ANIMAL HEALTH IRELAND

Contributing to a profitable and sustainable farming and agri-food sector through improved animal health

PRUDENT PRESCRIBING OF DRY-COW AND IN-LACTATION ANTIBIOTICS

GUIDELINES FOR PVPs

- Animal-level information necessary for responsible prescribing
- Herd-level information to support responsible prescribing

Animal Health ireland

FACT SHEET

NATIONAL MASTITIS CONTROL PROGRAMME

Animal Health Ireland, 2-5 The Archways, Carrick-on-Shannon, Co. Leitrim, N41 WN27

CellCheck Animal Health Ireland.ie

AHI gratefully acknowledges the financial and other contributions of our stakeholders.

NATIONAL MASTITIS CONTROL PROGRAMME

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Animal-level information necessary for responsible prescribing

Individual assessment of specific animals with clinical or subclinical mastitis

Cases of clinical mastitis, often in-lactation, are identified based on clinical signs of inflammation or systemic illness, or abnormal changes in the appearance of milk. Subclinical infection is diagnosed on the basis of individual cow somatic cell count (SCC) levels. There should also be ongoing collection and bacteriology testing of milk samples from animals with clinical or subclinical mastitis, both to guide individual clinical decisions and equally importantly as part of the broader assessment and monitoring of mastitis pathogen challenge(s) and antibiotic resistance patterns on the farm, as outlined below.

Ongoing assessment of all lactating animals

Milk recording

The TWG recommends milk recording every 4-6 weeks as best practice, for prescribing decisions and mastitis monitoring, with a minimum of 6 recordings throughout the lactation, including one shortly prior to drying off and one shortly following calving.

- Milk recording results are currently accepted internationally as best-practice in identifying cows at the end of their lactation with probable infected quarters, and for prescribing dry-cow antibiotic treatment. While it may be possible to improve the accuracy of diagnosing infection through the additional measures of clinical disease history, bulk tank SCC trends and milk culture results, milk recording is a mainstay of this decision-making process, due to the relative practicality of delivery and multiple additional benefits to farm management.
- Several recent studies, from the Netherlands[1] and New Zealand[2], have shown that a single milk recording, taken within 4-6 weeks of drying off, can provide useful information about infection status at drying off. However, this is insufficient to guide mastitis control throughout the year. Care should be taken when interpreting studies from other countries where prevalence rates and pathogen profiles may differ. Note that the composition of late lactation milk can cause sampling and testing difficulties.
- Milk recording from all lactating cows using milk meters or eDIY equipment provides a representative milk sample from all four quarters, and thus are repeatable and reliable. Conversely, a sample taken manually from each cow by the farmer and sent to a laboratory for SCC measurement does not provide a representative composite sample and is not recommended by the CellCheck TWG.
- CellCheck resources, including the Farm Summary Report, are available, highlighting the value of, and return from, milk recording data.

[1]Lipkens Z, Piepers S, De Visscher A, De Vliegher S. Evaluation of test-day milk somatic cell count information to predict intramammary infection with major pathogens in dairy cattle at drying off. *J Dairy Sci.* 2019;102(5):4309-4321. doi:10.3168/jds.2018-15642

[2]McDougall S, Williamson J, Gohary K, Lacy-Hulbert J. Detecting intramammary infection at the end of lactation in dairy cows. *J Dairy Sci.* 2021;104(9):10232-10249. doi:10.3168/jds.2020-20036

Alternatives to milk recording are available, but are currently of limited practical value:

- Individual cow bacterial culture or polymerase chain reaction (PCR)-based techniques are the gold standard for indicating presence of bacteria or bacterial DNA, respectively, and thus may be proposed as suitable individual cow information for the purposes of prescribing dry-cow antibiotics. However, in Irish farming systems with seasonal calving and hence block drying off, the logistics of aseptically sampling large numbers of cows shortly before drying off, as well as the time and direct costs, may render this proposal impractical for most herds.
- The California mastitis test (CMT) is a simple cow-side test that is quick, and low cost and may be used to define if the cow is likely to be infected in one or more glands at a point in time. The CMT should be performed by the prescriber on all cows shortly before drying off, which may be impractical and prohibitive. However, interpretation of the results is subjective, and the test can be negative with SCC levels of less than 500,000 cells/mL. Further, according to UK[3] and US[4] studies, using a CMT to determine infection status at the point of drying off is known to be less accurate in high SCC herds infected with gram positive pathogens. Although a CMT may be a feasible short-term or temporary solution, there is no opportunity without regular milk recording information to monitor the outcomes from the drying-off decision-making and dry period management, as well as mastitis control throughout lactation.

Herd-level information to support responsible prescribing

In addition to individual cow information, each of the following factors are also needed to support responsible prescribing, both for dry-cow and in-lactation antibiotics:

- **A bona fide relationship with the herdowner**, which enables the veterinary practitioner to carry out clinical examinations and exercise clinical judgement. This forms the basis of a robust Client Patient Practice Relationship (CPPR).
- **A sophisticated understanding of the farm** in general, including the herd, the people, the facilities and farm management (in general, during lactation and at drying off). As clearly articulated in Article 107(1) of 2019/6, antimicrobial medicinal products should not be applied routinely nor used to compensate for poor hygiene, inadequate animal husbandry or lack of care or to compensate for poor farm management. In the case of a new client, engagement with the farmer, along with farm visits, clinical examinations, and appropriate ancillary testing will establish the necessary baseline of knowledge for responsible prescribing.

[3] Swinkels JM, Leach KA, Breen JE, et al. Randomized controlled field trial comparing quarter and cow level selective dry cow treatment using the California Mastitis Test. *J Dairy Sci.* 2021;104(8):9063-9081. doi:10.3168/jds.2020-19258

[4] Godden SM, Royster E, Timmerman J, Rapnicki P, Green H. Evaluation of an automated milk leukocyte differential test and the California Mastitis Test for detecting intramammary infection in early- and late-lactation quarters and cows. *J Dairy Sci.* 2017;100(8):6527-6544. doi:10.3168/jds.2017-12548

- **Knowledge and oversight of all antibiotics prescribed and used,** and a holistic and coherent understanding of the rationale and strategy for antibiotic prescribing and use. The practical approaches used to achieve this should be consistent with international best-practice in antimicrobial stewardship.
- A thorough knowledge of the milk quality patterns of the farm, including **temporal trends** in bulk tank SCC and milk recording results, and access to accurate clinical mastitis records. The latter should also include treatment details, including outcomes.
- A detailed knowledge of **the mastitis pathogen challenge(s) on-farm,** through regular milk culturing of individual cases (clinical and subclinical), and potentially also from the bulk tank (PCR testing). **Antimicrobial susceptibility testing (AST)** should also be performed regularly, to guide appropriate antibiotic selection, and identify existing or emerging antibiotic resistance. This should include ongoing collection and analysis of the following milk samples, which may be frozen if necessary:
  - » A pre-treatment milk sample from all clinical cases.
  - » Milk samples from cows with high SCC, ensuring a mixture of young and old cows, with evidence of both recent and chronic infections, based on sampling conducted at different points throughout lactation.
- A detailed understanding of CellCheck resources, including **the use of the CellCheck Dashboard as an investigative tool,** to inform the farm assessment and prescribing decisions.
- **Records of mastitis events, treatments administered and related outcomes,** preferably captured electronically, to facilitate monitoring and assessment, as well as improvement of treatment protocols.
- A strong professional relationship between the prescriber and **other professional farm service providers** to ensure a holistic approach to milk quality and broader animal health and welfare.

With regards to Article 105 (3) of Regulation 2019/6, which states that a veterinary prescription shall be issued only after a clinical examination or any other proper assessment, it is the view of the CellCheck TWG that both animal and herd-level information will be required, as presented in detail above.

GUIDANCE FOR THE PRESCRIBING PVP (DRY-COW ANTIBIOTICS) FROM 28TH JANUARY 2022

LOWER RISK HERDS - PRESCRIBING DECISIONS

Those where there is objective evidence that mastitis is under good control and the prevalence of infection is consistently low. Examples in support could include unadjusted bulk milk SCC consistently below 200,000 cells/mL, a dry period new infection rate of less than 10% etc.

MILK RECORDING

Follow the current CellCheck Dry Cow Strategy.

Make prescribing decisions informed by:

- Individual animal information *(as above),*
- Herd-level information *(as above)*, and
- European Medicines Agency (EMA) guidelines.

NO MILK RECORDING

In the absence of milk recording data, the prescribing PVP should use the following to identify individual cows that have evidence of infection, and therefore require antibiotic treatment:

- A single milk recording from each cow shortly prior to drying off, or
- Individual cow milk culture results, or
- Individual CMT, as carried out by the prescriber.

Prescribing decisions should be made using this information, informed by:

- The current CellCheck Dry Cow Strategy,
- Herd-level information (as above), and
- EMA guidelines.

A comprehensive whole herd milk recording programme should commence with the start of the next lactation.

GUIDANCE FOR THE PRESCRIBING PVP (DRY-COW ANTIBIOTICS) FROM 28TH JANUARY 2022

LOWER RISK HERDS - MASTITIS CONTROL DECISIONS

Those where there is objective evidence that mastitis is under good control and the prevalence of infection is consistently low. Examples in support could include unadjusted bulk milk SCC consistently below 200,000 cells/mL, a dry period new infection rate of less than 10% etc.

MILK RECORDING	NO MILK RECORDING
Provide professional support to maintain optimal mastitis control. At the time of dry-cow prescribing: • Conduct a review of treatment of in-lactation cases in the past season, and • Develop/agree a standard operating procedure for the treatment of in-lactation cases in the following season.	The farmer should immediately commence whole herd milk recording. Provide professional support to maintain optimal mastitis control. At the time of dry-cow prescribing: • Conduct a review of treatment of in-lactation cases in the past season, and • Develop/agree a standard operating procedure for the treatment of in-lactation cases in the following season.

GUIDANCE FOR THE PRESCRIBING PVP (DRY-COW ANTIBIOTICS) FROM 28TH JANUARY 2022

HIGHER RISK HERDS - PRESCRIBING DECISIONS (ALL OTHER HERDS)

MILK RECORDING	NO MILK RECORDING
Follow the current CellCheck Dry Cow Strategy, with consideration to reduce the individual cow SCC threshold for antibiotic treatment from 100,000 cells/mL to 50,000 cells/mL. Make prescribing decisions informed by: • Individual animal information *(as above),* • Herd-level information *(as above),* and • EMA guidelines. If the prescribing PVP considers that prophylactic use of dry-cow antibiotic is justified in order to protect cow welfare, in situations where the risk of new infection over the dry period is unacceptable, it is critical that these risk factors are addressed and resolved, certainly prior to the next dry period.	In the absence of milk recording data, the prescribing PVP should use the following to identify individual cows that have evidence of infection, and therefore require antibiotic treatment: • A single milk recording from each cow shortly prior to drying off, or • Individual cow milk culture results, or • Individual CMT, as carried out by the prescriber. Prescribing decisions should be made using this information, informed by: • The current CellCheck Dry Cow Strategy, • Herd-level information *(as above)*, and • EMA guidelines. If the prescribing PVP considers that prophylactic use of dry-cow antibiotic is justified in order to protect cow welfare, in situations where the risk of new infection over the dry period is unacceptable, it is critical that these risk factors are addressed and resolved, certainly prior to the next dry period. A comprehensive whole herd milk recording programme should commence with the start of the next lactation.

▶ GUIDANCE FOR THE PRESCRIBING PVP (DRY-COW ANTIBIOTICS) FROM 28TH JANUARY 2022

HIGHER RISK HERDS - MASTITIS CONTROL DECISIONS (ALL OTHER HERDS)

MILK RECORDING	NO MILK RECORDING
The farmer should engage with their PVP and other milk quality professionals to sustainably resolve constraints to effective mastitis control. Each of the following will be needed: • A detailed understanding of the factors (including cause(s) and driver(s)) contributing to suboptimal mastitis control based on a detailed on- and off-farm investigation, • A plan developed and agreed with the farmer to robustly and sustainably address each of these factors, including agreed actions and timelines and objective measures to monitor progress, and • Ongoing and regular assessment and review. At the time of dry-cow prescribing: • Conduct a review of treatment of in-lactation cases in the past season, and • Develop or agree a standard operating procedure for the treatment of in-lactation cases in the following season.	The farmer should immediately commence comprehensive whole herd milk recording. The farmer should engage with their PVP and other milk quality professionals to sustainably resolve constraints to effective mastitis control. Each of the following will be needed: • A detailed understanding of the factors (including cause(s) and driver(s)) contributing to suboptimal mastitis control based on a detailed on- and off-farm investigation, • A plan developed and agreed with the farmer to robustly and sustainably address each of these factors, including agreed actions and timelines and objective measures to monitor progress, and • Ongoing and regular assessment and review. At the time of dry-cow prescribing: • Conduct a review of treatment of in-lactation cases in the past season, and • Develop or agree a standard operating procedure for the treatment of in-lactation cases in the following season.

GUIDANCE FOR THE PRESCRIBING PVP (IN-LACTATION ANTIBIOTICS) FROM 28TH JANUARY 2022

ALL HERDS - PRESCRIBING DECISIONS

FARM MASTITIS PATHOGEN CHALLENGE(S)/ANTIBIOTIC RESISTANCE PATTERNS ARE KNOWN	FARM MASTITIS PATHOGEN CHALLENGE(S)/ANTIBIOTIC RESISTANCE PATTERNS ARE NOT KNOWN
Confirm diagnosis of mastitis during lactation, by clinical examination or other proper assessment. Select appropriate antibiotic, based on both cow and farm factors: • Cow factors such as clinical findings, lactation number and treatment history, and • Farm factors such as farm pathogen profile, antimicrobial susceptibility testing (AST) and previous treatment outcomes. Choose an antibiotic from the lowest category possible on the EMA Antimicrobial Advice Ad Hoc Expert Group (AMEG) list that has been shown to be effective, given knowledge of the farm mastitis pathogen challenge(s) and antibiotic resistance patterns.	Confirm diagnosis of mastitis during lactation, by clinical examination or other proper assessment. Choose an antibiotic from the 'EMA Category D: Prudence' category. Antibiotics from 'higher' categories (EMA Categories B: Restrict, C: Caution) should only be considered with supporting milk culture and antibiotic susceptibility results and only when there are no antibiotics in a lower category that could be clinically effective

GUIDANCE FOR THE PRESCRIBING PVP (IN-LACTATION ANTIBIOTICS) FROM 28TH JANUARY 2022

ALL HERDS - MASTITIS CONTROL DECISIONS

FARM MASTITIS PATHOGEN CHALLENGE(S)/ANTIBIOTIC RESISTANCE PATTERNS ARE KNOWN	FARM MASTITIS PATHOGEN CHALLENGE(S)/ANTIBIOTIC RESISTANCE PATTERNS ARE NOT KNOWN
Mastitis events, treatments administered, and related outcomes should be recorded by the farmer and made available to the PVP for analysis to assist with future treatment decisions. In-lactation mastitis incidence should be monitored. Develop or conduct an annual review of a mastitis treatment plan for in-lactation cases.	Mastitis events, treatments administered, and the related outcomes should be recorded by the farmer and made available to the PVP for analysis to assist with future treatment decisions. In-lactation mastitis incidence should be monitored. Instigate measures to gain a detailed knowledge of the mastitis pathogen challenge(s) and antibiotic resistance patterns on the farm. This should include ongoing collection and analysis of the following milk samples, which may be frozen if necessary: • A pre-treatment milk sample from all clinical cases, and • Milk samples from cows with high SCC, ensuring a mixture of young and old cows, with evidence of both recent and chronic infections, based on sampling conducted at different points throughout lactation. Develop or conduct an annual review of a mastitis treatment plan for in-lactation cases.

▶ HIGHEST PRIORITY CRITICALLY IMPORTANT ANTIBIOTICS (INJECTABLE AND INTRAMAMMARY) LICENSED IN IRELAND FOR USE IN CATTLE

ANTIMICROBIAL CLASS	ACTIVE SUBSTANCE	EXAMPLES OF PRODUCTS		EMA CATEGORY
		INJECTABLE	INTRAMAMMARY	
3rd & 4th generation Cephalosporins	ceftiofur	**Alfacef, Cefavex, Cefenil, Cefokel, Ceftiocyl, Cemay, Cevaxel, Curacef, Eficur, Excenel, Naxcel**		**RESTRICT (EMA Category B)** • Not for prophylactic, or preventive use. • Not for **first** line of treatment. • Should not be used without first having culture/ susceptibility results showing no effective alternative. • In exceptional circumstances, treatment can commence before laboratory results return. • Records of all relevant laboratory results must be kept.
	cefquinome	**Ceffect, Cobactan, Qivitan**	**Ceffect LC, Cefimam DC/LC, Cefquinome DC/LC, Cephaguard DC, Cobactan LC, Plenix LC, Qivitan LC**	
Fluoroquinolones	enrofloxacin	**Baytril, Doraflox, Enrocare, Enrodexil, Enrotril, Enrotron, Enroxil, Fenoflox, Floxibac, Quinoflox, Roxacin, Unisol, Valemas**		
	marbofloxacin	**Boflox, Forcyl, Kelacyl, Marbim, Marbocare, Marbocyl, Marbonor, Marbosyva, Marbox, Marfloxin**		

Product names sourced from Health Products Regulatory Authority and European Medicines Agency websites. Correct as of January 2020.

▶ HIGHEST PRIORITY CRITICALLY IMPORTANT ANTIBIOTICS (INJECTABLE AND INTRAMAMMARY) LICENSED IN IRELAND FOR USE IN CATTLE

ANTIMICROBIAL CLASS	ACTIVE SUBSTANCE	EXAMPLES OF PRODUCTS		EMA CATEGORY
		INJECTABLE	INTRAMAMMARY	
Macrolides	gamithromycin	**Zactran**		**CAUTION (EMA Category C)** • Not for prophylactic use. • Not for **first** line of treatment, where possible. • Should only be considered when there are no alternatives to a HP-CIA, that could be clinically effective.
	tildipirosin	**Zuprevo**		
	tilmicosin	**Hymatil, Keytil, Micotil, Milbotyl, Tilmodil, Tilmovet**		
	tulathromycin	**Draxxin, Tulaxa, Tuloxxin**		
	tylosin	**Bilovet, Pharmasin, Tylan, Tyljet, Tylo, Tylosin, Tylosin Biovet JSC, Tylovet, Tylucyl**		

Product names sourced from Health Products Regulatory Authority and European Medicines Agency websites. Correct as of January 2020.

EMA Categorisation of antibiotics for use in animals for prudent and responsible use

Categorisation of antibiotic classes for veterinary use
(with examples of substances authorised for human or veterinary use in the EU)

A — AVOID

Amdinopenicillins
mecillinam
pivmecillinam

Ketolides
telithromycin

Monobactams
aztreonam

Rifamycins (except rifaximin)
rifampicin

Carboxypenicillin and ureidopenicillin, including combinations with beta lactamase inhibitors
piperacillin-tazobactam

Carbapenems
meropenem
doripenem

Lipopeptides
daptomycin

Oxazolidinones
linezolid

Riminofenazines
clofazimine

Sulfones
dapsone

Streptogramins
pristinamycin
virginiamycin

Drugs used solely to treat tuberculosis or other mycobacterial diseases
isoniazid
ethambutol
pyrazinamide
ethionamide

Other cephalosporins and penems (ATC code J01DI), including combinations of 3rd-generation cephalosporins with beta lactamase inhibitors
ceftobiprole
ceftaroline
ceftolozane-tazobactam
faropenem

Glycopeptides
vancomycin

Glycylcyclines
tigecycline

Phosphonic acid derivates
fosfomycin

Pseudomonic acids
mupirocin

Substances newly authorised in human medicine following publication of the AMEG categorisation
to be determined

B — RESTRICT

Cephalosporins, 3rd- and 4th-generation, with the exception of combinations with β-lactamase inhibitors
cefoperazone
cefovecin
cefquinome
ceftiofur

Polymyxins
colistin
polymyxin B

Quinolones: fluoroquinolones and other quinolones
cinoxacin
danofloxacin
difloxacin
enrofloxacin
flumequine
ibafloxacin
marbofloxacin
norfloxacin
orbifloxacin
oxolinic acid
pradofloxacin

EMA Categorisation of antibiotics for use in animals for prudent and responsible use

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C — CAUTION

Aminoglycosides (except spectinomycin)
- amikacin
- apramycin
- dihydrostreptomycin
- framycetin
- gentamicin
- kanamycin
- neomycin
- paromomycin
- streptomycin
- tobramycin

Aminopenicillins, in combination with beta lactamase inhibitors
- amoxicillin + clavulanic acid
- ampicillin + sulbactam

Cephalosporins, 1st- and 2nd-generation, and cephamycins
- cefacetrile
- cefadroxil
- cefalexin
- cefalonium
- cefalotin
- cefapirin
- cefazolin

Amphenicols
- chloramphenicol
- florfenicol
- thiamphenicol

Lincosamides
- clindamycin
- lincomycin
- pirlimycin

Pleuromutilins
- tiamulin
- valnemulin

Macrolides
- erythromycin
- gamithromycin
- oleandomycin
- spiramycin
- tildipirosin
- tilmicosin
- tulathromycin
- tylosin
- tylvalosin

Rifamycins: rifaximin only
- rifaximin

D — PRUDENCE

Aminopenicillins, without beta-lactamase inhibitors
- amoxicillin
- ampicillin
- metampicillin

Tetracyclines
- chlortetracycline
- doxycycline
- oxytetracycline
- tetracycline

Aminoglycosides: spectinomycin only
- spectinomycin

Anti-staphylococcal penicillins (beta-lactamase-resistant penicillins)
- cloxacillin
- dicloxacillin
- nafcillin
- oxacillin

Natural, narrow-spectrum penicillins (beta lactamase-sensitive penicillins)
- benzathine benzylpenicillin
- benzathine phenoxymethylpenicillin
- benzylpenicillin
- penethamate hydriodide
- pheneticillin
- phenoxymethylpenicillin
- procaine benzylpenicillin

Sulfonamides, dihydrofolate reductase inhibitors and combinations
- formosulfathiazole
- phthalylsulfathiazole
- sulfacetamide
- sulfachlorpyridazine
- sulfaclozine
- sulfadiazine
- sulfadimethoxine
- sulfadimidine
- sulfadoxine
- sulfafurazole
- sulfaguanidine
- sulfalene
- sulfamerazine
- sulfamethizole
- sulfamethoxazole
- sulfamethoxypyridazine
- sulfamonomethoxine
- sulfanilamide
- sulfapyridine
- sulfaquinoxaline
- sulfathiazole
- trimethoprim

Cyclic polypeptides
- bacitracin

Steroid antibacterials
- fusidic acid

Nitroimidazoles
- metronidazole

Nitrofuran derivatives
- furaltadone
- furazolidone

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Source: https://www.ema.europa.eu/en/documents/report/infographic-categorisation-antibiotics-use-animals-prudent-responsible-use_en.pdf