism of resistance
Resistance to isoxazolyl penicillins (‘methicillin resistance’) is caused by the bacteria producing an altered penicillin-binding protein. Cross-resistance arises within the beta-lactam group (penicillins and cephalosporins). Methicillin-resistant staphylococci generally are resistant to all beta-lactam antibiotics.

Susceptibility testing breakpoints
MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for flucloxacillin and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx
Antibacterial spectrum
The prevalence of acquired resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species	*Staphylococcus aureus*, methicillin-susceptible Streptococci especially group C and G *Streptococcus pyogenes*
Species for which acquired resistance may be a problem	Coagulase-negative staphylococci
Resistant organisms	Methicillin-resistant staphylococci Enterococci Gram-negative bacteria Anaerobic bacteria *Clostridium difficile*

Streptococci and pneumococci are more susceptible to benzylpenicillin (penicillin G) and phenoxymethylpenicillin (penicillin V) than to flucloxacillin.

Liver injury
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 500–1 000 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.

5.2 Pharmacokinetic properties

Flucloxacillin is well absorbed after peroral administration. Administration with meals has a negative effect on absorption. The biological half-life in serum is approx. 80–90 minutes and binding to serum proteins amounts to 94–95%. Of the various isoxazolyl penicillins, flucloxacillin produces the highest proportion of free (non-protein-bound) penicillin in serum. Elimination of flucloxacillin occurs mainly through the kidneys via tubular secretion and glomerular filtration. Within 6 hours, approx. 50–55% of a peroral dose is excreted in the urine.

5.3 Preclinical safety data

There is no further preclinical data of relevance for the safety assessment other than the information already included in this summary of product characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Magnesium stearate
Povidone
Croscarmellose sodium
Microcrystalline cellulose

Film-coat:
Titanium dioxide
Hypromellose
Macrogols
Paraffin, light liquid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE container, polypropylene closure with induction sealing liner, desiccant.

500 mg film-coated tablets
30, 50 and 100 tablets

750 mg film-coated tablets
20, 30, 50 and 100 tablets

1 g film-coated tablets
21, 30, 50 and 75 tablets

Not all pack sizes may be marketed.

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 AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: To be completed nationally.
Date of latest renewal: To be completed nationally.

10. DATE OF REVISION OF THE TEXT

13/12/2024