

# Supplementary Materials: The Development of Third-Generation Tetracycline Antibiotics and New Perspectives

Aura Rusu and Emanuela Lorena Buta

**Table S1.** The representatives of tetracyclines class from first and second generations and their approval in therapy (FDA – USA Food and Drug Administration, EMA – European Medicine Agency, MHRA - UK Medicines and Healthcare Products Regulatory Agency).

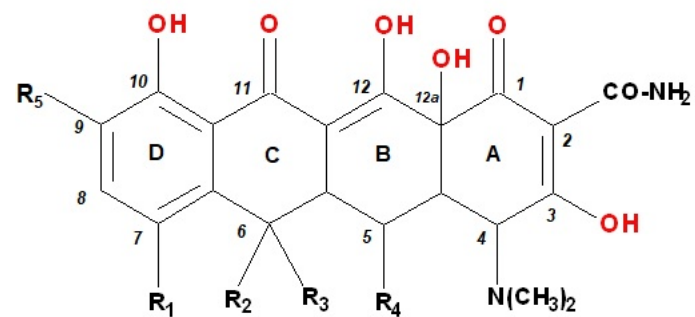
Generic name (Commercial name)	Generation	Year of approval	The authoriz- ing entity	IUPAC name	Reference
<b>Chlortetracycline</b> (Aureomycin)	First	1948	FDA	(4 <i>S</i> ,4 <i>aS</i> ,5 <i>aS</i> ,6 <i>S</i> ,12 <i>aR</i> )-7-chloro-4-(dimethylamino)-1,6,10,11,12 <i>a</i> -pentahydroxy-6-methyl-3,12-dioxo-4,4 <i>a</i> ,5,5 <i>a</i> -tetrahydrotetracene-2-carboxamide	[1–4]
<b>Oxytetracycline</b> (Terramycin)	First	1950	FDA	(4 <i>S</i> ,4 <i>aR</i> ,5 <i>S</i> ,5 <i>aR</i> ,6 <i>S</i> ,12 <i>aR</i> )-4-(dimethylamino)-1,5,6,10,11,12 <i>a</i> -hexahydroxy-6-methyl-3,12-dioxo-4,4 <i>a</i> ,5,5 <i>a</i> -tetrahydrotetracene-2-carboxamide	[1,5]
<b>Tetracycline</b> (Achromycin)	First	1954	FDA	(4 <i>S</i> ,4 <i>aS</i> ,5 <i>aS</i> ,6 <i>S</i> ,12 <i>aR</i> )-4-(dimethylamino)-1,6,10,11,12 <i>a</i> -pentahydroxy-6-methyl-3,12-dioxo-4,4 <i>a</i> ,5,5 <i>a</i> -tetrahydrotetracene-2-carboxamide	[1,6,7]
<b>Rolitetracycline</b> (Reverin)	First	1959	FDA	(4 <i>S</i> ,4 <i>aS</i> ,5 <i>aS</i> ,6 <i>S</i> ,12 <i>aR</i> )-4-(dimethylamino)-1,6,10,11,12 <i>a</i> -pentahydroxy-6-methyl-3,12-dioxo- <i>N</i> -(pyrrolidin-1-ylmethyl)-4,4 <i>a</i> ,5,5 <i>a</i> -tetrahydrotetracene-2-carboxamide	[8,9]
<b>Demeclocycline</b> (DMCT)	First	1960	FDA	(4 <i>S</i> ,4 <i>aS</i> ,5 <i>aS</i> ,6 <i>S</i> ,12 <i>aR</i> )-7-chloro-4-(dimethylamino)-1,6,10,11,12 <i>a</i> -pentahydroxy-3,12-dioxo-4 <i>a</i> ,5,5 <i>a</i> ,6-tetrahydro-4 <i>H</i> -tetracene-2-carboxamide	[10]
<b>Doxycycline</b> (Vibramycin)	Second	1967	FDA	(4 <i>S</i> ,4 <i>aR</i> ,5 <i>S</i> ,5 <i>aR</i> ,6 <i>R</i> ,12 <i>aR</i> )-4-(dimethylamino)-1,5,10,11,12 <i>a</i> -pentahydroxy-6-methyl-3,12-dioxo-4 <i>a</i> ,5,5 <i>a</i> ,6-tetrahydro-4 <i>H</i> -tetracene-2-carboxamide	[1,11]
<b>Minocycline</b> (Minocyn)	Second	1971	FDA	(4 <i>S</i> ,4 <i>aS</i> ,5 <i>aR</i> ,12 <i>aR</i> )-4,7-bis(dimethylamino)-1,10,11,12 <i>a</i> -tetrahydroxy-3,12-dioxo-4 <i>a</i> ,5,5 <i>a</i> ,6-tetrahydro-4 <i>H</i> -tetracene-2-carboxamide	[12]
<b>Methacycline</b> (Randomycin)	Second	1982???	FDA	(4 <i>S</i> ,4 <i>aR</i> ,5 <i>S</i> ,5 <i>aR</i> ,12 <i>aR</i> )-4-(dimethylamino)-1,5,10,11,12 <i>a</i> -pentahydroxy-6-methylidene-3,12-dioxo-4,4 <i>a</i> ,5,5 <i>a</i> -tetrahydrotetracene-2-carboxamide	[13,14]
<b>Lymecycline</b> (Tetralysal)	Second	1995	MHRA and EMA	(2 <i>S</i> )-6-[[[(4 <i>S</i> ,4 <i>aS</i> ,5 <i>aS</i> ,6 <i>S</i> ,12 <i>aR</i> )-4-(dimethylamino)-1,6,10,11,12 <i>a</i> -pentahydroxy-6-methyl-3,12-dioxo-4,4 <i>a</i> ,5,5 <i>a</i> -tetrahydrotetracene-2-carbonyl]amino]methylamino]-2-aminohexanoic acid	[15,16]

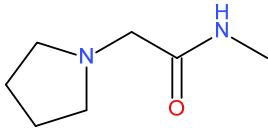
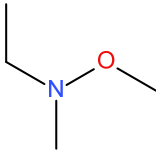
**Table S2.** Modern tetracyclines of the third generation introduced in therapy.

Compound name (Commercial name)	Year of approval	The authorizing entity	IUPAC name	Approved use in therapy	Reference
<b>Tigecycline (Tygacil)</b>	2005, 2006	FDA, EMA	(4 <i>S</i> ,4 <i>aS</i> ,5 <i>aR</i> ,12 <i>aR</i> )-9-[[2-(tert-butylamino)acetyl]amino]-4,7-bis(dimethylamino)-1,10,11,12 <i>a</i> -tetrahydroxy-3,12-dioxo-4 <i>a</i> ,5,5 <i>a</i> ,6-tetrahydro-4 <i>H</i> -tetracen-2-carboxamide	Complicated skin and soft tissue infections Complicated intra-abdominal infections Community-acquired bacterial pneumonia	[17][18][19]
<b>Omadacycline (Nuzyra)</b>	2018	FDA	4 <i>S</i> ,4 <i>aS</i> ,5 <i>aR</i> ,12 <i>aR</i> )-4,7-bis(dimethylamino)-9-[(2,2-dimethylpropylamino)methyl]-1,10,11,12 <i>a</i> -tetrahydroxy-3,12-dioxo-4 <i>a</i> ,5,5 <i>a</i> ,6-tetrahydro-4 <i>H</i> -tetracene-2-carboxamide	Complicated skin and soft tissue infections Complicated intra-abdominal infections	[20]
<b>Eravacycline (Xerava)</b>	2018	FDA, EMA	(4 <i>S</i> ,4 <i>aS</i> ,5 <i>aR</i> ,12 <i>aR</i> )-4-(dimethylamino)-7-fluoro-1,10,11,12 <i>a</i> -tetrahydroxy-3,12-dioxo-9-[(2-pyrrolidin-1-ylacetyl)amino]-4 <i>a</i> ,5,5 <i>a</i> ,6-tetrahydro-4 <i>H</i> -tetracene-2-carboxamide	Complicated intra-abdominal infections	[21,22]
<b>Sarecycline (Seysara)</b>	2018	FDA	(4 <i>S</i> ,4 <i>aS</i> ,5 <i>aR</i> ,12 <i>aR</i> )-4-(dimethylamino)-1,10,11,12 <i>a</i> -tetrahydroxy-7-[[methoxy(methyl)amino]methyl]-3,12-dioxo-4 <i>a</i> ,5,5 <i>a</i> ,6-tetrahydro-4 <i>H</i> -tetracene-2-carboxamide	Moderate to severe non-nodular acne vulgaris	[23]

**Table S3.** Essential structural features of tetracycline antibiotics.

Tetracycline representatives	C9 (R <sub>5</sub> )	C7 (R <sub>1</sub> )	C6 (R <sub>2</sub> )	C6 (R <sub>3</sub> )	C5 (R <sub>4</sub> )	C2
Chlortetracycline	-	Cl	OH	-CH <sub>3</sub>	-	-CO-NH <sub>2</sub>
Oxytetracycline	-	-	OH	-CH <sub>3</sub>	OH	-CO-NH <sub>2</sub>
Tetracycline	-	-	OH	-CH <sub>3</sub>	-	-CO-NH <sub>2</sub>
Rolitetracycline	-	-	OH	-CH <sub>3</sub>	-	
Demeclocycline	-	Cl	OH	-	-	-CO-NH <sub>2</sub>
Metacycline	-	-	-	=CH <sub>2</sub>	OH	-CO-NH <sub>2</sub>
Doxycycline	-	-	-	CH <sub>3</sub>	OH	-CO-NH <sub>2</sub>
Minocycline	-	-N(CH <sub>3</sub> ) <sub>2</sub>	-	-	-	-CO-NH <sub>2</sub>
Limecycline	-	-	OH	-CH <sub>3</sub>	-	-CO-NH-CH <sub>2</sub> -NH-(CH <sub>2</sub> ) <sub>4</sub> -CH(NH <sub>2</sub> )-COOH
Sancycline	-	-	-	-	-	-CO-NH <sub>2</sub>
Tigecycline		-N(CH <sub>3</sub> ) <sub>2</sub>	-	-	-	-CO-NH <sub>2</sub>
Omadacycline		-N(CH <sub>3</sub> ) <sub>2</sub>	-	-	-	-CO-NH <sub>2</sub>



Tetracycline representatives	C9 (R <sub>5</sub> )	C7 (R <sub>1</sub> )	C6 (R <sub>2</sub> )	C6 (R <sub>3</sub> )	C5 (R <sub>4</sub> )	C2
Eravacycline		-F	-	-	-	-CO-NH <sub>2</sub>
Sarecycline	-		-	-	-	-CO-NH <sub>2</sub>

**Table S4.** Physicochemical properties of third-generation tetracyclines.

<b>Tigecycline</b>	<b>Properties</b>	<b>References</b>
Chemical formula	C <sub>29</sub> H <sub>39</sub> N <sub>5</sub> O <sub>8</sub>	[24]
Molecular weight (g/mol)	586.6	[24]
Aspect	odourless, crystalline orange powder	[25]
Solubility	14.55 mg/L at 25°C (water); 0.45 mg/mL (water) (ALOGPS); highly ionisable throughout the pH range	[24,26]
LogP	0.8 (experimental), 0.66 (ALOGPS), -3.9 (ChemAxon)	[26]
pKa	3.17 (strongest acidic), 8.97 (strongest basic); 2.8; 4.4; 7.4; 8.9; 9.5	[26,27]
Melting point	163-173°C; decomposition at 188.6°C	[28,29]
Storage	2–8 °C; under –20 °C	[25,28]
<b>Omadacycline</b>	<b>Properties</b>	<b>References</b>
Chemical formula	C <sub>29</sub> H <sub>40</sub> N <sub>4</sub> O <sub>7</sub>	[30,31]
Molecular weight (g/mol)	556.66	[30,31]
Aspect	powder	[32]
Solubility	0.213 mg/mL (in water)	[30]
LogP	0.92 (ALOGPS), -2.2 (ChemAxon)	[30]
pKa	2.87 (strongest acidic), 10.54 (strongest basic) (Chemaxon)	[31]
Melting point	Not available	
Storage	under –20 °C	[32]
<b>Omadacycline (tosilate)</b>	<b>Properties</b>	<b>References</b>
Chemical formula	C <sub>36</sub> H <sub>48</sub> N <sub>4</sub> O <sub>10</sub> S	[33]
Molecular weight (g/mol)	728.85	[33]
Aspect	Not available	
Solubility	100 mg/mL at 25 °C (water, ethanol, <sup>1</sup> DMSO)	[33]
LogP	4.736	[34]
pKa	2.87 (strongest acidic), 10.54 (strongest basic) (Chemaxon)	[35]
Melting point	Not available	

Storage	three years at -20°C (powder) two years at -80°C (in solvent)	[33]
<b>Eravacycline</b>	<b>Properties</b>	<b>References</b>
Chemical formula	C <sub>27</sub> H <sub>31</sub> FN <sub>4</sub> O <sub>8</sub>	[36]
Molecular weight (g/mol)	558,56	[36]
Aspect	Pale yellow to dark yellow cake	[37]
Solubility	0.838 mg/mL (water)( ALOGPS)	[38]
LogP	0.24 (ALOGPS), -3.5 (ChemAxon)	[38]
pKa	-2.96 (strongest acidic), 9 (strongest basic)	[38]
Melting point	Not available	
Storage	Not available	
<b>Eravacycline (dihydrochloride)</b>	<b>Properties</b>	<b>References</b>
Chemical formula	C <sub>27</sub> H <sub>33</sub> Cl <sub>2</sub> FN <sub>4</sub> O <sub>8</sub>	[39]
Molecular weight (g/mol)	631.5	[39]
Aspect	Powder, pale yellow to dark yellow	[37]
Solubility	0.838 mg/mL (water)( ALOGPS); 50 mg/mL(water), 220 mg/mL ( <sup>1</sup> DMSO); Unstable in solutions, use freshly prepared.	[40,41]
LogP	0.24 (ALOGPS), -3.5 (ChemAxon)	[40]
pKa	-2.96 (strongest acidic), 9 (strongest basic)	[40]
Melting point	Not available	
Storage	-80°C; protected from light, stored under nitrogen	[41]
<b>Sarecycline</b>	<b>Properties</b>	<b>References</b>
Chemical formula	C <sub>24</sub> H <sub>29</sub> N <sub>3</sub> O <sub>8</sub>	[42]
Molecular weight (g/mol)	487.5	[42]
Aspect	Not available	
Solubility	2.01 mg/mL (water)(ALOGPS);	[43]
LogP	-0.17 (ALOGPS), -3.1 (ChemAxon)	[43]
pKa	3.31 (strongest acidic), 8.699 (strongest basic)	[43]
Melting point	Not available	
Storage	0-4°C (days to weeks; dry and dark place) -20°C (months to years)	[44]
<b>Sarecycline (hydrochloride)</b>	<b>Properties</b>	<b>References</b>
Chemical formula	C <sub>24</sub> H <sub>30</sub> ClN <sub>3</sub> O <sub>8</sub>	[45]
Molecular weight (g/mol)	524.0	[45]
Aspect	Solid powder	[44]

Solubility	2.01 mg/mL (water)(ALOGPS); soluble in <sup>1</sup> DMSO	[44,46]
LogP	-0.17 (ALOGPS), -3.1 (ChemAxon)	[46]
pKa	3.31 (strongest acidic), 8.69 (strongest basic)	[46]
Melting point	Not available	
Storage	4°C (stored under nitrogen)	[47]

<sup>1</sup> DMSO—Dimethyl sulfoxide.

**Table S5.** The antibacterial spectrum of the newly approved tetracyclines.

Tetracycline	Gram-positive pathogens	Gram-negative pathogens	Other pathogens	References
<b>Tigecycline</b>	<b>Aerobes</b>  <b>-Cocci:</b> <i>Staphylococcus aureus</i> , coagulase-negative staphylococci, <i>Streptococcus pneumoniae</i> , <i>Enterococcus faecalis</i> , <i>Enterococcus faecium</i> , <i>Enterococcus avium</i> , <i>Enterococcus casseliflavus</i> , <i>Enterococcus fallinarum</i> , <i>Enterococcus raffinosus</i> , Group A and B streptococci, Viridans streptococci  <b>Anaerobes</b> <b>-Cocci:</b> <i>Peptostreptococcus</i> spp., <b>-Bacilli:</b> <i>Bacteroides fragilis</i> , <i>Clostridium perfringens</i> , <i>Clostridium difficile</i> , <i>Propionibacterium acnes</i> , <i>Fusobacterium</i> spp., <i>Prevotella</i> spp., <i>Porphyromonas</i> spp.	<b>Aerobes</b> <b>-Bacilli:</b> -Enterobacteriaceae: <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Klebsiella oxytoca</i> , <i>Morganella morganii</i> , <i>Proteus mirabilis</i> , <i>Proteus vulgaris</i> , <i>Providencia</i> spp., <i>Shigella</i> spp., <i>Salmonella</i> spp., <i>Citrobacter freundii</i> , <i>Enterobacter cloacae</i> , <i>Enterobacter aerogenes</i> , <i>Serratia marcescens</i> -Non-Enterobacteriaceae: <i>Stenotrophomonas maltophilia</i> , <i>Pseudomonas aeruginosa</i> , <i>Burkholderia cepacia</i> , <i>Acinetobacter baumannii</i> (coccobacillus) -Respiratory pathogens: <i>Haemophilus influenzae</i> (coccobacillus), <i>Moraxella catarrhalis</i> (diplococcus) -Other: <i>Neisseria gonorrhoeae</i> (coccus), <i>Eikenella corrodens</i> (bacillus)	<b>Atypical bacteria:</b>  <b>-Bacilli:</b> <i>Mycobacterium abscessus</i> , <i>Mycobacterium chelonae</i> , <i>Mycobacterium fortuitum</i> group, <i>Mycobacterium avium</i> complex, <i>Mycobacterium lentiflavum</i> , <i>Mycobacterium marinum</i> , <i>Mycobacterium kansasii</i> , <i>Chlamydophila pneumoniae</i> , <b>-Pleomorphic:</b> <i>Mycoplasma hominis</i> , <i>Mycoplasma pneumoniae</i> , <i>Ureaplasma urealyticum</i>	[48–71]
<b>Omadacycline</b>	<b>Aerobes</b>  <b>-Cocci:</b> <i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i> , coagulase-	<b>Aerobes</b>  <b>-Bacilli:</b> <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Klebsiella oxytoca</i> , <i>Enterobacter</i>	<b>Atypical bacteria:</b>  <b>-Bacilli:</b> <i>Legionella pneumophila</i> , <i>Chlamydophila pneumoniae</i> ,	[71–88]

Tetracycline	Gram-positive pathogens	Gram-negative pathogens	Other pathogens	References
	negative staphylococci, <i>Staphylococcus lugdunensis</i> , <i>Staphylococcus pseudintermedius</i> , <i>Enterococcus</i> spp., <i>Enterococcus faecium</i> , <i>Streptococcus pneumoniae</i> , <i>Streptococcus anginosus</i> group, Viridans streptococci, $\beta$ -hemolytic streptococci, <i>Streptococcus pyogenes</i> , <i>Streptococcus agalactiae</i> , <b>-Bacilli:</b> <i>Corynebacterium</i> spp., <i>Bacillus anthracis</i> , <i>Listeria monocytogenes</i>	<i>cloacae</i> , <i>Citrobacter freundii</i> , <i>Proteus mirabilis</i> , <i>Salmonella</i> spp., <i>Serratia marcescens</i> , <i>Shigella</i> spp., <i>Yersinia pestis</i> , <i>Pseudomonas aeruginosa</i> , <i>Strenotrophomonas maltophilia</i> , <i>Burkholderia cepacia</i> , <i>Eikenella corrodens</i> , <i>Bergeyella zoohelcum</i> <b>-Coccobacilli:</b> <i>Acinetobacter baumannii</i> , <i>Haemophilus influenzae</i> , <i>Pasteurella canis</i> , <i>Pasteurella multocida</i> <b>-Diplococci:</b> <i>Moraxella catarrhalis</i> , <i>Neisseria gonorrhoeae</i> , <i>Neisseria weaveri</i> , <i>Neisseria zoodegmatis</i> <b>Anaerobes</b> <b>-Bacilli:</b> <i>Bacteroides fragilis</i> , <i>Bacteroides ovatus</i> , <i>Bacteroides thetaiotaomicron</i> , <i>Bacteroides vulgatus</i> , <i>Bacteroides pyogenes</i> , <i>Fusobacterium</i> spp., <i>Porphyromonas</i> spp., <i>Prevotella</i> spp.	<i>Mycobacterium abscessus</i> , <i>Mycobacterium fortuitum</i> , <i>Mycobacterium chelonae</i> <b>-Pleomorphic:</b> <i>Mycoplasma hominis</i> , <i>Mycoplasma pneumoniae</i> , <i>Ureaplasma</i> spp.	
Eravacycline	Aerobes	Aerobes		
	<b>-Cocci:</b> <i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i> , <i>Streptococcus agalactiae</i> , <i>Streptococcus pneumoniae</i> , <i>Streptococcus pyogenes</i> , <i>Enterococcus faecalis</i> , <i>Enterococcus faecium</i>	<b>-Bacilli:</b> <i>Citrobacter freundii</i> , <i>Enterobacter aerogenes</i> , <i>Enterobacter cloacae</i> , <i>Escherichia coli</i> , <i>Klebsiella oxytoca</i> , <i>Klebsiella pneumoniae</i> , <i>Morganella morganii</i> , <i>Proteus mirabilis</i> , <i>Proteus vulgaris</i> , <i>Pseudomonas aeruginosa</i> , <i>Salmonella</i> spp., <i>Salmonella</i> spp., <i>Serratia marcescens</i> , <i>Strenotrophomonas maltophilia</i> <b>-Diplococci:</b> <i>Moraxella catarrhalis</i> , <i>Neisseria gonorrhoeae</i> <b>-Coccobacilli:</b> <i>Haemophilus influenzae</i>		[71,89–93]
	<b>Anaerobes</b> <b>-Cocci:</b> <i>Anaerococcus</i> spp., <i>Peptostreptococcus anaerobius</i> , <i>Peptostreptococcus micros</i>	<b>Anaerobes</b> <b>-Bacilli:</b> <i>Bacteroides fragilis</i> , <i>Bacteroides ovatus</i> , <i>Bacteroides thetaiotaomicron</i> , <i>Fusobacterium</i> spp., <i>Prevotella bivia</i> , <i>Prevotella buccae</i> ,		



Tetracycline	Gram-positive pathogens	Gram-negative pathogens	Other pathogens	References
	<b>-Bacilli:</b> <i>Clostridium difficile</i> , <i>Clostridium perfringens</i> , <i>Lactobacillus</i> spp., <i>Propionibacterium</i> spp	<i>Prevotella disiens</i> , <i>Prevotella intermedia</i> , <i>Prevotella melaninogenica</i>		
Sarecycline	Aerobes	Aerobes		
	<b>-Cocci:</b> <i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i> , <i>Staphylococcus haemolyticus</i> , <i>Streptococcus pyogenes</i> , <i>Streptococcus agalactiae</i> , <i>Enterococcus faecalis</i> , <i>Enterococcus faecium</i>	<b>-Bacilli:</b> <i>Enterobacter cloacae</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Proteus mirabilis</i> , <i>Salmonella</i> spp.		[94,95]
	Anaerobes			
	<b>-Bacilli:</b> <i>Cutinebacterium acnes</i>			

**Table S6.** Pharmacokinetics parameters of modern tetracyclines (iv - intravenous, AUC - area under the curve, C<sub>max</sub> - maximum concentration observed, ss - steady state, D - dose, T<sub>max</sub> - time of maximum concentration, T<sub>1/2</sub> - half life, FMO - flavin-containing monooxygenase) [96–99].

	Tigecycline	Omadacycline		Eravacycline	Sarecycline
Dosage and route of administration	initial dose of 100 mg iv; followed by iv infusion (30 minutes) of 50 mg every 12 hours	100 mg iv	300 mg orally	intermittent dosing-unique and repeated iv infusion (60 minutes) of 1 mg/kg every 12 hours	60 mg orally
Pharmacokinetic parameters (medium values)					
C <sub>max ss</sub> (µg/ml)	0.87	2.12	0.952	1.825	
AUC <sub>ss</sub> (µg /L)	4.7 (AUC <sub>0-24h</sub> )	12.14	11.126	6.309 (AUC <sub>0-12h</sub> )	
Accumulation ratio		1.5		1.45	1.5-1.6
Absorption					
Bioavailability (%)	100	100	34.5	100	
Medium T <sub>max ss</sub> (hours)		0.5	2.5		
Distribution					
Plasma protein binding	71-89%	20% (independent of concentration)		79%-90% (increases with increasing plasma concentrations, with 79% to 90% at plasma concentrations ranging from 0.1 to 10 µg/mL)	62.5%-64.7%
Volume of distribution <sub>ss</sub> (L)	639	190	-	321	91.4-97

Elimination					
$T_{1/2\text{ ss}}$	42.4	16	15.5	20	21-22
Systemic clearance <sub>ss</sub> (L/hour)	23.8	8.8	-		3 (apparent oral clearance)
Renal clearance <sub>ss</sub> (L/hour)	51.0	2,4-3,3			
<b>Metabolism</b>	<20%	No		CYP3A4 and FMO	<15% by microsomal enzymes

## References

- Nelson, M.L.; Levy, S.B. The History of the Tetracyclines. *Annals of the New York Academy of Sciences* **2011**, *1241*, 17–32, doi:10.1111/j.1749-6632.2011.06354.x.
- PubChem Chlortetracycline Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/54675777> (accessed on 6 October 2021).
- Finland, M. Twenty-Fifth Anniversary of the Discovery of Aureomycin: The Place of the Tetracyclines in Antimicrobial Therapy. *Clin Pharmacol Ther* **1974**, *15*, 3–8, doi:10.1002/cpt19741513.
- Raistrick, H. Aureomycin, a New Antibiotic. *Nature* **1949**, *163*, 159–160, doi:10.1038/163159a0.
- PubChem Oxytetracycline Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/54675779> (accessed on 6 October 2021).
- PubChem Tetracycline Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/54675776> (accessed on 6 October 2021).
- Stephens, C.R.; Conover, L.H.; Hochstein, F.A.; Regna, P.P.; Pilgrim, F.J.; Brunings, K.J.; Woodward, R.B. TERRAMYCIN. VIII. STRUCTURE OF AUREOMYCIN AND TERRAMYCIN. *J. Am. Chem. Soc.* **1952**, *74*, 4976–4977, doi:10.1021/ja01139a533.
- PubChem Rolitetracycline Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/54682938> (accessed on 6 October 2021).
- NCATS Inxight: Drugs — ROLITETRACYCLINE Available online: <https://drugs.ncats.io/substance/GH9IW85221> (accessed on 6 October 2021).
- PubChem Demeclocycline Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/54680690> (accessed on 6 October 2021).
- PubChem Doxycycline Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/54671203> (accessed on 6 October 2021).
- PubChem Minocycline Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/54675783> (accessed on 6 October 2021).
- PubChem Methacycline Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/54675785> (accessed on 6 October 2021).
- Lucelia, M. da S.; Herida, R.N.S. Methacycline: A Review of Analytical Methods. *Current Pharmaceutical Analysis* **2012**, *8*, 2–13.
- PubChem Lymecycline Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/54707177> (accessed on 6 October 2021).
- Tetralysal 300mg Hard Capsules - Summary of Product Characteristics (SmPC) - (Emc) Available online: <https://www.medicines.org.uk/emc/product/926/smpc#gref> (accessed on 29 September 2021).
- Link: RCP Tygacil FDA Available online: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2007/021821s0071bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021821s0071bl.pdf).
- Tygacil | European Medicines Agency Available online: <https://www.ema.europa.eu/en/medicines/human/EPAR/tygacil> (accessed on 2 October 2021).
- Stein, G.E.; Babinchak, T. Tigecycline: An Update. *Diagnostic Microbiology and Infectious Disease* **2013**, *75*, 331–336, doi:10.1016/j.diagmicrobio.2012.12.004.
- Zhanel, G.G.; Esquivel, J.; Zelenitsky, S.; Lawrence, C.K.; Adam, H.J.; Golden, A.; Hink, R.; Berry, L.; Schweizer, F.; Zhanel, M.A.; et al. Omadacycline: A Novel Oral and Intravenous Aminomethylcycline Antibiotic Agent. *Drugs* **2020**, *80*, 285–313, doi:10.1007/s40265-020-01257-4.
- Heaney, M.; Mahoney, M. V.; Gallagher, J.C. Eravacycline: The Tetracyclines Strike Back. *Annals of Pharmacotherapy* **2019**, *53*, 1124–1135, doi:10.1177/1060028019850173.

22. Alosaimy, S.; Abdul-Mutakabbir, J.C.; Kebriaei, R.; Jorgensen, S.C.J.; Rybak, M.J. Evaluation of Eravacycline: A Novel Fluorocycline. *Pharmacotherapy* **2020**, *40*, 221–238, doi:10.1002/phar.2366.
23. Haidari, W.; Bruinsma, R.; Cardenas-de la Garza, J.A.; Feldman, S.R. Sarecycline Review. *Annals of Pharmacotherapy* **2020**, *54*, 164–170, doi:10.1177/1060028019873111.
24. PubChem Tigecycline Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/54686904> (accessed on 2 August 2021).
25. Tigecycline---Chemical Information Search Available online: [https://www.chemicalbook.com/ProductList\\_En.aspx?kwd=tigecycline](https://www.chemicalbook.com/ProductList_En.aspx?kwd=tigecycline) (accessed on 5 October 2021).
26. Tigecycline | DrugBank Online Available online: <https://go.drugbank.com/drugs/DB00560> (accessed on 2 August 2021).
27. Arias, K.; Robinson, S.G.; Lyngaas, S.S.; Cherala, S.S.; Hartzell, M.; Mei, S.; Vilic, A.; Girel, J.K.; Kuemmell, A.; Vrettos, J.S.; et al. Minocycline and Tigecycline Form Higher-Order Ca<sup>2+</sup> Complexes of Stronger Affinity than Tetracycline. *Inorganica Chimica Acta* **2016**, *441*, 181–191, doi:10.1016/j.ica.2015.10.037.
28. 220620-09-7 Tigecycline AKSci E414 Available online: [https://aksci.com/item\\_detail.php?cat=E414](https://aksci.com/item_detail.php?cat=E414) (accessed on 5 October 2021).
29. Silva, L.M. da; Almeida, A.E. de; Salgado, H.R.N. Thermal Analysis and Validation of UV and Visible Spectrophotometric Methods for the Determination of New Antibiotic Tigecycline in Pharmaceutical Product. *Advances in Analytical Chemistry* **2012**, *2*, 10–15.
30. PubChem Omadacycline Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/54697325> (accessed on 5 October 2021).
31. Omadacycline Available online: <https://go.drugbank.com/drugs/DB12455> (accessed on 7 October 2021).
32. Omadacycline | 389139-89-3 Available online: <http://www.sigmaaldrich.com/> (accessed on 7 October 2021).
33. Omadacycline Tosylate | ≥99%(HPLC) | Selleck | Bacterial Chemical Available online: <https://www.selleckchem.com/products/omadacycline-tosylate.html> (accessed on 5 October 2021).
34. Omadacycline (Tosylate) Available online: [https://www.chemsrc.com/en/cas/1075240-43-5\\_1349361.html](https://www.chemsrc.com/en/cas/1075240-43-5_1349361.html) (accessed on 5 October 2021).
35. Omadacycline Tosylate | DrugBank Online Available online: <https://go.drugbank.com/salts/DBSALT002607> (accessed on 7 October 2021).
36. PubChem Eravacycline Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/54726192> (accessed on 7 October 2021).
37. European Medicines Agency Xerava Available online: <https://www.ema.europa.eu/en/medicines/human/EPAR/xerava> (accessed on 3 August 2021).
38. Eravacycline Available online: <https://go.drugbank.com/drugs/DB12329> (accessed on 7 October 2021).
39. PubChem Eravacycline Dihydrochloride Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/56951485> (accessed on 7 October 2021).
40. Eravacycline Dihydrochloride | DrugBank Online Available online: <https://go.drugbank.com/salts/DBSALT002787> (accessed on 7 October 2021).
41. Eravacycline Dihydrochloride (TP-434 Dihydrochloride) | Anti-Bacterial Agent | MedChemExpress Available online: [https://www.medchemexpress.com/Eravacycline\\_dihydrochloride.html](https://www.medchemexpress.com/Eravacycline_dihydrochloride.html) (accessed on 7 October 2021).
42. PubChem Sarecycline Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/54681908> (accessed on 4 October 2021).
43. Sarecycline Available online: <https://go.drugbank.com/drugs/DB12035> (accessed on 7 October 2021).
44. Welcome to Medkoo Biosciences Available online: <https://medkoo.com/> (accessed on 7 October 2021).
45. Sarecycline Hydrochloride | C24H30ClN3O8 - PubChem Available online: <https://pubchem.ncbi.nlm.nih.gov/compound/71296095> (accessed on 7 October 2021).
46. Sarecycline Hydrochloride | DrugBank Online Available online: <https://go.drugbank.com/salts/DBSALT002125> (accessed on 7 October 2021).
47. Sarecycline Hydrochloride | Antibiotic | MedChemExpress Available online: <https://www.medchemexpress.com/sarecycline-hydrochloride.html> (accessed on 7 October 2021).
48. Noskin, G.A. Tigecycline: A New Glycylcycline for Treatment of Serious Infections. *Clinical Infectious Diseases* **2005**, *41*, S303–S314, doi:10.1086/431672.

49. Biedenbach, D.J.; Beach, M.L.; Jones, R.N. In Vitro Antimicrobial Activity of GAR-936 Tested against Antibiotic-Resistant Gram-Positive Blood Stream Infection Isolates and Strains Producing Extended-Spectrum  $\beta$ -Lactamases. *Diagnostic Microbiology and Infectious Disease* **2001**, *40*, 173–177, doi:10.1016/S0732-8893(01)00269-3.
50. Postier, R.G.; Green, S.L.; Klein, S.R.; Ellis-Grosse, E.J.; Loh, E.; Tigecycline 200 Study Group Results of a Multicenter, Randomized, Open-Label Efficacy and Safety Study of Two Doses of Tigecycline for Complicated Skin and Skin-Structure Infections in Hospitalized Patients. *Clin Ther* **2004**, *26*, 704–714, doi:10.1016/s0149-2918(04)90070-7.
51. Petersen, P.J.; Jacobus, N.V.; Weiss, W.J.; Sum, P.E.; Testa, R.T. In Vitro and in Vivo Antibacterial Activities of a Novel Glycylcycline, the 9-t-Butylglycylamido Derivative of Minocycline (GAR-936). *Antimicrob Agents Chemother* **1999**, *43*, 738–744, doi:10.1128/AAC.43.4.738.
52. van Ogtrop, M.L.; Andes, D.; Stamstad, T.J.; Conklin, B.; Weiss, W.J.; Craig, W.A.; Vesga, O. In Vivo Pharmacodynamic Activities of Two Glycylcyclines (GAR-936 and WAY 152,288) against Various Gram-Positive and Gram-Negative Bacteria. *Antimicrob Agents Chemother* **2000**, *44*, 943–949, doi:10.1128/AAC.44.4.943-949.2000.
53. Betriu, C.; Rodríguez-Avial, I.; Sánchez, B.A.; Gómez, M.; Álvarez, J.; Picazo, J.J. In Vitro Activities of Tigecycline (GAR-936) against Recently Isolated Clinical Bacteria in Spain. *Antimicrob Agents Chemother* **2002**, *46*, 892–895, doi:10.1128/AAC.46.3.892-895.2002.
54. Goldstein, E.J.; Citron, D.M.; Merriam, C.V.; Warren, Y.; Tyrrell, K. Comparative in Vitro Activities of GAR-936 against Aerobic and Anaerobic Animal and Human Bite Wound Pathogens. *Antimicrob Agents Chemother* **2000**, *44*, 2747–2751, doi:10.1128/AAC.44.10.2747-2751.2000.
55. Milatovic, D.; Schmitz, F.-J.; Verhoef, J.; Fluit, A.C. Activities of the Glycylcycline Tigecycline (GAR-936) against 1,924 Recent European Clinical Bacterial Isolates. *Antimicrob Agents Chemother* **2003**, *47*, 400–404, doi:10.1128/AAC.47.1.400-404.2003.
56. Cercenado, E.; Cercenado, S.; Gómez, J.A.; Bouza, E. In Vitro Activity of Tigecycline (GAR-936), a Novel Glycylcycline, against Vancomycin-Resistant Enterococci and Staphylococci with Diminished Susceptibility to Glycopeptides. *J Antimicrob Chemother* **2003**, *52*, 138–139, doi:10.1093/jac/dkg289.
57. Low, D.E.; Kreiswirth, B.N.; Weiss, K.; Willey, B.M. Activity of GAR-936 and Other Antimicrobial Agents against North American Isolates of Staphylococcus Aureus. *Int J Antimicrob Agents* **2002**, *20*, 220–222, doi:10.1016/s0924-8579(02)00132-2.
58. Boucher, H.W.; Wennersten, C.B.; Eliopoulos, G.M. In Vitro Activities of the Glycylcycline GAR-936 against Gram-Positive Bacteria. *Antimicrobial Agents and Chemotherapy* **2000**, *44*, 2225–2229, doi:10.1128/AAC.44.8.2225-2229.2000.
59. Kitzis, M.D.; Ly, A.; Goldstein, F.W. In Vitro Activities of Tigecycline (GAR-936) against Multidrug-Resistant Staphylococcus Aureus and Streptococcus Pneumoniae. *Antimicrob Agents Chemother* **2004**, *48*, 366–367, doi:10.1128/AAC.48.1.366-367.2004.
60. Zhanel, G.G.; Palatnick, L.; Nichol, K.A.; Bellyou, T.; Low, D.E.; Hoban, D.J. Antimicrobial Resistance in Respiratory Tract Streptococcus Pneumoniae Isolates: Results of the Canadian Respiratory Organism Susceptibility Study, 1997 to 2002. *Antimicrobial Agents and Chemotherapy* **2003**, *47*, 1867–1874, doi:10.1128/AAC.47.6.1867-1874.2003.
61. Betriu, C.; Culebras, E.; Rodríguez-Avial, I.; Gómez, M.; Sánchez, B.A.; Picazo, J.J. In Vitro Activities of Tigecycline against Erythromycin-Resistant Streptococcus Pyogenes and Streptococcus Agalactiae: Mechanisms of Macrolide and Tetracycline Resistance. *Antimicrob Agents Chemother* **2004**, *48*, 323–325, doi:10.1128/AAC.48.1.323-325.2004.
62. Patel, R.; Rouse, M.S.; Piper, K.E.; Steckelberg, J.M. In Vitro Activity of GAR-936 against Vancomycin-Resistant Enterococci, Methicillin-Resistant Staphylococcus Aureus and Penicillin-Resistant Streptococcus Pneumoniae. *Diagn Microbiol Infect Dis* **2000**, *38*, 177–179, doi:10.1016/s0732-8893(00)00193-0.
63. Petersen, P.J.; Bradford, P.A.; Weiss, W.J.; Murphy, T.M.; Sum, P.E.; Projan, S.J. In Vitro and in Vivo Activities of Tigecycline (GAR-936), Daptomycin, and Comparative Antimicrobial Agents against Glycopeptide-Intermediate Staphylococcus Aureus and Other Resistant Gram-Positive Pathogens. *Antimicrob Agents Chemother* **2002**, *46*, 2595–2601, doi:10.1128/AAC.46.8.2595-2601.2002.

64. Gales, A.C.; Jones, R.N.; Andrade, S.S.; Pereira, A.S.; Sader, H.S. In Vitro Activity of Tigecycline, a New Glycylcycline, Tested against 1,326 Clinical Bacterial Strains Isolated from Latin America. *Braz J Infect Dis* **2005**, *9*, 348–356, doi:10.1590/s1413-86702005000500001.
65. Betriu, C.; Rodríguez-Avil, I.; Sánchez, B.A.; Gómez, M.; Picazo, J.J. Comparative in Vitro Activities of Tigecycline (GAR-936) and Other Antimicrobial Agents against *Stenotrophomonas Maltophilia*. *J Antimicrob Chemother* **2002**, *50*, 758–759, doi:10.1093/jac/dkf196.
66. Henwood, C.J.; Gatward, T.; Warner, M.; James, D.; Stockdale, M.W.; Spence, R.P.; Towner, K.J.; Livermore, D.M.; Woodford, N. Antibiotic Resistance among Clinical Isolates of *Acinetobacter* in the UK, and in Vitro Evaluation of Tigecycline (GAR-936). *J Antimicrob Chemother* **2002**, *49*, 479–487, doi:10.1093/jac/49.3.479.
67. Edlund, C.; Nord, C.E. In-Vitro Susceptibility of Anaerobic Bacteria to GAR-936, a New Glycylcycline. *Clin Microbiol Infect* **2000**, *6*, 159–163, doi:10.1046/j.1469-0691.2000.00034-6.x.
68. Wallace, R.J.; Brown-Elliott, B.A.; Crist, C.J.; Mann, L.; Wilson, R.W. Comparison of the in Vitro Activity of the Glycylcycline Tigecycline (Formerly GAR-936) with Those of Tetracycline, Minocycline, and Doxycycline against Isolates of Nontuberculous Mycobacteria. *Antimicrob Agents Chemother* **2002**, *46*, 3164–3167, doi:10.1128/AAC.46.10.3164-3167.2002.
69. Rhomberg, P.R.; Jones, R.N. In Vitro Activity of 11 Antimicrobial Agents, Including Gatifloxacin and GAR936, Tested against Clinical Isolates of *Mycobacterium Marinum*. *Diagn Microbiol Infect Dis* **2002**, *42*, 145–147, doi:10.1016/s0732-8893(01)00332-7.
70. Roblin, P.M.; Hammerschlag, M.R. In Vitro Activity of GAR-936 against *Chlamydia Pneumoniae* and *Chlamydia Trachomatis*. *Int J Antimicrob Agents* **2000**, *16*, 61–63, doi:10.1016/s0924-8579(00)00198-9.
71. Grossman, T.H. Tetracycline Antibiotics and Resistance. *Cold Spring Harb Perspect Med* **2016**, *6*, a025387, doi:10.1101/cshperspect.a025387.
72. Zhanel, G.G.; Esquivel, J.; Zelenitsky, S.; Lawrence, C.K.; Adam, H.J.; Golden, A.; Hink, R.; Berry, L.; Schweizer, F.; Zhanel, M.A.; et al. Omadacycline: A Novel Oral and Intravenous Aminomethylcycline Antibiotic Agent. *Drugs* **2020**, *80*, 285–313, doi:10.1007/s40265-020-01257-4.
73. Zhanel, G.G.; Homenuik, K.; Nichol, K.; Noreddin, A.; Vercaigne, L.; Embil, J.; Gin, A.; Karlowisky, J.A.; Hoban, D.J. The Glycylcyclines: A Comparative Review with the Tetracyclines. *Drugs* **2004**, *64*, 63–88, doi:10.2165/00003495-200464010-00005.
74. Karlowisky, J.A.; Steenbergen, J.; Zhanel, G.G. Microbiology and Preclinical Review of Omadacycline. *Clin Infect Dis* **2019**, *69*, S6–S15, doi:10.1093/cid/ciz395.
75. Huband, M.D.; Pfaller, M.A.; Shortridge, D.; Flamm, R.K. Surveillance of Omadacycline Activity Tested against Clinical Isolates from the United States and Europe: Results from the SENTRY Antimicrobial Surveillance Programme, 2017. *J Glob Antimicrob Resist* **2019**, *19*, 56–63, doi:10.1016/j.jgar.2019.02.017.
76. Pfaller, M.A.; Rhomberg, P.R.; Huband, M.D.; Flamm, R.K. Activity of Omadacycline Tested against *Streptococcus Pneumoniae* from a Global Surveillance Program (2014). *Diagn Microbiol Infect Dis* **2018**, *90*, 143–147, doi:10.1016/j.diagmicrobio.2017.10.010.
77. Pfaller, M.A.; Rhomberg, P.R.; Huband, M.D.; Flamm, R.K. Activities of Omadacycline and Comparator Agents against *Staphylococcus Aureus* Isolates from a Surveillance Program Conducted in North America and Europe. *Antimicrob Agents Chemother* **2017**, *61*, e02411-16, doi:10.1128/AAC.02411-16.
78. Pfaller, M.A.; Huband, M.D.; Rhomberg, P.R.; Flamm, R.K. Surveillance of Omadacycline Activity against Clinical Isolates from a Global Collection (North America, Europe, Latin America, Asia-Western Pacific), 2010-2011. *Antimicrob Agents Chemother* **2017**, *61*, e00018-17, doi:10.1128/AAC.00018-17.
79. Lee, H.; Kim, H.; Seo, Y.H.; Yong, D.; Jeong, S.H.; Lee, K.; Chong, Y. In Vitro Activity of Tigecycline Alone and Antimicrobial Combinations against Clinical *Neisseria Gonorrhoeae* Isolates. *Diagn Microbiol Infect Dis* **2017**, *87*, 160–162, doi:10.1016/j.diagmicrobio.2016.10.022.
80. Stapert, L.; Wolfe, C.; Shinabarger, D.; Marra, A.; Pillar, C. In Vitro Activities of Omadacycline and Comparators against Anaerobic Bacteria. *Antimicrob Agents Chemother* **2018**, *62*, e00047-18, doi:10.1128/AAC.00047-18.
81. Shoen, C.; Benaroch, D.; Sklaney, M.; Cynamon, M. In Vitro Activities of Omadacycline against Rapidly Growing Mycobacteria. *Antimicrobial Agents and Chemotherapy* **2019**, *63*, e02522-18, doi:10.1128/AAC.02522-18.

82. Goldstein, E.J.C.; Citron, D.M.; Tyrrell, K.L.; Leoncio, E.; Merriam, C.V. Comparative In Vitro Activity of Omadacycline against Dog and Cat Bite Wound Isolates. *Antimicrob Agents Chemother* **2018**, *62*, e02551-17, doi:10.1128/AAC.02551-17.
83. Steenbergen, J.; Tanaka, S.K.; Miller, L.L.; Halasohoris, S.A.; Hershfield, J.R. In Vitro and In Vivo Activity of Omadacycline against Two Biothreat Pathogens, *Bacillus Anthracis* and *Yersinia Pestis*. *Antimicrob Agents Chemother* **2017**, *61*, e02434-16, doi:10.1128/AAC.02434-16.
84. Pfaller, M.A.; Rhomborg, P.R.; Huband, M.D.; Flamm, R.K. Activity of Omadacycline Tested against Enterobacteriaceae Causing Urinary Tract Infections from a Global Surveillance Program (2014). *Diagn Microbiol Infect Dis* **2018**, *91*, 179–183, doi:10.1016/j.diagmicrobio.2018.01.019.
85. Carvalhaes, C.G.; Huband, M.D.; Reinhart, H.H.; Flamm, R.K.; Sader, H.S. Antimicrobial Activity of Omadacycline Tested against Clinical Bacterial Isolates from Hospitals in Mainland China, Hong Kong, and Taiwan: Results from the SENTRY Antimicrobial Surveillance Program (2013 to 2016). *Antimicrob Agents Chemother* **2019**, *63*, e02262-18, doi:10.1128/AAC.02262-18.
86. Fluit, A.C.; van Gorkum, S.; Vlooswijk, J. Minimal Inhibitory Concentration of Omadacycline and Doxycycline against Bacterial Isolates with Known Tetracycline Resistance Determinants. *Diagn Microbiol Infect Dis* **2019**, *94*, 78–80, doi:10.1016/j.diagmicrobio.2018.11.010.
87. Waites, K.B.; Crabb, D.M.; Liu, Y.; Duffy, L.B. In Vitro Activities of Omadacycline (PTK 0796) and Other Antimicrobial Agents against Human Mycoplasmas and Ureaplasmas. *Antimicrob Agents Chemother* **2016**, *60*, 7502–7504, doi:10.1128/AAC.01734-16.
88. Kohlhoff, S.A.; Huerta, N.; Hammerschlag, M.R. In Vitro Activity of Omadacycline against *Chlamydia Pneumoniae*. *Antimicrob Agents Chemother* **2019**, *63*, e01907-18, doi:10.1128/AAC.01907-18.
89. Sutcliffe, J.A.; O'Brien, W.; Fyfe, C.; Grossman, T.H. Antibacterial Activity of Eravacycline (TP-434), a Novel Fluorocycline, against Hospital and Community Pathogens. *Antimicrob. Agents Chemother.* **2013**, *57*, 5548–5558, doi:10.1128/AAC.01288-13.
90. Solomkin, J.S.; Ramesh, M.K.; Cesnauskas, G.; Novikovs, N.; Stefanova, P.; Sutcliffe, J.A.; Walpole, S.M.; Horn, P.T. Phase 2, Randomized, Double-Blind Study of the Efficacy and Safety of Two Dose Regimens of Eravacycline versus Ertapenem for Adult Community-Acquired Complicated Intra-Abdominal Infections. *Antimicrob Agents Chemother* **2014**, *58*, 1847–1854, doi:10.1128/AAC.01614-13.
91. Abdallah, M.; Olafisoye, O.; Cortes, C.; Urban, C.; Landman, D.; Quale, J. Activity of Eravacycline against Enterobacteriaceae and *Acinetobacter Baumannii*, Including Multidrug-Resistant Isolates, from New York City. *Antimicrob Agents Chemother* **2015**, *59*, 1802–1805, doi:10.1128/AAC.04809-14.
92. Zhanel, G.G.; Baxter, M.R.; Adam, H.J.; Sutcliffe, J.; Karlowsky, J.A. In Vitro Activity of Eravacycline against 2213 Gram-Negative and 2424 Gram-Positive Bacterial Pathogens Isolated in Canadian Hospital Laboratories: CANWARD Surveillance Study 2014-2015. *Diagn Microbiol Infect Dis* **2018**, *91*, 55–62, doi:10.1016/j.diagmicrobio.2017.12.013.
93. Snyderman, D.R.; McDermott, L.A.; Jacobus, N.V.; Kerstein, K.; Grossman, T.H.; Sutcliffe, J.A. Evaluation of the In Vitro Activity of Eravacycline against a Broad Spectrum of Recent Clinical Anaerobic Isolates. *Antimicrobial Agents and Chemotherapy* **2018**, *62*, e02206-17, doi:10.1128/AAC.02206-17.
94. Zhanel, G.; Critchley, I.; Lin, L.-Y.; Alvandi, N. Microbiological Profile of Sarecycline, a Novel Targeted Spectrum Tetracycline for the Treatment of Acne Vulgaris. *Antimicrob. Agents Chemother.* **2019**, *63*, e01297-18, doi:10.1128/AAC.01297-18.
95. Moore, A.Y.; Charles, J.E.M.; Moore, S. Sarecycline: A Narrow Spectrum Tetracycline for the Treatment of Moderate-to-Severe Acne Vulgaris. *Future Microbiol.* **2019**, *14*, 1235–1242, doi:10.2217/fmb-2019-0199.
96. FDA Drug Approval Package: NUZYRA Available online: [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2018/209816Orig1s000,209817Orig1s000TOC.cfm](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/209816Orig1s000,209817Orig1s000TOC.cfm) (accessed on 4 October 2021).
97. FDA Drug Approval Package: Seysara (Sarecycline) Available online: [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2018/209521Orig1s000TOC.cfm](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/209521Orig1s000TOC.cfm) (accessed on 7 October 2021).

98. FDA Drug Approval Package: Tygacil (Tigecycline) NDA #021821 Available online: [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2005/21-821\\_Tygacil.cfm](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/21-821_Tygacil.cfm) (accessed on 4 October 2021).
99. FDA Drug Approval Package: XERAVA (Eravacycline) Available online: [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2018/211109Orig1s000TOC.cfm](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211109Orig1s000TOC.cfm) (accessed on 30 November 2021).