

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Blujepa 750 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains gepotidacin mesilate dihydrate equivalent to 750 mg of gepotidacin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Yellow, capsule-shaped (approximately 21.4×10.5 mm in size), film-coated tablets, debossed with “GS GU3” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Blujepa is indicated for the treatment of female adults and adolescents, from 12 years of age, both weighing at least 40 kg, with uncomplicated urinary tract infections (uUTI; acute cystitis) that are proven or strongly suspected to be caused by susceptible organisms (see section 4.4 and 5.1).

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

4.2 Posology and method of administration

Posology

Adults and adolescents

The recommended dose of Blujepa is 1500 mg taken orally, twice daily (approximately 12 hours apart), for 5 days (in patients weighing at least 40 kg).

Missed dose

If a dose is missed, it should be taken as soon as possible. Double-doses must not be taken to make up for a missed dose.

Paediatric population

The safety and efficacy of Blujepa have not been established in children less than 12 years of age or in adolescents weighing less than 40 kg (see section 5.2). No data are available.

Elderly

No dosage adjustment is required (see section 5.2).

Renal impairment

No dosage adjustment is required in patients with mild impairment (creatinine clearance [CrCl] 60-89 mL/min), or moderate impairment (CrCl 30-59 mL/min). Limited data are available in patients with severe renal impairment (CrCl 15-29 mL/min). Blujepa is not recommended in patients with severe renal impairment or kidney failure (CrCl <30 mL/min), including those receiving dialysis, due to increased exposure to gepotidacin and the risk of QT prolongation (see sections 4.4 and 5.2).

Hepatic impairment

No dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh Class A/B). Blujepa should be avoided in patients with severe hepatic impairment (Child-Pugh Class C) due to increased exposure to gepotidacin and the risk of QT prolongation (see sections 4.4 and 5.2).

Special populations

Dosing recommendations have not been established in immunocompromised or obese patients (see section 4.4).

Method of administration

Oral use.

Blujepa tablets should be taken after a meal to reduce the possibility of gastrointestinal intolerance.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

QT Prolongation

A dose and concentration-dependent prolongation of the QT interval has been observed with gepotidacin (see section 5.1). Blujepa should be avoided in patients with a history of QT interval prolongation, or those with relevant pre-existing cardiac disease, patients with uncorrected electrolyte imbalances (e.g. hypokalaemia, hypomagnesaemia), patients taking antiarrhythmics, or other medications that may potentially prolong the QT interval. Elderly patients and women may be more susceptible to drug associated effects on the QT interval.

Due to an increase in gepotidacin exposure (C_{max}) and the risk of QT prolongation, avoid concomitant administration of Blujepa with strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, grapefruit juice) and in patients with severe hepatic impairment (Child-Pugh Class C); Blujepa is not recommended in patients with severe renal impairment ($CrCl < 30$ mL/min) (see sections 4.2 and 4.5).

If clinically indicated, monitor and correct serum electrolyte abnormalities and collect an ECG prior to administration and during treatment.

Acetylcholinesterase inhibition

Gepotidacin is a rapidly reversible acetylcholinesterase inhibitor (see section 5.3). Adverse events consistent with acetylcholinesterase inhibition have been reported with Blujepa (see section 4.8). Increased cholinergic effects can be associated with severe adverse effects including atrioventricular block, seizures/convulsions, bronchospasm, and vasovagal syncope.

Patients with medical conditions that may be exacerbated by acetylcholinesterase inhibition should be monitored.

Blujepa, as an acetylcholinesterase inhibitor, may exaggerate the neuromuscular effects of suxamethonium chloride-type (also known as succinylcholine-type) muscle relaxation during anaesthesia. Blujepa may augment the effect of other acetylcholinesterase inhibitors (e.g. donepezil). Patients should be monitored for exaggerated neuromuscular blockade or excessive cholinergic effects.

As Blujepa may antagonise the effects of systemic anticholinergic medications (e.g. benztropine) or non-depolarizing neuromuscular blocking agents, patients should be monitored if Blujepa is concomitantly administered with these medications (see section 4.5).

Limitations of the Clinical Data

In the two clinical trials (EAGLE-2 and EAGLE-3), immunocompromised patients or patients with altered immune defences (e.g persistent granulocytopenia, or receipt of significant immunosuppressive therapy) were excluded. Patients with HIV were not excluded unless they had a CD4 count of <200 cells/mm³. Patients with BMI ≥40.0 kg/m² or BMI ≥35.0 kg/m² with obesity-related health conditions were also excluded.

Antibiotic-associated diarrhoea and *Clostridium difficile* (*C. difficile*) associated diarrhoea

Antibiotic-associated diarrhoea and *Clostridium difficile*-associated diarrhoea (CDAD), have been reported in clinical trials with Blujepa (see section 4.8). CDAD may range in severity from mild diarrhoea to fatal colitis. If CDAD or pseudomembranous colitis is suspected or confirmed, treatment with Blujepa should be discontinued. Appropriate supportive measures together with the administration of specific treatment for *C. difficile* should be considered.

Non-susceptible microorganisms

Prolonged use may result in the overgrowth of non-susceptible organisms which may require interruption of treatment or other appropriate measures. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Excipients

This medicinal product 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

CYP3A4 Inhibitors

Concomitant administration of a strong inhibitor of CYP3A4 (itraconazole; 200 mg per day for 3 days), and a single 1500 mg dose of Blujepa resulted in an increase in the maximum concentration ($C_{\max}$) of gepotidacin of approximately 1.4-fold and area under the curve (AUC) of approximately 1.5-fold.

Concomitant administration of Blujepa with strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, grapefruit juice) should be avoided, as this may result in increased plasma concentrations of gepotidacin (see section 4.4).

CYP3A4 Substrates

Concomitant administration of midazolam (2 mg single dose) with gepotidacin (two doses of 3000 mg, given 12 hours apart) resulted in a 1.9-fold increase in midazolam $AUC_{(0-\infty)}$, indicating that gepotidacin is a weak CYP3A4 inhibitor.

Concomitant administration of Blujepa with medicinal products that are extensively metabolised by CYP3A4 and have a narrow therapeutic index should be avoided (e.g. ciclosporin, quinidine).

Digoxin

Concomitant administration of a single 0.5 mg dose of digoxin with two 3000 mg doses of gepotidacin (an *in vitro* P-glycoprotein inhibitor) given 12 hours apart resulted in a 1.5-fold increase in the digoxin $C_{\max}$ (at 3 hours post dose), a 1.1-fold increase in the digoxin $AUC_{(0-\infty)}$ and a delayed digoxin $T_{\max}$.

Concomitant administration of Blujepa with digoxin may result in increased digoxin exposure. Monitoring of digoxin serum concentrations should be considered, as appropriate.

Cholinergic/Anticholinergic Medications

As gepotidacin is an acetylcholinesterase inhibitor, there is potential for an exaggerated effect of concomitantly administered suxamethonium chloride-type (also known as succinylcholine-type) neuromuscular blocking agents, resulting in a delay in recovery of neuromuscular function. Gepotidacin may augment the effect of other acetylcholinesterase inhibitors (e.g. donepezil). Patients should be monitored for exaggerated neuromuscular blockade or excessive cholinergic effects.

There is potential for an antagonistic effect of systemic anticholinergic medications (e.g. benztropine) or non-depolarizing neuromuscular blocking agents. The potential for this interaction should be considered if Blujepa is administered concomitantly with anticholinergic medications (see section 4.4).

Medications that Prolong the QT Interval

The concomitant administration of Blujepa with other medications which have the potential to prolong the QT interval may increase the risk of QT prolongation (e.g. Class IA and III antiarrhythmics, antipsychotics, macrolide antibiotics [azithromycin, clarithromycin, erythromycin], fluoroquinolones [moxifloxacin, ciprofloxacin, levofloxacin], and tricyclic antidepressants). Concomitant administration of Blujepa with such medications should be avoided (see section 4.4).

Substrates of MATE

In vitro studies indicate that gepotidacin is a MATE1 and MATE2-k inhibitor. It is unknown whether coadministration with gepotidacin increases concentrations of metformin, a MATE substrate drug. Therefore, caution is recommended for coadministration of gepotidacin with metformin.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are insufficient data on the use of Blujepa in pregnant women; therefore, the effect on human pregnancy is unknown.

At clinically relevant exposures, embryofoetal development studies in mice and rats showed no evidence of foetal malformations; however, decreased foetal growth and/or increased foetal loss were observed in the presence of maternal toxicity. The pre and postnatal study showed no signs of foetal harm or effects on birth weight or postnatal growth and development (see section 5.3).

Blujepa should be used during pregnancy only if the expected benefits to the mother outweigh the potential risks to the foetus.

Breast-feeding

It is not known whether gepotidacin is secreted into human breast milk. In animal studies, gepotidacin was detected in the plasma of mice pups exposed during both gestation and lactation from dams who received gepotidacin at clinically relevant exposures, without any adverse effects on the offspring.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Blujepa therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No fertility data are available in humans. Animal studies do not indicate any direct or indirect effects on fertility or reproduction (see section 5.3).

4.7 Effects on ability to drive and use machines

Blujepa may have a minor influence on the ability to drive or use machines. Patients should be informed about the possible occurrence of symptoms such as blurred vision, dizziness, vertigo and presyncope whilst taking Blujepa (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse drug reactions are diarrhoea (16%), nausea (9%), abdominal pain (4%), flatulence (3%), headache (2%), and soft faeces (2%).

Pooled safety data from two Phase III studies in a total of 1570 patients (complete dataset) are summarised in Table 1.

Tabulated list of adverse reactions

Adverse reactions are listed by MedDRA body system organ class and frequency (see Table 1).

Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ to $< 1/1\ 000$) and very rare ($< 1/10\ 000$).

Table 1. Adverse reactions

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Common	Vulvovaginal candidiasis
	Uncommon	<i>Clostridioides difficile</i> -associated diarrhoea (CDAD)
Immune system disorders	Uncommon	Hypersensitivity ^a
Nervous system disorders	Common	Headache Dizziness
	Uncommon	Presyncope Dysarthria
Eye disorders	Uncommon	Vision blurred
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Uncommon	Tachycardia
Vascular disorders	Uncommon	Hot flush
Gastrointestinal disorders	Very common	Diarrhoea
	Common	Nausea Vomiting Abdominal pain Flatulence Soft faeces
	Uncommon	Abdominal distension Dyspepsia ^b Salivary hypersecretion ^c
Skin and subcutaneous tissue	Uncommon	Rash Hyperhidrosis
General disorders and administration site conditions	Uncommon	Fatigue
Investigations	Uncommon	Alanine aminotransferase/Aspartate aminotransferase increased

^a Includes drug-hypersensitivity allergic type reactions.

^b Includes epigastric discomfort, eructation.

^c Reported in Phase 1 and 2 clinical trials with oral daily doses of Blujepa (ranging from 100-6000 mg) in adults and adolescents. The frequency is based on the total exposure in these trials and the pooled Phase 3 trials. Not reported in the Phase 3 uUTI clinical studies (EAGLE-2 and EAGLE-3).

Diarrhoea

In the uUTI studies (EAGLE-2 and EAGLE-3), diarrhoea was reported in 258/1570 (16%) patients receiving gepotidacin, all of which were non-serious (11% mild, 5% moderate and <1% severe). The majority started within the first 2 days of treatment and were self-limiting (81% of patients who experienced diarrhoea did not require treatment for diarrhoea during the study). The median duration was 4 days. Discontinuation of study treatment due to diarrhoea was reported in 40/1570 (3%) patients receiving gepotidacin.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no specific treatment for an overdose with Blujepa. There is a risk of QT prolongation with overdosage. Haemodialysis is not likely to substantially remove gepotidacin from systemic circulation. Further management should be as clinically indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, other antibacterials, ATC code: J01XX13.

Mechanism of action

Gepotidacin is a triazaacenaphthylene antibacterial that inhibits bacterial DNA gyrase and topoisomerase IV, thereby inhibiting bacterial DNA replication.

Gepotidacin has bactericidal activity against pathogens as determined by time-kill studies. *In vitro* studies demonstrated a gepotidacin post-antibiotic effect ranging from 1.8 to 2.2 hours for *Escherichia coli* (*E. coli*), 1 to >6.6 hours for *Klebsiella pneumoniae* (*K. pneumoniae*), 1.4 to 3 hours for *Proteus mirabilis* (*P. mirabilis*), 1 to 2.6 hours for *Citrobacter freundii* (*C. freundii*), 2.7 to 4.3 hours for *Staphylococcus saprophyticus* (*S. saprophyticus*) and 1.2 to 2.7 hours for *Enterococcus faecalis* (*E. faecalis*) at 5 times the minimum inhibitory concentration (MIC).

Resistance

Potential mechanisms that may impact gepotidacin activity are gepotidacin specific alterations of DNA gyrase (GyrA, GyrB) and/or topoisomerase IV (ParC, ParE) gene targets, plasmid-mediated quinolone resistance genes (especially *qnr*) and efflux. Well-balanced inhibition (approximately equal inhibition) of both DNA gyrase and topoisomerase IV in most uropathogens indicates that a single target-specific mutation may not significantly impact gepotidacin activity. While it has been demonstrated *in vitro* that efflux, and potentially the presence of the plasmid-mediated quinolone resistance gene *qnr*, impacts the antibacterial activity of gepotidacin, no clear mechanisms of resistance to gepotidacin have been identified. Gepotidacin activity against *E. coli* and *K. pneumoniae* is unrelated to beta-lactam resistance mechanism, or fluoroquinolone susceptibility, including common fluoroquinolone-resistant amino acid substitutions in GyrA and ParC.

The frequency of resistance development to gepotidacin due to spontaneous mutations in gram-negative and gram-positive uropathogens *in vitro* at 10 times MIC ranged from 10^{-9} to 10^{-10} .

Target-specific cross-resistance with other classes of antibacterial medical products has not been identified; therefore, isolates resistant to other medical products may be susceptible to gepotidacin.

Antibacterial activity in combination with other antibacterial agents

In *in vitro* studies, no antagonism against Enterobacterales or gram-positive isolates was observed for gepotidacin in combination with multiple antibacterials, including fluoroquinolones, sulphonamides, cephalosporins, macrolides, tetracyclines, aminoglycosides, glycopeptides, carbapenems, nitrofurans, monobactams, and oxazolidinones.

Susceptibility testing interpretive criteria

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for gepotidacin and are listed here: https://www.eucast.org/clinical_breakpoints.

Organism	MIC breakpoints (mg/L)	
	Susceptible ≤	Resistant >
<i>Escherichia coli</i>	8 ^a	8 ^a
<i>Enterococcus faecalis</i>	8 ^a	8 ^a
<i>Staphylococcus saprophyticus</i>	0.25 ^a	0.25 ^a

^a Uncomplicated UTI only

Pharmacokinetic/pharmacodynamic (PK-PD) relationship

The 24 h free-drug AUC to MIC ratio has been shown in animal infection and *in vitro* PK-PD models to be the PK-PD index predictive of gepotidacin antibacterial efficacy.

Clinical efficacy against specific pathogens

Efficacy has been demonstrated in clinical studies against the following pathogens that were susceptible to gepotidacin *in vitro*:

- Aerobic Bacteria:
 - Gram-Positive Bacteria:
 - *Staphylococcus saprophyticus*
 - *Enterococcus faecalis*
 - Gram-Negative Bacteria (see Table 3 for success rates for these pathogens):
 - *Escherichia coli*
 - *Klebsiella pneumoniae*
 - *Citrobacter freundii* complex

Clinical efficacy has not been established against the following pathogens that are relevant to the approved indication although *in vitro* studies suggest that they would be susceptible to gepotidacin in the absence of acquired mechanisms of resistance:

- Aerobic Bacteria
 - Gram-Negative Bacteria:
 - *Citrobacter koseri*
 - *Enterobacter cloacae* complex
 - *Klebsiella aerogenes*
 - *Klebsiella oxytoca/ Raoltella ornithinolytica*
 - *Morganella morganii*
 - *Providencia rettgeri*
 - *Proteus mirabilis*

Effects on the electrocardiogram

The effect of gepotidacin on the QT interval was evaluated in a randomised, active-(moxifloxacin 400 mg) and placebo-controlled, double-blind cross-over trial in healthy subjects, who received single intravenous (IV) infusions of gepotidacin over 2 hours. A dose- and concentration-dependent QTc prolongation effect of gepotidacin was observed. The mean placebo-corrected change from baseline heart rate values around T_{max} were approximately 6 bpm at 1000 mg IV, and approximately 10 bpm at 1800 mg IV. The mean placebo-corrected change from baseline QTcF values around T_{max} were 12 msec at 1000 mg IV and 22 msec at 1800 mg IV (see section 4.4).

Clinical trials

Blujepa demonstrated efficacy in replicate multicentre, randomised, active-controlled Phase 3 trials in female patients with uUTI. In both trials (EAGLE-2 and EAGLE-3), non-inferiority between Blujepa (1500 mg twice daily for 5 days) and nitrofurantoin (100 mg twice daily for 5 days) was demonstrated in patients with a microbiologically-confirmed uUTI due to nitrofurantoin-susceptible uropathogen(s) based on therapeutic success at Test of Cure (TOC; Day 10-13); superiority of Blujepa was also demonstrated in EAGLE-3. Therapeutic success was defined as combined clinical success (complete symptom resolution and no new symptoms) and microbiological success (eradication), without the participant receiving other non-study antimicrobials. Results for therapeutic, clinical, and microbiological success at TOC are shown in Table 2.

Table 2: Therapeutic, clinical, and microbiological success rates at the TOC visit (EUCAST micro-ITT NTF-S population; complete dataset)

Study Endpoint	Blujepa n/N (%)	Nitrofurantoin n/N (%)	Treatment Difference (95% CI) ^a
EAGLE-2			
Composite Endpoint - Therapeutic success	166/323 (51.4)	132/288 (45.8)	5.9 (-2.0, 13.7)
Clinical success	215/323 (66.6)	187/288 (64.9)	2.3 (-5.2, 9.7)
Microbiological success	236/323 (73.1)	190/288 (66.0)	7.0 (-0.3, 14.2)
EAGLE-3			
Composite Endpoint - Therapeutic success	161/273 (59.0)	117/262 (44.7)	14.0 (5.7, 22.2)
Clinical success	187/273 (68.5)	169/262 (64.5)	4.3 (-3.6, 12.1)

Microbiological success	197/273 (72.2)	152/262 (58.0)	14.1 (6.2, 22.0)
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TOC = Test of Cure; EUCAST micro-ITT NTF-S = microbiological Intent to Treat nitrofurantoin-susceptible (based on EUCAST breakpoints and interpretive criteria); CI=confidence interval

^aTreatment difference (Blujepa – nitrofurantoin) calculated using Miettinen and Nurminen Summary Score method adjusting for age group and history of recurrent uUTI status.

The efficacy of Blujepa compared to nitrofurantoin was consistent across prespecified subgroups of interest, including patients over the age of 50 years, patients with a history of recurrent uUTI infections, and patients with ESBL+ or fluoroquinolone-resistant (FQ-R) uropathogens.

Table 3 summarises the therapeutic, clinical, and microbiological success rates at the TOC visit for *E. coli*, *K. pneumoniae*, *C. freundii* complex, *S. saprophyticus* and *E. faecalis* across both trials in the micro-ITT population, which comprised all patients who received at least one dose of study medication and had at least one baseline qualifying uropathogen ($\geq 10^5$ CFU/mL).

Table 3: Therapeutic, clinical, and microbiological success rates at TOC visit by baseline uropathogen (EAGLE-2 and EAGLE-3 pooled; micro-ITT population; [complete dataset])

Pathogen ^{a,d}	Blujepa			Nitrofurantoin		
	Therapeutic success ^b n/N (%)	Clinical success ^b n/N (%)	Micro success ^c n/N (%)	Therapeutic success ^b n/N (%)	Clinical success ^b n/N (%)	Micro success ^c n/N (%)
<i>E. coli</i>	322/591 (54.5)	402/591 (68.0)	431/598 (72.1)	241/556 (43.3)	356/556 (64.0)	339/561 (60.4)
<i>K. pneumoniae</i>	21/54 (38.9)	27/54 (50.0)	38/56 (67.9)	16/57 (28.1)	29/57 (50.9)	27/58 (46.6)
<i>C. freundii</i> complex	9/13 (69.2)	9/13 (69.2)	12/13 (92.3)	2/6 (33.3)	2/6 (33.3)	6/6 (100.0)
<i>S. saprophyticus</i>	9/15 (60.0)	9/15 (60.0)	12/15 (80.0)	11/14 (78.6)	13/14 (92.9)	12/14 (85.7)
<i>E. faecalis</i>	8/14 (57.1)	8/14 (57.1)	12/14 (85.7)	2/7 (28.6)	3/7 (42.9)	6/7 (85.7)

TOC = Test of Cure; micro-ITT = microbiological Intent to treat;

Micro = Microbiological

^a Patients may have been infected with 1-2 uropathogens at baseline

^b A patient is counted once under a uropathogen category if multiple qualifying uropathogens within that category are isolated at baseline for the patient.

^c A patient is counted more than once under a uropathogen category if multiple qualifying uropathogens within that category are isolated at baseline for the patient.

^d Among gepotidacin-treated patients, therapeutic, clinical and microbiological success rates at TOC were lower for *K. pneumoniae* than for other pathogens, particularly in those patients with history of recurrent infections.

Paediatric population

The Medicines and Healthcare products Regulatory Agency (MHRA) has deferred the obligation to submit the results of studies with Blujepa in one or more subsets of

the paediatric population in treatment of uncomplicated urinary tract infections (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The absolute bioavailability of gepotidacin is 45%. Following repeat oral twice daily administration of Blujepa 1500 mg to females with uUTI, median T_{max} values were 1.50 to 1.92 hours. Steady-state plasma exposure was attained by Day 3. Food has no meaningful effect on gepotidacin plasma exposure.

Distribution

Plasma protein binding of gepotidacin is estimated at 33%. The volume of distribution at steady state is 160 L (similar in healthy subjects and patients with uUTI).

Biotransformation

Following a single oral administration of [^{14} C]-gepotidacin, unchanged gepotidacin was the predominant circulating component; one major circulating metabolite, formed via oxidation of the triazaacenaphthylene moiety, was detected. *In vitro* data showed that CYP3A4 is responsible for gepotidacin metabolism.

Elimination

Following oral administration of [^{14} C]-gepotidacin, the mean recovery of radioactivity from faeces was approximately 53%, and the mean recovery of radioactivity in urine was approximately 31% of the administered dose.

There was a moderate accumulation of 40% in gepotidacin plasma exposure following twice daily administration with a terminal elimination half-life of 9 hours. Following oral 1500 mg twice daily administration of gepotidacin for 5 days, approximately 20% of the dose was excreted in urine over the 12-hour dosing interval on Day 1, which increased to 31% on Day 4. Overall exposure to gepotidacin in urine ($AUC_{[0-\tau]}$) increased from 3740 $\mu\text{g.h/mL}$ on Day 1 to 5970 $\mu\text{g.h/mL}$ on Day 4. Urine gepotidacin concentrations exceeded plasma concentrations over the entire 12-hour dosing period.

Linearity/non-linearity

Gepotidacin exposure generally increases in a dose-proportional manner within the clinically relevant dose range.

Special populations

Children and adolescents

Based on modelling and simulation analyses, plasma exposures in adolescent patients (12 to <18 years and weighing at least 40 kg) following 1500 mg twice daily oral administration of Blujepa for 5 days trended higher compared to adults, with substantial overlap in exposure distributions. Urine gepotidacin exposure was similar

in adult and adolescent patients. The difference in plasma exposures between adult and adolescent patients is not considered to be clinically relevant.

Elderly patients

Modelling and simulation analyses of gepotidacin showed no clinically relevant effect of age on gepotidacin exposure.

Renal impairment

The pharmacokinetics of gepotidacin were evaluated in subjects with moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 59 mL/min per 1.73 m²) and in subjects with severe renal impairment/end stage renal disease (ESRD) on haemodialysis and not on haemodialysis (eGFR <30 mL/min per 1.73 m²). Gepotidacin plasma C_{max} and AUC in subjects with moderate renal impairment were 1.2-fold and 1.5-fold higher than matched healthy controls, respectively. Gepotidacin plasma C_{max} and AUC in severe renal impairment/ESRD not on dialysis were 1.6-fold and 1.9-fold higher than matched healthy controls, respectively. Gepotidacin plasma C_{max} and AUC in ESRD subjects requiring haemodialysis were 2.3-fold and 2.4-fold higher before haemodialysis than healthy matching subjects, respectively, and were 6.0-fold and 4.1-fold higher after haemodialysis than matched healthy controls, respectively. Gepotidacin urinary exposure (AUCs) and amount excreted in urine decreased with decreasing renal function, ranging from 34% to 79% for urinary AUC and a 41% to 97% reduction in total amount excreted in urine in patients with renal impairment compared to matched healthy controls.

Hepatic impairment

Moderate hepatic impairment did not have a clinically relevant effect on gepotidacin pharmacokinetics. In patients with severe hepatic impairment compared with patients with normal hepatic function, gepotidacin plasma exposure parameters (C_{max} and AUC) were increased by approximately 1.9-fold and 1.7-fold, respectively. Gepotidacin urinary exposure (AUCs) in patients with moderate and severe hepatic impairment were 3.2-fold and 3.9-fold higher than in matched healthy controls, respectively, and the total amount excreted in urine in patients with moderate and severe hepatic impairment were 1.5-fold and 2.6-fold higher than in matched healthy controls, respectively.

5.3 Preclinical safety data

Carcinogenesis/mutagenesis

Long term carcinogenicity studies have not been conducted.

Although positive *in vitro* findings for clastogenicity consistent with a mechanism related to mammalian topoisomerase II inhibition were found, *in vivo* data indicate that gepotidacin does not pose a genotoxic hazard to humans.

Reproductive Toxicology

Fertility

Gepotidacin did not cause adverse effects on male or female reproductive organs or spermatogenesis when administered for up to 13 weeks to rats at 750 mg/kg/day and

to dogs at up to 250 mg/kg/day (up to 7.5 times the exposure (AUC) at the maximum recommended human dose [MRHD]).

No functional effects on male or female mating or fertility were observed in rats given gepotidacin at doses up to 750 mg/kg/day.

Pregnancy

In embryo-foetal development studies, where foetuses were delivered by caesarean section, there were no gepotidacin-related malformations at exposure of 2.6 times the MRHD in mice and 4.3 times the MRHD in rats. Developmental toxicity was evident as decreased foetal weights in rats following oral administration of gepotidacin at ≥ 450 mg/kg/day (≥ 1.2 times the exposure at the MRHD of 1500 mg twice daily) and decreased foetal weights and increased foetal mortality in mice following oral administration of gepotidacin at ≥ 500 mg/kg/day (≥ 0.7 times the exposure at the MRHD) in the presence of maternal toxicity.

These findings were not reproduced in the pre and postnatal development study when pregnant mice were given oral doses of gepotidacin at 1000 mg/kg/day (approximately 2.6 times the exposure in humans at the MRHD), for a longer duration throughout pregnancy and lactation and delivered their pups naturally. In this study, there were no effects on parturition, lactation, birth weights or postnatal growth and development of offspring and no evidence of foetal mortality.

Animal toxicology and/or pharmacology

Gepotidacin was a rapidly reversible inhibitor of acetylcholinesterase *in vitro* (median IC_{50} value of 4.8 μ g/mL), a concentration 1.6 times free plasma concentrations based on an unbound fraction of 67% and highest clinical oral total C_{max} of 4.26 μ g/mL.

Microscopic effects were seen with gepotidacin in the kidneys of rats (reversible and in conjunction with serum chemistry or urinalysis changes) in studies up to 4 weeks duration at ≥ 1.2 times exposure (AUC in humans at the MRHD). However no microscopic changes in the kidney were noted after 13 weeks in rats at 4.3 times the MRHD exposure. There were non-adverse, reversible serum chemistry or urinalysis changes related to the kidney in studies up to 13 weeks duration in dogs at ≥ 3.1 times MRHD with no clear microscopic effects in the kidneys.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose (E460)
Colloidal silicon dioxide (E551)
Croscarmellose sodium (E468)
Magnesium stearate (E470B)

Tablet coating

Polyvinyl alcohol (E1203)
Polyethylene glycol (E1521)
Talc (E553b)
Titanium dioxide (E171)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

White opaque high density polyethylene (HDPE) bottles with child resistant polypropylene closures.

Each bottle contains 20 tablets.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline UK Limited
79 New Oxford Street
London
WC1A 1DG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 19494/0317

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

27/08/2025

10 DATE OF REVISION OF THE TEXT

27/08/2025