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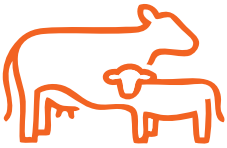
TECHNICAL BULLETIN



Dry-cow therapy with SPECTRAMAST® DC and ORBESAL®: Impact on economics in the lactation following treatment

Zoetis
10 Sylvan Way
Parsippany, NJ 07054

In 4 studies, a SPECTRAMAST® DC plus ORBESEAL® dry-cow treatment regimen proved to be economically justified, providing excellent mastitis protection with no milk discard.

KEY POINTS

- A series of four on-farm demonstration studies investigated the economic impacts of a SPECTRAMAST® DC (ceftiofur hydrochloride) Sterile Suspension and ORBESEAL® dry-cow treatment regimen compared alternative regimens consisting of either ToMorrow® or ALBADRY PLUS® (penicillin G procaine and novobiocin sodium) Suspension and ORBESEAL.[1-4]
- In three of the four studies, the SPECTRAMAST DC/ORBESEAL dry-cow regimen reduced the risk of mastitis in early lactation (cases/100 cows ≤ 20 DIM) compared to use of an alternative regimen.
- In all four studies, net financial returns through 128 DIM were greater for cows that had received SPECTRAMAST DC/ORBESEAL at dry-off.
- A meta-analysis of three studies quantified an overall economic advantage of about $21 for each cow treated with SPECTRAMAST DC/ORBESEAL at dry-off vs treatment with ToMorrow/ORBESEAL.
- Use of SPECTRAMAST DC offered the advantage of no milk discard upon calving, allowing fresh cows to immediately enter the milking herd.
- The SPECTRAMAST DC/ORBESEAL dry-cow program proved to be economically justified and not inferior to other programs.

Mastitis continues as a perpetual and costly threat to dairy profitability that requires every operation to implement management protocols aimed at reducing disease incidence and severity. Intramammary infections that persist from the previous lactation, or new infections that develop during the dry period, can contribute to the incidence of both clinical and subclinical mastitis during the new lactation.[5] Cows are at great risk of developing intramammary bacterial infections during the dry period, which often remain quiescent until parturition.[6] Cases that occur soon after parturition, before peak milk-yield

Mastitis Costs, Impacts, & Losses:

Short-Term —

- Reduced milk production (up to 2650 lb per lactation)
- Older age at 1st calving
- Reduced profits

Long-Term —

- Increased risk of culling and mortality
- Poor reproductive performance
- Undiagnosed problems caused by subclinical mastitis

Spectramast® DC is the premier dry-cow intramammary antimicrobial, providing potent mastitis efficacy with no milk withdrawal.

Orbeseal® enhances effectiveness of intramammary antimicrobials and requires no milk or preslaughter withdrawal.

is achieved, are particularly impactful and costly because milk-yield losses and the risk of culling or death are greatly increased compared to infections that occur later in lactation.[7,8]

Clinical mastitis represents a significant health and financial risk that impacts productivity, longevity, and reproduction of cows.[9-17] It is well known that mastitis has a far-reaching, negative impact on milk-yield in dairy cows. One research study investigated the impact of several disorders common to early lactation cows (mastitis, metritis, retained placenta, dystocia, ketosis, displaced abomasum, etc.) on the magnitude of total lactation milk-yield losses.[18] Using a modeling technique, the researchers determined that milk losses associated with clinical mastitis in a single lactation were as much as 1550 lb for primiparous cows, and 2650 lb for multiparous cows. Furthermore, high-producing cows are at greater risk of developing clinical mastitis than their lower-producing counterparts.[11,12]

Subclinical mastitis can also depress milk production, and cows with subclinical mastitis are at increased risk of developing clinical mastitis than uninfected cows.[19] One analysis concluded that the overall effect of each doubling of the crude somatic cell count (SCC) in milk above 50,000 cells/mL resulted in a 1.1 lb/day decrease in milk production.[12]

Mastitis status prior to breeding intervals has been shown to impact reproductive performance in dairy cows. One study found that cows with clinical or subclinical mastitis before first service experienced a longer interval to first service, longer interval for days open, and increased services per conception.[20] Another research group studied the impact of Gram-positive and Gram-negative mastitis-causing bacteria on conception in dairy cows.[15]

The researchers concluded that clinical mastitis occurring anytime between 14 days before to 35 days after insemination was associated with reduced probability of conception, and that the risk of failure to conceive increased as the mastitis event occurred closer to the time of insemination.

To help reduce mastitis events in early lactation, administration of intramammary antimicrobials at the time of dry-off has become common practice, thereby helping cure existing infections and preventing development of new infections during the dry period. In fact, dry-cow therapy with intramammary antimicrobials has been endorsed by the National Mastitis Council for reducing mastitis risk. In addition to antimicrobial treatments, use of internal teat sealants has become an increasingly common component of dry-cow treatment protocols. Researchers have reported that up to 26% of teats undergoing involution failed to naturally develop a keratin plug within six weeks following dry-off,[9] and when milk yield was more than 46 lb/day at the time of dry-off, as many as 70% of teat ends remained open seven days after dry-off, and up to 50% were open six weeks after dry-off.[10] Failure of the teat canal to naturally seal would be expected to increase the likelihood of a new infection developing during the dry period.

Financial benefits of dry-cow treatments are typically manifested in the lactation following treatment. A series of four studies were conducted to investigate the economic benefits of intramammary dry-cow antimicrobials when combined with use of a teat sealant, with emphasis on health and productivity impacts during the lactation following use of the dry-cow regimen.[1-4]

SPECTRAMAST® DC and ORBESEAL®

SPECTRAMAST® DC (*ceftiofur hydrochloride*) Sterile Suspension is the premier dry-cow intramammary antimicrobial that provides potent efficacy with no milk withdrawal, allowing treated cows to immediately enter the milking herd after calving. SPECTRAMAST DC is indicated for the treatment of subclinical mastitis in dairy cattle at the time of dry-off associated with *Staphylococcus aureus*, *Streptococcus dysgalactiae*, and *Streptococcus uberis*. Infusion of one syringe into each affected quarter at the time of dry-off provides excellent control of more major mastitis pathogens than other dry-cow therapies. SPECTRAMAST DC also offers greater flexibility in milk- and cattle-management decisions due to zero milk discard at calving (after 30-day dry period) and the shortest meat withdrawal (16 days).

ORBESEAL® is a sterile, non-antibiotic intramammary infusion in the form of a viscous paste that is indicated for the prevention of new intramammary infections throughout the dry period. ORBESEAL acts as a physical barrier against mastitis-causing bacteria, locking them out for the entire dry period. Infusing a single ORBESEAL tube into each teat at dry-off mimics the function of the cow's natural keratin plug by instantly sealing teats. ORBESEAL requires no milk or preslaughter withdrawal, but when used in conjunction with a dry-cow antimicrobial, withdrawal time on the antimicrobial label should be followed. Research has demonstrated that ORBESEAL enhances effectiveness of intramammary antimicrobials, provides a physical barrier to invading micro-organisms, and reduces the risk that new intramammary infections will develop during the dry period.[21-23]

Experiment Design

A series of four non-clinical demonstration studies investigated the economic impacts of an intramammary dry-cow treatment regimen consisting of SPECTRAMAST DC and ORBESEAL (SDC/O) compared to a competitive regimen consisting of another antimicrobial product (either ToMorrow® or ALBADRY PLUS®) and ORBESEAL.[1-4] Each of the four studies followed a similar general protocol with cows enrolled into the study at the time of dry treatment (one tube of each product infused in each quarter following the last milking at dry-off).

Response criteria measured after dry-cow treatment included SCC, incidence of clinical mastitis, milk yield, 305-day

In 4 similar studies, dry-cow treatment with SPECTRAMAST® DC and ORBESEAL® was compared to ToMorrow® or ALBADRY PLUS® and ORBESEAL®

Table 1 – Study A results: mastitis risk and economics related to dry treatments (≤128 DIM; LS means).*

Item	Treatment	
	TM/O	SDC/O
No. cows enrolled	65	64
Mean lactation number	2.7	2.6
Days dry	55.5	55.8
Mastitis cases/100 cows (≤20 DIM)	**25**	**14**
Expenses ($/cow enrolled)	**1034.27**	**997.95**
Dry-cow treatment cost	16.60	24.78
Mastitis treatment cost	43.11	38.83
Mastitis milk withhold expense	37.73	33.18
Mastitis culling losses	59.05	33.64
Mastitis death loss	29.24	0.00
Estimated feed cost	824.14	861.15
Returns ($/cow enrolled)	**2173.15**	**2317.81**
Pregnancy value	86.54	95.19
Milk value	2086.62	2222.62
Returns minus expenses ($/cow enrolled)	**1140.66**	**1308.77**
Treatment benefit ($/cow enrolled)		**+168.11**

*Treatment LS means for each row independently estimated; manual computation will not yield values identical to LS means for expenses or returns. Economic values used in analysis: milk value $17.50/cwt; discard milk feeding value $11.38/cwt; replacement heifer value $1760; cull (beef) cow value $1033; feed cost $0.13/lb DM containing 0.78 Mcal NE_L/lb; pregnancy value $278.[24]

SPECTRAMAST® DC + ORBESEAL® generated an economic benefit of $168/cow in the WI study, and $10/cow in the MO study.

mature equivalents (305ME), longevity/culls, reproductive parameters, and economic factors associated with the dry-cow treatments (e.g., treatment cost, milk discard, etc.). DairyComp records were used for quantifying all production data. Economic evaluation of the various treatment regimens was based on measures of these parameters from the time of dry-cow treatment through 128 days in milk (DIM) of the subsequent lactation. Collected data were analyzed as least squares (LS) means by appropriate statistical methods, using a model that considered effects of treatment, parity, and treatment×parity interactions, plus covariates that were included as appropriate.

Since these studies were designed as demonstration trials (not controlled clinical studies), the normal management practices and preferences of each individual dairy were maintained. Thus, each study included elements unique to that particular dairy and no attempt was made to alter procedures or standardize husbandry practices across the various operations. The non-clinical nature of the demonstration studies often precluded detection of statistical differences between treatments. This outcome was acceptable since the intent was to allow dairy producers to witness 'real-world' use of the dry-cow regimens on their particular operations and make their own appraisals of regimen value.

Table 2 – Study B results: mastitis risk and economics related to dry treatments (≤128 DIM; LS means).*

Item	Treatment	
	TM/O	SDC/O
No. cows enrolled	283	241
Mean lactation number	2.71	2.83
Days dry	57.7	57.9
Mastitis cases/100 cows (≤20 DIM)	**3.8**	**6.3**
Expenses ($/cow enrolled)	**686.05**	**697.87**
Dry-cow treatment cost	17.08	25.57
Mastitis treatment cost	1.59	1.88
Mastitis milk withhold expense	1.80	1.68
Mastitis culling losses	9.98	16.04
Mastitis death loss	3.99	0.00
Estimated feed cost	651.17	653.81
Returns ($/cow enrolled)	**1722.45**	**1725.63**
Pregnancy value	150.17	157.26
Milk value	1598.10	1594.05
Returns minus expenses ($/cow enrolled)	**1016.84**	**1027.40**
Treatment benefit ($/cow enrolled)		**+10.56**

*Treatment LS means for each row independently estimated; manual computation will not yield values identical to LS means for expenses or returns. Economic values used in analysis: milk value $17.30/cwt; discard milk feeding value $11.25/cwt; replacement heifer value $1760; cull (beef) cow value $1043; feed cost $0.13/lb DM containing 0.78 Mcal NE_L/lb; pregnancy value $278.[24]

Study A: Wisconsin

The first study[1] involved a Wisconsin Holstein herd consisting of approximately 1200 lactating cows (milked three times daily), 150 dry cows, and 500 replacement heifers, with an average 305ME of approximately 29,500 lb. This herd offered an excellent opportunity for evaluating intramammary dry-cow therapies because cows were bedded with digested manure solids. This continuous exposure of mammary glands to environmental pathogens was expected to enhance the likelihood that dry-cow treatment responses could be documented. Cows were assigned to two treatment groups on alternating weeks (March 9-June 8), receiving either SPECTRAMAST DC and ORBESEAL (SDC/O, n=64) or ToMorrow (cephapirin benzathine) and ORBESEAL (TM/O, n=65).

Results

Outcomes for Study A summarized in Table 1 show that the risk of mastitis in early lactation was reduced for cows receiving the SDC/O dry-cow regimen (14 cases/100 cows) compared to those treated with the TM/O regimen (25 cases/100 cows). Even though the SDC/O dry-cow regimen was more expensive than the TM/O program, this difference was offset by modest decreases in mastitis therapeutic treatment costs, milk withheld from the bulk tank, mastitis culling losses, and mastitis death losses. The net effect of specified expenses and financial returns considered in the economic analysis was a trend for cows dry-treated with SDC/O to return approximately $168/head more than cows dry-treated with TM/O. This sizeable economic difference represents a substantial benefit that could potentially impact overall profit potential of the dairy. The SDC/O regimen clearly was not inferior to the TM/O program and appeared to offer an economic advantage for this operation.

Study B: Missouri

The second study[2] involved a large, predominately Holstein herd consisting of approximately 3400 lactating cows, 350 dry cows, and replacement heifers, with an average 305ME of approximately 23,000 lb. Cows in this large study were assigned to two treatment groups on alternating weeks (May 25-July 20), receiving either the SDC/O regimen (n=241) or the TM/O regimen (n=283).

Results

A summary of data from Study B (Table 2) shows that mastitis incidence in this herd was relatively low, with no significant difference between treatment groups for mastitis cases in early lactation (P = 0.41). Over the period of the study, net economic returns averaged $1027 for cows treated with SDC/O and $1017 for cows treated with TM/O (P = 0.83). The difference in net returns between treatments amounted to approximately $10/cow in favor of SDC/O, even after accounting for the greater cost of the regimen.

Though overall results from this on-farm trial lacked clear definition in the form of statistically significant treatment differences, outcomes suggest that use of the SPECTRAMAST DC and ORBESEAL regimen for treatment of cows at dry-off is economically justified

ORBESEAL® benefited the CA dairy by $140/cow compared to ToMorrow® used alone; SPECTRAMAST® DC added an additional $19/cow.

Table 3 – Study C results: mastitis risk and economics related to dry treatments (≤128 DIM; LS means).*

Item	Treatment		
	TM	TM/O	SDC/O
No. cows enrolled	217	217	206
Mean lactation number	2.67	2.71	2.70
Days dry	50.9	49.8	50.8
Mastitis cases/100 cows (≤20 DIM)	**10.0**	**8.0**	**3.6**
Expenses ($/cow enrolled)	**862.15[a]**	**923.96[b]**	**910.20[ab]**
Dry-cow treatment cost	8.19	17.08	25.56
Mastitis treatment cost	4.41	5.58	3.68
Mastitis milk withhold expense	14.66	18.48	15.12
Mastitis culling losses	50.15	41.80	34.23
Mastitis death loss	14.40	5.28	6.15
Estimated feed cost	763.64[a]	828.24[b]	824.28[b]
Returns ($/cow enrolled)	**2125.01[a]**	**2326.11[b]**	**2330.49[b]**
Pregnancy value	157.49[a]	179.56[ab]	195.41[b]
Milk value	1989.02[a]	2159.48[b]	2154.92[b]
Returns minus expenses ($/cow enrolled)	**1262.52[a]**	**1402.3[b]**	**1420.99[b]**
Treatment benefit ($/cow enrolled):			
TM vs TM/O (ORBESEAL effect)		**+$139.79**	
TM/O vs SDC/O (SPECTRAMAST DC effect)			**+$18.68**

*Treatment LS means for each row independently estimated; manual computation will not yield values identical to LS means for expenses or returns. Economic values used in analysis: milk value $17.50/cwt; discard milk feeding value $5.80/cwt; replacement heifer value $1760; cull (beef) cow value $1033; feed cost $0.13/lb DM containing 0.78 Mcal NE_L/lb; pregnancy value $278.[24]

[ab]Means in rows with different superscripts are significantly different ($P \leq 0.05$).

SPECTRAMAST® DC + ORBESEAL® generated a $10/cow benefit compared to ALBADRY PLUS® and ORBESEAL®

and appropriate for consideration. In addition, evaluation of somatic cell scores (SCS) from cows at the time of dry-off and again at the first test day following calving showed that the 'true new infection rate' [defined as cows with first test SCS ≥ 4.0 expressed as a percent of cows at risk of becoming infected (< 4.0 at dry-off)] was significantly improved (P = 0.03) among cows treated with SDC/O (32.3%) compared to those treated with TM/O (47.0%).

Study C: California

A third study[3] was conducted in California at a large Holstein dairy consisting of approximately 9200 lactating cows (milked three times daily), 1200 dry cows, and replacement heifers, with an average 305ME of approximately 27,800 lb. Like the Wisconsin herd of Study A, cows in this herd were bedded with digested manure solids, thus offering continuous exposure of mammary glands to environmental pathogens and enhancing the likelihood that dry-cow treatment responses might be detected.

In this large study, cows were assigned to *three treatment groups* each week (August 25-December 22); on each dry-off day, the first cow received ToMorrow alone (TM, n=217), the next cow received the TM/O regimen (n=217), and the next cow received the SDC/O regimen (n=206). This sequential process was performed on cows presented for dry treatment each week until all cows had been dried off.

Results

Mastitis incidence in this herd was moderate, and treatment-related differences in clinical mastitis risk rates (mastitis cases/100 cows) through 20 DIM approached significance (P = 0.10). As shown in Table 3, the lowest risk of mastitis cases occurred in the SDC/O group (3.6) with a rate lower than that of groups treated with TM (10.0) or TM/O (8.0).

Consistent with the other studies, the SDC/O dry-cow regimen was more expensive than either of the other programs, with the singular TM program the cheapest. Product cost and feed costs contributed toward the TM program incurring the lowest overall expenses (P = 0.05). However, both total returns (pregnancy plus milk) and net returns for cows treated with TM were lower ($P \leq 0.02$) than either of the other regimens that included ORBESEAL. Net returns favored the TM/O group by about $140/cow compared to the TM group, and net returns further favored the SDC/O group by about $19/cow compared

Table 4 – Study D results: mastitis risk and economics related to dry treatments (≤128 DIM; LS means).*

Item	Treatment	
	ALB/O	SDC/O
No. cows enrolled	179	171
Mean lactation number	2.9	2.8
Days dry	70.3	66.3
Mastitis cases/100 cows (≤20 DIM)	**6.5**	**3.6**
Expenses ($/cow enrolled)	**968.59**[a]	**924.04**[b]
Dry-cow treatment cost	18.39	24.78
Dry treatment milk discard (3 days)	12.99[a]	0.00[b]
Mastitis treatment cost	7.66	7.13
Mastitis milk withhold expense	12.30	11.31
Mastitis culling losses	51.61	22.59
Mastitis death loss	0.00	0.00
Estimated feed cost	857.85	856.18
Returns ($/cow enrolled)	**2020.20**	**1988.03**
Pregnancy value	122.64	101.89
Milk value	1901.36	1885.86
Returns minus expenses ($/cow enrolled)	**1051.87**	**1062.21**
Treatment benefit ($/cow enrolled)		**+10.34**

*Treatment LS means for each row independently estimated; manual computation will not yield values identical to LS means for expenses or returns. Economic values used in analysis: milk value $17.50/cwt; discard milk feeding value $11.38/cwt; replacement heifer value $1760; cull (beef) cow value $1033; feed cost $0.13/lb DM containing 0.78 Mcal NE_L/lb; pregnancy value $278.[24]

[ab]Means in rows with different superscripts are significantly different ($P \leq 0.01$).

to the TM/O group. Under the conditions of this study, the difference in net returns between TM and TM/O essentially represented the financial return from ORBESEAL ($140/cow), with the net return difference between cows treated with TM/O compared to SDC/O representing the relative value of the two antimicrobials in the presence of ORBESEAL ($19/cow in favor of SPECTRAMAST DC).

Results from this on-farm evaluation reveal that the addition of ORBESEAL to TM treatment yielded a substantial and significant positive impact on overall dairy economics during the first 128 DIM compared to TM alone. Outcomes further suggest that SPECTRAMAST DC represents an economically justified choice for intramammary antimicrobial therapy.

Study D: Wisconsin

The final study[4] involved a Wisconsin herd (65% Holstein, 35% crossbreds) consisting of approximately 1600 lactating cows, 200 dry cows, and 500 replacement heifers, with an average 305ME of approximately 26,000 lb. Cows in this study were assigned to two treatment groups on alternating weeks (April 14-August 25), receiving either the SDC/O regimen (n=171) or ALBADRY PLUS and ORBESEAL (ALB/O, n=179). The ALBADRY PLUS

Table 5 – Meta-analysis results for Studies A, B, and C: mastitis risk and economics related to dry treatments (≤128 DIM; LS means).*

Item	Treatment	
	TM/O	SDC/O
No. cows enrolled	565	511
Mean lactation number	2.71	2.75
Days dry	58.3	58.9
Mastitis cases/100 cows (≤20 DIM)	**11.0**	**8.4**
Expenses ($/cow enrolled)	**848.82**	**835.65**
Dry-cow treatment cost	17.08	25.57
Dry treatment milk discard (3 days†)	8.30 †a	0 b
Mastitis treatment cost	16.86	14.88
Mastitis milk withhold expense	19.22	16.56
Mastitis culling losses	31.75	28.30
Mastitis death loss	7.97	2.48
Estimated feed cost	743.53	743.78
Returns ($/cow enrolled)	**2008.70**	**2011.67**
Pregnancy value	142.92	150.78
Milk value	1884.74	1882.26
Returns minus expenses ($/cow enrolled)	**1193.90**	**1214.97**
Treatment benefit ($/cow enrolled)		**+21.07**

*Treatment LS means for each row independently estimated; manual computation will not yield values identical to LS means for expenses or returns. Economic values used in analysis: milk value $17.30/cwt; discard milk feeding value $11.25/cwt; replacement heifer value $1760; cull (beef) cow value $1033; feed cost $0.13/lb DM containing 0.78 Mcal NE_L/lb; pregnancy value $278.[24]

†Data from each study adjusted to reflect full 3-day milk discard at calving mandated by ToMorrow label.

abMeans in rows with different superscripts are significantly different ($P \leq 0.0001$).

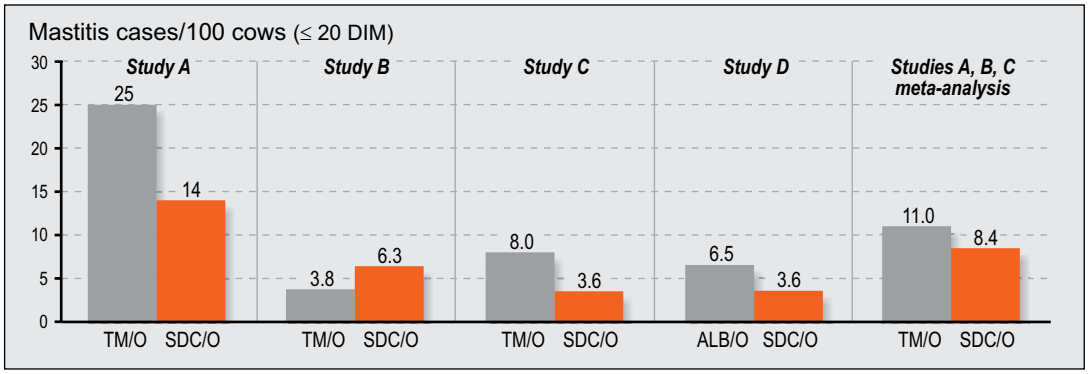


Figure 1 – Summary of mastitis risk in 4 studies and 3-trial meta-analysis.

Meta-analysis showed an average benefit of $21/cow for SPECTRAMAST® DC and ORBESEAL® vs ToMorrow® and ORBESEAL®

Table 6 – Withdrawal times for dry-cow intramammary antimicrobials.

Product	Antimicrobial(s)	Dry period minimum	Milk discard*	Pre-slaughter withdrawal
SPECTRAMAST DC	ceftiofur hydrochloride	30 days	**0 hours**	**16 days**
ToMorrow	cephapirin benzathine	30 days	72 hours	42 days
ALBADRY PLUS	penicillin + novobiocin	30 days	72 hours	30 days

*Milk discard times begin at first milking post-freshening and require completion of a minimum dry-cow period.

With no milk-discard requirement, the SPECTRAMAST® DC + ORBESEAL® dry-cow regimen allows fresh cows to immediately enter the milking herd.

label dictates that milk from treated cows not be used for human consumption during the first 72 hours after calving.

Results

A summary of data from Study D (Table 4) shows that mastitis incidence in this herd was relatively low, with no statistical difference between treatment groups for mastitis cases in early lactation (P = 0.37). Still, the rate of mastitis cases in the SDC/O group was approximately half that of the ALP/O group. Over the period of the study, the increased cost of dry-cow treatment with SDC/O was offset by modest decreases in labeled milk discard expenses, mastitis therapeutic treatment costs, milk withheld from the bulk tank, and mastitis culling losses which culminated in a statistically significant decrease (P = 0.01) in expenses for the SDC/O group compared to the ALB/O group. As a result, differences in net economic returns between treatments amounted to approximately $10/ cow in favor of SDC/O, even after accounting for the greater cost of dry-cow treatment. While treatment effects for most economic outcomes were not statistically significant, study outcomes suggest that use of the SPECTRAMAST DC and ORBESEAL regimen for treatment of cows at dry-off is economically justified and appropriate for adoption into management protocols at the dairy.

Meta-analysis: Studies A, B, C

A meta-analysis was conducted using data from studies A, B, and C to compare overall results generated by the SDC/O and TM/O dry-cow regimens. By combining trial data, the analysis compared outcomes for over 500 cows in each treatment group. In this analysis, calculations were performed assuming milk from cows treated with ToMorrow was discarded for three days following parturition, which is consistent with product labeling. The meta-analysis assumed that post-parturition milk discarded in the TM/O group was pasteurized and used for feeding calves, so the analysis reflected its value as a nutrient source.

Results

Table 5 summarizes the results of the three-trial meta-analysis. The risk of mastitis in early lactation was reduced for cows receiving the SDC/O dry-cow regimen (8.4 cases/100 cows) compared to those treated with the TM/O regimen (11.0 cases/100 cows). Figure 1 further summarizes the mastitis impact of the SDC/O dry-cow regimen in all four individual studies reviewed earlier, and for the overall three-trial meta-analysis.

For the three studies included in the meta-analysis, the SDC/O dry-cow regimen averaged $8.49/ cow more expensive than the TM/O program.

However, this difference was offset in the SDC/O group by reduced costs related to dry-treatment milk discard ($P \leq 0.0001$) and by consistent cost decreases in all expense categories related to mastitis (therapeutic treatment costs, milk withheld from the bulk tank, culling losses, death losses). The net outcome of expenses and returns considered in the economic analysis was financial benefit of about $21 for each cow dry-treated with SDC/O compared to cows dry-treated with TM/O, even after accounting for the greater cost of SDC/O.

Though overall results from these on-farm trials generally lacked statistically significant treatment differences, results of the meta-analysis suggest that use of the SPECTRAMAST DC and ORBESEAL regimen for treatment of cows at dry-off is economically justified and not inferior to outcomes provided by ToMorrow and ORBESEAL. In addition, evaluation of SCS from cows at the time of dry-off and again at the first test day following calving showed that the true new infection rate tended to improve ($P = 0.18$) among cows treated with SDC/O (17.9%) compared to cows treated with TM/O (24.7%).

Residue Avoidance

One concern that arose on several occasions during the course of these four demonstration studies related to the issue of residue avoidance and food safety. As mentioned earlier, both the ToMorrow and ALBADRY PLUS labels state that milk from dry-treated cows should not be used for food (human consumption) during the first 72 hours (three days) after calving (Table 6). The presence of these antimicrobials in the udder is sufficient to taint milk and thus pose a threat for violative residues in the bulk tank. Judicious use of antimicrobials is a critical concern for the dairy industry, and the economic impact of bulk-tank residues can be devastating for any dairy. Thus, dairy producers should always carefully follow label directions and make every effort to ensure the milk they produce is free of drug residues.

The use of SPECTRAMAST DC offers the benefit of having no milk discard requirement for cows completing a dry period of at least 30 days. Cows treated during the dry period with SPECTRAMAST DC are eligible for immediate introduction into the milking herd without the hassle or costs associated with milk discard. In addition, the SPECTRAMAST DC label specifies a slaughter withdrawal period of only 16 days in contrast to the 42-day slaughter withdrawal period for ToMorrow and a 30-day withdrawal for ALBADRY PLUS.

ORBESEAL has no milk discard or slaughter withdrawal requirements. When ORBESEAL is used in conjunction with a dry-cow antimicrobial, withdrawal on the antimicrobial label should be followed.

Conclusions

Results from four demonstration studies suggest that a dry-cow treatment regimen involving SPECTRAMAST DC and ORBESEAL helps minimize mastitis risk in early lactation, with outcomes typically comparable or better than similar regimens employing competitive antimicrobial products. In addition, economic analyses consistently demonstrated a financial advantage for dairies using the SPECTRAMAST DC and ORBESEAL dry-cow program, suggesting that the regimen is economically justified and certainly not inferior to other programs. Notably, use of SPECTRAMAST DC as the dry-off therapy offers the advantage of no milk discard upon calving, allowing fresh cows to immediately enter the milking herd.

IMPORTANT SAFETY INFORMATION: People with known hypersensitivity to penicillin or cephalosporins should avoid exposure to SPECTRAMAST DC. Product requires a 30-day dry cow period, and has a 16-day pre-slaughter withdrawal period following last treatment. Use of this product in a manner other than indicated on the label, or failure to adhere to the proper milk discard period, will result in violative residues. See full Prescribing Information at the end.

References

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3. Data on file, Study Report No. 11PETSDC04, Zoetis Inc.
4. Data on file, Study Report No. 11PETSDC02, Zoetis Inc.
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SPECTRAMAST® DC

brand of ceftiofur hydrochloride sterile suspension

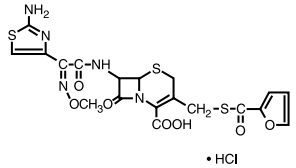
For **Intramammary** Infusion in Dry Dairy Cattle Only

FOR USE IN ANIMALS ONLY — NOT FOR HUMAN USE

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Federal Law prohibits extra-label use of this drug in dry dairy cattle for disease prevention purposes; at unapproved doses, frequencies, durations, or routes of administration; and in unapproved major food producing species/production classes.

DESCRIPTION: Ceftiofur hydrochloride is a cephalosporin antibiotic.

Chemical Structure of Ceftiofur Hydrochloride U-64279A



Chemical Name of Ceftiofur Hydrochloride

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7 - [[2-(2- amino-4-thiazolyl) - 2 -(methoxyimino)acetyl]amino]-3-[[(2-furanyl-carbonyl)thio] methyl]-8-oxo, hydrochloride.

Ceftiofur Hydrochloride Sterile Suspension is an oil based sterile suspension.

Each 10 mL PLASTET® Disposable Syringe Contains:

Ceftiofur Equivalents (as the hydrochloride salt)	500 mg
Microcrystalline Wax	700 mg
Oleoyl Polyoxylglyceride	500 mg
Cottonseed Oil	q.s.

INDICATIONS FOR USE

SPECTRAMAST® DC Ceftiofur Hydrochloride Sterile Suspension is indicated for the treatment of subclinical mastitis in dair cattle at the time of dry off associated with *Staphylococcus aureus*, *Streptococcus dysgalactiae*, and *Streptococcus uberis*. **SPECTRAMAST® DC** Ceftiofur Hydrochloride Sterile Suspension has been proven effective against *Staphylococcus aureus*, *Streptococcus dysgalactiae*, and *Streptococcus uberis*.

DOSAGE

Infuse one (1) syringe into each affected quarter at the time of dry off.

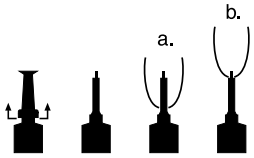
DIRECTIONS FOR USING THE PLASTET® DISPOSABLE SYRINGE

The syringe is designed to provide the choice of either insertion of the full cannula as has traditionally been practiced, or insertion of no more than 1/8 inch of the cannula, as reported by Eberhart, R.J., et. al. 1987. Current Concepts of Bovine Mastitis, 3rd Edition, National Mastitis Council, Arlington, VA.

a. Full insertion: Remove the red end cap by pulling straight up as shown. Gently insert the full cannula into the teat canal; carefully infuse the product.

b. Partial insertion: Remove the red end cap by pulling straight up as shown. Gently insert the exposed white tip into the teat canal; carefully infuse the product.

ADMINISTRATION



Treatment: Wash teats thoroughly with warm water containing a suitable dairy antiseptic. Dry teats thoroughly. Milk out udder completely. Using an alcohol pad provided, wipe off the end of the affected teat using a separate pad for each teat. Choose the desired insertion length (full or partial) and insert tip into teat canal; push plunger to dispense entire contents, massage the quarter to distribute the suspension into the milk cistern.

Reinfection: After successful treatment, reinfection may occur unless good herd management, sanitation, and mechanical safety measures are practiced. Affected cows should be watched carefully to detect recurrence of infection and possible spread to other animals.

CONTRAINDICATIONS

As with all drugs, the use of **SPECTRAMAST® DC** Sterile Suspension is contraindicated in animals previously found to be hypersensitive to the drug.

Discard Empty Container: DO NOT REUSE

KEEP OUT OF REACH OF CHILDREN

WARNINGS

Penicillins and cephalosporins can cause allergic reactions in sensitized individuals. Topical exposures to such antimicrobials, including ceftiofur, may elicit mild to severe allergic reactions in some individuals. Repeated or prolonged exposure may lead to sensitization. Avoid direct contact of the product with the skin, eyes, mouth and clothing. Sensitization of the skin may be avoided by wearing protective gloves.

Persons with a known hypersensitivity to penicillin or cephalosporins should avoid exposure to this product.

In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. If allergic reaction occurs (e.g., skin rash, hives, difficult breathing), seek medical attention.

The material safety data sheet contains more detailed occupational safety information. To report adverse effects in users, to obtain more information or to obtain a material safety data sheet, call Zoetis Inc. at 1-888-963-8471.

RESIDUE WARNINGS

1. Milk taken from cows completing a 30-day dry cow period may be used for food with no milk discard due to ceftiofur residues.
2. Following label use, no pre-slaughter withdrawal period is required for neonatal calves born from treated cows regardless of colostrum consumption.
3. Following intramammary infusion, a 16-day pre-slaughter withdrawal period is required for treated cows.
4. Use of this product in a manner other than indicated under DOSAGE might result in violative residues.

CLINICAL MICROBIOLOGY

Ceftiofur is a broad-spectrum cephalosporin antibiotic that exerts its effect by inhibiting bacterial cell wall synthesis. Like other ß-lactam antimicrobial agents, the cephalosporins inhibit cell wall synthesis by interfering with the enzymes essential for peptidoglycan synthesis. This effect results in lysis of the bacterial cell and accounts for the bactericidal nature of these agents. Ceftiofur has demonstrated *in vitro* activity against clinical isolates and isolates from diagnostic laboratories. The results of susceptibility testing of these isolates against ceftiofur are presented in Tables 1 and 2. Appropriate reference strains were also susceptibility tested and their minimum inhibitory concentration (MIC) values and zone of inhibition with a 30 µg disk are presented in Table 4.

Table 1. Ceftiofur MIC values for isolates from a multi -site clinical field study evaluating subclinical mastitis in dry dairy cows in the U.S. during 2000

Organism	No.	MIC_{90}* (µg/mL)	MIC range (µg/mL)
Staphylococcus aureus	300	1.0	≤0.06 to 2.0
Streptococcus dysgalactiae	55	≤0.06	≤0.06 to >64.0
Streptococcus uberis	58	1.0	≤0.06 to 4.0

* The MIC for 90% of the isolates.

Table 2. Ceftiofur MIC values* for mastitis pathogens from diagnostic laboratories in the U.S. and Canada

Organism	No.	Date isolated	MIC_{90}** (µg/mL)	MIC range (µg/mL)
Staphylococcus aureus	135	1991–1992	1.0	0.13 to 2.0
	10	1993	1.0	0.25 to 1.0
	107	1995	1.0	0.25 to 2.0
	61	2000	1.0	≤0.06 to 2.0
Coagulase (-) staphylococci	139	2000–2001	1.0	≤0.06 to 2.0
Streptococcus dysgalactiae	15	1991–1992	1.0	≤0.06 to 2.0
	15	1993	≤0.0039	No range†
	152	1997–1999	0.25	0.25 to 4.0
	64	2000	≤0.06	≤0.06 to 0.5
Streptococcus uberis	22	1991–1992	0.5	≤0.06 to 4.0
	15	1993	0.03	≤0.0039 to 0.06
	133	1997–1999	0.5	0.5 to 8.0
	20	2000	1.0	<0.06 to 2.0
Escherichia coli	39	1991–1992	1.0	0.25 to 1.0
	40	1993	0.5	0.13 to 1.0
	52	2000	0.5	≤0.06 to 1.0

* The above *in vitro* data are available, but their clinical significance is unknown.
** The MIC for 90% of the isolates.
† No range, all isolates yielded the same value.

Based on pharmacokinetic, milk residue and clinical effectiveness studies in dairy cattle following intramammary infusion of ceftiofur and the MIC and disk (30 µg) diffusion data from mastitis pathogens, the following breakpoints are recommended by the National Committee for Clinical Laboratory Standards [now the Clinical and Laboratories Standards Institute (CLSI)] (Table 3).

Table 3. Current recommended interpretive criteria established by CLSI for ceftiofur for Bovine Mastitis

Bovine Mastitis Organisms	Disk Content	Zone Diameter (mm)			MIC break-point (µg/mL)		
		S	I	R	S	I	R
Staphylococcus aureus *Streptococcus dysgalactiae* *Streptococcus uberis* *Streptococcus agalactiae* *Escherichia coli*	30 µg	≥21	18–20	≤17	≤2.0	4.0	≥8.0

S–Susceptible I–Intermediate R–Resistant

Standardized procedures require the use of laboratory control organisms for both standardized diffusion techniques and standardized dilution techniques. The 30 µg ceftiofur sodium disk should give the following zone diameters and the ceftiofur sodium standard reference powder (or disk) should provide the following MIC values for the reference strain. The ceftiofur sodium disks or standard reference powder is appropriate for ceftiofur hydrochloride (Table 4).

Table 4. Acceptable quality control ranges for ceftiofur against CLSI recommended American Type Culture Collection (ATCC) reference strains

Organism (ATCC No.)	Zone Diameter* (mm)	MIC range (µg/mL)
Escherichia coli (25922)	26 to 31	0.25 to 1.0
Staphylococcus aureus (29213)	—	0.25 to 1.0
Staphylococcus aureus (25923)	27 to 31	—
Pseudomonas aeruginosa (27853)	14 to 18	16.0 to 64.0

*All testing performed using a 30 µg disk.

EFFECTIVENESS

The effectiveness of a single intramammary (IMM) infusion of ceftiofur hydrochloride for the treatment of subclinical mastitis present at the time of dry off was demonstrated in a randomized block design study. Nineteen veterinary investigators enrolled cows in 21 herds and from these 21 herds, 431 cows and 1708 quarters met enrollment criteria in the study and calved within a 45 to 60 day period following enrollment. The enrollment criteria were whole udder somatic cell counts greater than 400,000 cells/mL or a linear somatic cell count score greater than or equal to 5. Milk microbiologic samples were obtained prior to treatment and at Days 3 and 5 post-calving. There were 5 treatment groups including a negative control group. There were 43 cows in the negative control group and 51 cows in the 500 mg ceftiofur group that had a positive pre-treatment milk culture that were evaluated for treatment success. The primary decision variable was the microbiologic (therapeutic) cure in which bacteria isolated pre-treatment were absent from both post-treatment samples.

In another study in eleven study herds, 446 cows with a somatic cell count (SCC) greater than or equal to 400,000 cells/mL or a linear score greater than or equal to 5 were enrolled. Cows with a dry period of at least 45 days were blocked by lactation (1st + 2nd or ≥3rd). A single quarter milk sample was aseptically obtained from all four quarters for bacterial culture prior to treatment and on Days 3 and 5 post-calving. There were 4 treatment groups including a negative control. There were 84 cows in the negative control and 73 in the 500 mg ceftiofur group that had a positive pre-treatment milk culture that were evaluated for treatment success. The primary decision variable was the microbiologic (therapeutic) cure in which bac-teria isolated pre-treatment were absent from both post-treatment samples.

Ceftiofur was found to be effective against *Staphylococcus aureus*, *Streptococcus dysgalactiae*, and *Streptococcus uberis*, when compared to negative controls. This intramammary ceftiofur formulation was well tolerated. No adverse formulation related events were noted during the entire study. A large multi-location field dose confirmation study and a pilot study demonstrated that 500 mg of ceftiofur infused once per quarter at the time of dry off was effective for the treatment of subclinical mastitis in dairy cattle at the time of dry off.

ANIMAL SAFETY

An udder irritation study was conducted in 22 healthy lactating dairy cows to assess udder irritation following a single intramammary infusion of a sterile oil-based suspension containing 500 mg of ceftiofur into all four quarters followed by milk-out 12 hours later. Throughout the 10 day post-treatment observation period there was a clinically insignificant rise in SCC to mean levels <200,000 cells/mL from the pre-infusion level of <69,000 cells/mL. No clinical signs of udder irritation (swelling, pain, or redness), changes in rectal temperature, or changes in milk production were noted in this study. Clinical observations were made during a GLP residue depletion study of 36 cows following a single intramammary infusion of a sterile oil based suspension containing 500 mg of ceftiofur into all four quarters at the end of lactation. No report of udder irritation or adverse reaction was noted in the daily visual observations over the 14 days immediately following treatment. Collectively, these studies demonstrate that the intramammary infusion of an oil-based sterile suspension containing 500 mg of ceftiofur once into all four quarters at the end of lactation is clinically safe and non-irritating to the udder of non-lactating dairy cows.

MILK AND TISSUE RESIDUE DEPLETION

A metabolism study in cattle using radiolabeled ceftiofur provided the data to establish tolerances for ceftiofur-related residues (as desfuroylceftiofur) in tissue and milk. These tolerances of ceftiofur residues are 0.1 ppm in milk, 0.4 ppm in kidney, 2.0 ppm in liver, and 1.0 ppm in muscle.

Pivotal residue decline studies were conducted to assess the depletion of ceftiofur-related residues, measured as desfuroylceftio-fur using the official analytical method, in tissues of treated cows, in milk from treated cows, and in tissues of calves born to treated cows. In these studies, non-mastitic cows received 500 mg of ceftiofur per quarter into all four quarters once at dry off. The milk residue depletion study demonstrated that milk produced at calving may be used for human consumption with no discard period when the treatment to calving interval is 30 days or more. The tissue depletion study measured residues in the tissues of treated cows and in the tissues of neonatal calves born to treated cows. In neonatal calves born to treated cows, tissue residues were less than the codified tolerances for kidney, liver and muscle. These data support a zero day pre-slaughter withdrawal period for calves born to treated cows when the treatment to calving interval is 30 days or more, regardless of colostrum consumption. The tissue residue depletion data support a 16-day pre-slaughter withdrawal period following intramammary infusion for treated cows.

STORAGE CONDITIONS

Store at controlled room temperature 20° to 25° C (68° to 77° F). Protect from light. Store plastets in carton until used.

HOW SUPPLIED

SPECTRAMAST® DC Sterile Suspension is available in cartons containing 1 unbroken package of 12–10 mL PLASTET® Disposable Syringes with 12 individually wrapped 70% isopropyl alcohol pads and in pails containing 12 unbroken packages of 12-10 mL PLASTET Disposable Syringes with 144 individually wrapped 70% isopropyl alcohol pads.

NADA# 141-239, Approved by FDA

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

zoetis

www.spectramast.com or call 1-888-963-8471

Revised: September 2013

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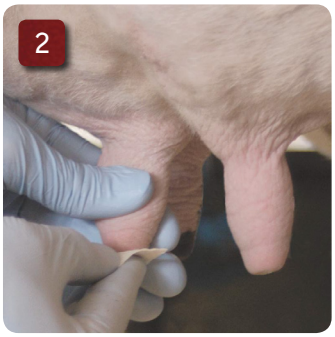
HOW TO USE ORBESEAL

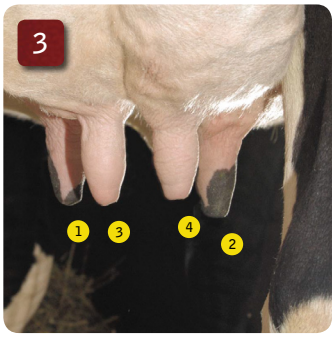
When managing dry cows, correct procedures must be followed to prevent mastitis infections. At all times, dry cow materials should be kept away or shielded from possible fecal/urine contamination. Disposable gloves should be worn during the disinfection process. Orbeseal® should be stored at room temperature (60°-85°F, 15°-30°C). If Orbeseal becomes difficult to administer in extremely cold weather, it should be warmed to room temperature. Individual tubes should not be immersed in water. The Orbeseal bucket can be lowered into a five-gallon bucket filled with warm water to warm the tubes.

AFTER USING YOUR CURRENT DRY COW TREATMENT PROGRAM, PERFORM THE FOLLOWING STEPS:

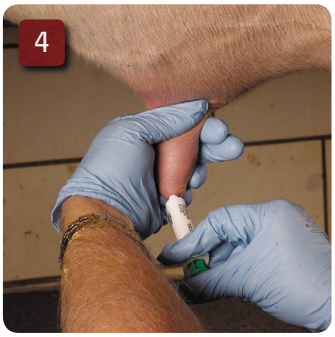
Teats should be clean and dry. If teats are not clean, CAREFULLY wash and dry them prior to disinfection.



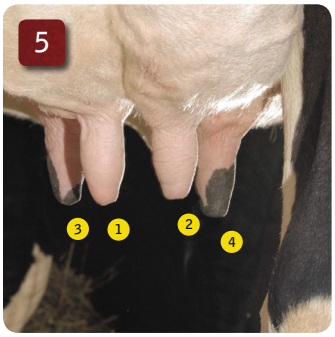
Using an alcohol pad, physically clean the end of the teat to remove any contaminated skin, dirt or manure. Repeat until the pad remains clean.



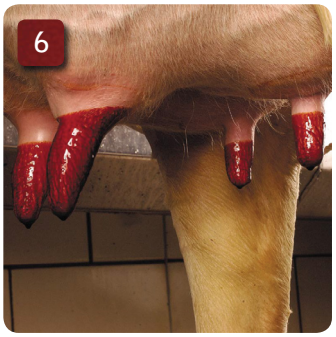
Disinfect the far teats before the near teats to avoid accidental contamination of previously disinfected teats.



Insert the Orbeseal syringe nozzle into the teat canal, grasp the base of the teat near the udder attachment with two fingers pressed firmly together and **slowly** inject all contents. Use one complete syringe per quarter. Do not massage. Orbeseal must remain in the teat canal to be effective.

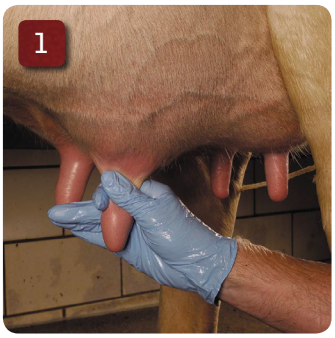


Insert Orbeseal into the nearest teats first to minimize contamination of teats that have not been treated.

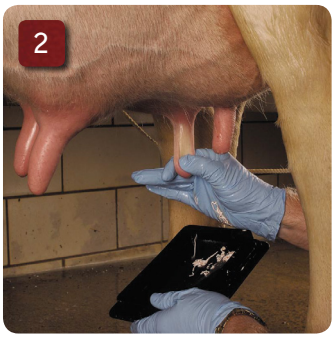


After inserting Orbeseal, mark the cow so others can tell she has been dried off. Then dip each teat with a quality teat dip.

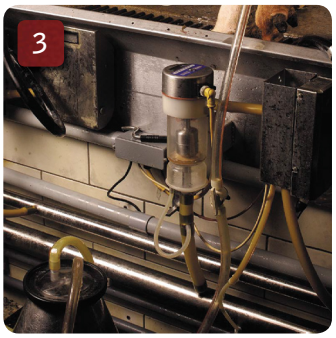
TO REMOVE ORBESEAL, PERFORM THE FOLLOWING STEPS:



To effectively strip Orbeseal, be sure to grab the top of the teat–where it meets the udder–and work all the way down. Don't grab the middle of the teat, squeeze, and work down. This will only clear the bottom half of the teat. Strip the entire quarter by starting at the top and working all the way down.



Strip aggressively–10 to 12 times per quarter–for the first 4 days post-freshening. This helps to ensure that you're removing the plug and all Orbeseal particles. **Do not remove Orbeseal by action of the milking machine.**



Milk into a bucket for the first 3 to 4 days post-freshening. This will help to remove any remaining Orbeseal particles.

Orbeseal requires no milk or preslaughter withdrawal. If Orbeseal is used in conjunction with a dry cow mastitis treatment program, follow the labeled withdrawal period of the antibiotic. Ask your veterinarian or Pfizer representative for more information.

PREVENT NEW INFECTIONS, NATURALLY™

Orbeseal®