TECHNICAL BULLETIN

Comparison Study: Cow Level Performance of Orbenin®-DC vs. Spectramast® DC in Two Commercial Dairies

This non-inferiority study compared the efficacy of Orbenin®-DC and Spectramast® DC on two commercial dairies and found no differences in the performance between the two tubes based on clinical mastitis, somatic cell count, reproductive performance, milk production and cow removal in the next lactation. Holstein and Jersey cows from two herds (Washington and Texas, respectively) were enrolled at dry off. At enrollment, cows were randomly treated with benzathine cloxacillin (ORB; Orbenin-DC Intramammary Infusion) or ceftiofur hydrochloride (SPDC; Spectramast DC Sterile Suspension). Retrospectively, data from cows with afunctional quarters and diagnosed with clinical diseases (mastitis, indigestion, lameness, etc.) within 60 d of dry-off were removed, resulting in records from 2,241 cows (Jersey: ORB = 283 and SPDC = 311; Holstein: ORB = 820 and SPDC = 827). Composite milk samples (all quarters combined) collected at dry-off and calving were submitted for bacteriological culture. Cows were followed for 100 days postpartum and incidence of clinical mastitis, milk yield and composition, somatic cell count, and reproductive performance were recorded. The prevalence of intramammary infections (IMI) at dry-off was not different between treatments (ORB = 49.0 vs. SPDC = 46.9%). There was no difference in the prevalence of new intramammary infections (NIMI) at calving between treatments (ORB = 42.2 vs. SPDC = 43.4%) and no treatment by herd interaction. Although treatment tended to affect linear somatic cell count in the first three months of lactation (ORB = 1.32 ± 0.05 vs. SPDC = 1.42 ± 0.05), the incidence of clinical mastitis in the first 100 days postpartum was not affected by treatment (ORB = 6.6 vs. SPDC = 7.6%). Milk yield in the first 100 days postpartum was also not affected by treatment (ORB = 38.3 ± 0.4 vs. SPDC = 38.6 ± 0.4 kg/d). Similarly, treatment did not affect the hazard of culling within 100 days postpartum or the percentage of cows pregnant after the first and second postpartum artificial insemination (ORB = 55.6 vs. SPDC = 55.0%). In conclusion, efficacy of Orbenin-DC as a dry-cow antimicrobial therapy to prevent NIMI in the dry period showed no difference to Spectramast DC. No significant differences in productive and reproductive performances between Orbenin-DC and Spectramast DC treatments were observed.

Orbenin-DC®
(benzathine cloxacillin)

MERCK
Animal Health

INTRODUCTION

Intramammary treatment of dairy cows, as a blanket treatment into all four quarters, with approved antimicrobials at dry-off is a critical strategy to reduce the occurrence of new intramammary infections (NIMI) during the dry period and to cure existing intramammary infections (IMI) present at dry-off has long been recommended by National Mastitis Council.[4] Several antimicrobial formulations are labeled for intramammary treatment of dairy cows at dry-off and producers often make their selection on which formulation to use based on efficacy, cost and withdrawal times. In 2013, a non-inferiority dry tube study compared the efficacy of Spectramast DC, ToMORROW® and Quartermaster® on six commercial dairies from four different states.[1,2] No differences in quarter-level or cow-level performance was detected between these three different antibiotic formulations.

Benzathine cloxacillin 500mg formulation (e.g. Orbenin-DC Intramammary Infusion or Dry-Clox®) is a semisynthetic beta-lactamase resistant penicillin antibiotic labeled for gram positive bacteria; *Streptococcus agalactiea* and *Staphylococcus aureus*. In a recent experiment conducted on four commercial dairy herds in Wisconsin treatment of cows at dry-off with benzathine cloxacillin (Dry-Clox) or Spectramast DC showed no difference in the efficacy of the two tubes at the level of the quarter or the cow based on bacteriologic cure, somatic cell count (SCC), mastitis and milk production in the next lactation.[3] In the current study, efficacy of Orbenin-DC and Spectramast DC dry-cow therapies were evaluated in two commercial dairy herds, one in Texas and one in Washington. The hypothesis was that no differences in efficacy between these two antimicrobial formulations for dry-cow therapy would be observed at the level of the cow.

MATERIAL AND METHODS

Jersey (n = 772) and Holstein (n = 1,819) cows from two herds, Texas and Washington respectively, were enrolled over three month periods at dry-off. Cows were randomly assigned to receive benzathine cloxacillin (ORB; 500mg Orbenin-DC Intramammary Infusion) or ceftiofur hydrochloride (SPDC; 500mg Spectramast DC Sterile Suspension). On the day of enrollment teats were sanitized and teat ends were wiped with alcohol pads, composite milk samples were collected from each cow, cows were milked completely, teat ends were wiped with alcohol pads, and antimicrobial treatments were applied according to the labels. The dairy in Texas followed all antimicrobial dry tube treatment with an internal teat sealant (Orbeseal®) according to label; however, the Washington dairy did not use a teat sealant. Both herds had a planned dry period length of 60 days, with cows being dried off and enrolled between 214-220 days carried calf. Within 10 days of calving, another composite milk sample was collected from each cow. Prior to milk sample collection, teats were sanitized and teat ends were wiped with alcohol pads. Milk culture and pathogen classification procedures followed recommendations of the National Mastitis Council for bovine mastitis[4]. After calving, cows were milked twice daily and at each milking herd personnel evaluated cows for signs of clinical mastitis (alteration in milk appearance and swelling/redness of the udder). Monthly milk yield and components, and SCC were determined for each individual cow during the Dairy Herd Improvement Association (DHIA) test. Additionally, reproductive performance data were retrieved from on-farm software. Lactating and non-lactating cows were housed in open lot pens in Washington and freestalls with composted manure solids in Texas. Retrospectively, data from cows with afunctional quarters, clinical diseases within 60 days of dry-off, and dry period length < 30 days and > 90 days were excluded (n = 350). Intramammary infection was characterized by the presence of one or more diagnosed pathogen in the sample collected at dry-off. A cow was considered to have cured IMI when at least one of the pathogens isolated in the sample collected at dry-off was not present in the sample collected at calving. A cow was considered to have a NIMI when no pathogens were isolated in the sample collected at dry-off and at least one pathogen was isolated in the milk sample collected at calving. Cows that had no pathogen in the milk sample collected at calving and had SCC > 200,000 cells/mL within two weeks of calving and no observed clinical mastitis were considered to have sub-clinical mastitis.

RESULTS AND DISCUSSION

Orbenin-DC is labeled for the treatment and prophylaxis of gram-positive organisms associated with mastitis such as *Staphylococcus aureus* and *Streptococcus agalactiae*. Spectramast DC is labeled for the treatment of subclinical mastitis in dairy cattle at the time of dry-off associated with *Staphylococcus aureus, Streptococcus dysgalactiae*, and *Streptococcus uberis*. Cows that cultured positive for *Staphylococcus aureus* at the time of dry off in this study were sold immediately after freshening or after results from the fresh sample were determined and removed from the analysis. No *Streptococcus agalactiae* positive milk samples were found at either of the study locations.

There were no ($P = 0.22$) differences between treatments in the prevalence of IMI at the level of the cow at dry-off (ORB = 49.0 vs. SPDC = 46.9%), but it was ($P < 0.01$) lower for the Jersey (37.1%) than the Holstein (51.5%) herd (Table 2). In Table 1, the frequency of bacteria isolated from the milk samples collected at dry-off and at calving are described according to treatment and site. At both locations, samples from dry-off grew coagulase negative *Staphylococcus ssp*. followed by coliforms most commonly. After calving the most common pathogen at the Texas dairy was coliforms followed by coagulase negative *Staphylococcus ssp*. and at the Washington dairy was coagulase negative *Staphylococcus ssp*. followed by coliforms.

The prevalence of NIMI at calving was not ($P = 0.32$) affected by treatment (ORB = 42.2 vs. SPDC = 43.3%; Table 2).

There was an interaction between treatment and herd affecting ($P = 0.04$) the likelihood of overall cure of IMI during the dry period because in the Jersey herd cure rate for ORB cows was 67.0% and for SPDC cows was 80.9%, and in the Holstein herd, the overall cure rates for ORB and SPDC cows were 57.4 and 56.2%, respectively (Table 2). This difference observed in cure rate could be contributed by; housing type, bedding type, region, use of an internal teat sealant, breed and management styles. The herds in this study were located in Texas and Washington and the cows were housed in freestalls and open lot respectively.

Treatment did not ($P = 0.77$) affect the IMI cure of cows infected with coagulase negative *Staphylococcus ssp*. at dry-off (Table 2). It is interesting to note that the herd with the lowest overall IMI cure rate during the dry period (Texas = 73.8 vs. Washington = 56.8%) also had the higher overall prevalence of NIMI at calving (Texas = 21.9 vs. Washington = 46.7%).

Surprisingly, treatment tended ($P = 0.09$) to affect linear somatic cell count in the first three months of lactation with ORB cows (1.32 ± 0.05) having lower linear somatic cell score than SPDC cows (1.42 ± 0.05; Figure 1). Although no ($P = 0.76$) difference in percentage of cows with SCC ≥ 200,000 cells/ml within two weeks postpartum was observed between treatments, treatment with ORB tended ($P = 0.08$) to reduce the likelihood of new cases of SCC ≥ 200,000 cells/ml within two weeks postpartum (Table 3).

Milk yield in the first 100 DIM was not ($P = 0.22$) affected by treatment (ORB = 38.3 ± 0.4 vs. SPDC = 38.6 ± 0.4 kg/d; Figure 2). Formulation of dry-cow therapy did not affect the incidence ($P = 0.31$; ORB = 6.8 vs. SPDC = 7.7%) and the hazard ($P = 0.31$; AHR = 0.86, 95% CI = 0.63, 1.16) of mastitis within 100 days postpartum (Table 2).

Finally, the percentage of cows pregnant after the first and second postpartum services ($P = 0.46$; ORB = 55.6 vs. SPDC = 55.0%) and the hazard of culling within 100 days postpartum ($P = 0.97$; AHR = 1.00, 95% CI = 0.79, 1.28) were not affected by treatment.

TABLE 1. Description and frequency of bacterial species for milk samples collected at dry-off and at 0 to 10 DIM.

	TEXAS		WASHINGTON	
	ORB[‡]	SPDC[§]	ORB[‡]	SPDC[§]
Bacterial culture dry-off (n)	271	300	868	863
Coliform, %	19.9	15.7	25.1	23.8
Strep non-ag, %	0.7	0.0	2.5	2.4
Staph. coag. neg., %	21.4	19.3	34.6	34.9
Staph. aureus, %	0.0	0.7	0.0	0.0
Bacterial culture at calving (n)	250	274	828	828
Coliform, %	19.2	14.2	34.8	36.7
Strep non-ag, %	0.8	0.7	6.5	6.3
Staph. coag. neg., %	5.6	7.3	42.2	42.9
Staph. aureus, %	0.0	0.0	0.0	0.1

[‡] *Benzathine cloxacillin: Orbenin-DC® Intramammary Infusion*
[§] *Ceftiofur hydrochloride: Spectramast® DC Sterile Suspension*

FIGURE 1. Effect of treatment of dry-cows with two intramammary antimicrobial formulations on linear somatic cell score in the first 3 months postpartum. Effect of: treatment – $P = 0.09$; month of lactation – $P < 0.01$; treatment x month of lactation – $P = 0.55$. Benzathine cloxacillin: Orbenin-DC Intramammary Infusion. Ceftiofur hydrochloride: Spectramast DC Sterile Suspension.

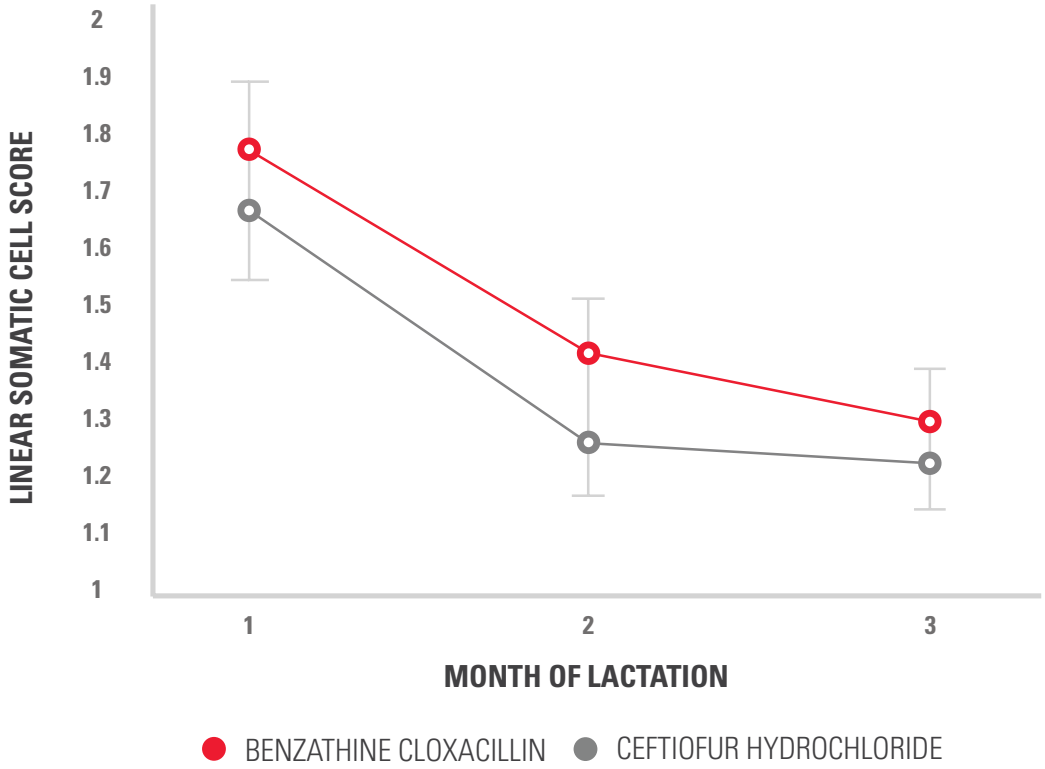

FIGURE 2. Effect of treatment of dry cows with two intramammary antimicrobial formulations on average milk yield in the first three months postpartum. Effect of: treatment – $P = 0.22$; month of lactation – $P < 0.01$; treatment x month of lactation – $P = 0.30$. Benzathine cloxacillin: Orbenin-DC Intramammary Infusion. Ceftiofur hydrochloride: Spectramast DC Sterile Suspension.

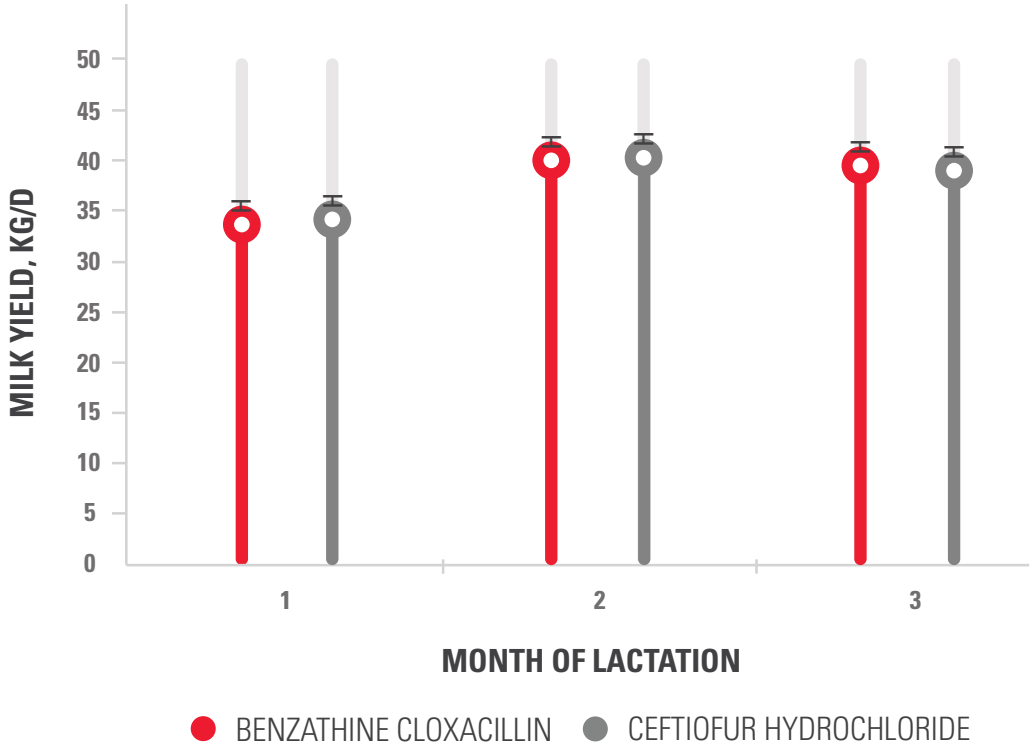

TABLE 2. Effect of treatment of dry cows with two intramammary antimicrobial formulations on udder health.

	TEXAS		WASHINGTON		*P* - VALUES		
ITEM	**ORB‡**	**SPDC§**	**ORB‡**	**SPDC§**	**TRT**	**HERD**	**TRT X HERD**
IMI* at dry-off	40.6%	51.6%	34.0%	51.3%	0.22	< 0.01	0.17
IMI* cure	67.0%	80.9%	57.4%	56.2%	0.12	< 0.01	0.04
Coliform, % (n)	75.6 (45)	90.2 (41)	65.5 (206)	61.7 (193)	0.16	< 0.01	0.06
Staph coagulase negative, % (n)	89.8 (49)	96.2 (52)	52.3 (283)	51.4 (290)	0.77	< 0.01	0.21
New IMI*	19.7%	46.0%	23.7%	47.4%	0.32	< 0.01	0.58
IMI* at calving	24.8%	60.0%	21.9%	62.0%	0.67	< 0.01	0.25
Clinical mastitis within 100 DIM	7.1%	10.3%	6.5%	6.5%	0.32	0.05	0.25

IMI – intramammary infection*
‡Benzathine cloxacillin: Orbenin-DC® Intramammary Infusion
§Ceftiofur hydrochloride: Spectramast® DC Sterile Suspension

TABLE 3. Effect of treatment of dry cows with two intramammary antimicrobial formulations on udder health.

	TEXAS		WASHINGTON		*P* - VALUES		
	ORB‡	**SPDC§**	**ORB‡**	**SPDC§**	**TRT**	**HERD**	**TRT X HERD**
Cows with SCC ≥ 200,000 within two weeks postpartum, % (n)	16.1 (93)	22.2 (99)	28.5 (386)	26.6 (376)	0.76	0.04	0.31
Resolution of high SCC during the dry period, % (n)	0 (3)	33.3 (3)	46.7 (15)	46.2 (13)	0.91	0.42	NA
New cases of high SCC postpartum, % (n)	0 (11)	28.6 (7)	28.1 (82)	34.2 (79)	0.08	0.10	0.97

Resolution of high SCC during the dry period: cows with SCC ≥ 200,000 within two weeks before dry-off and SCC < 200,000 within two weeks postpartum
New cases of high SCC postpartum: cows with SCC < 200,000 within two weeks before dry-off and SCC ≥ 200,000 within two weeks postpartum

CONCLUSIONS

Treatment of dairy cows with Orbenin-DC resulted in similar prevalence of NIMI at calving and similar incidence of clinical mastitis in the next lactation. There was a slight numerical decrease in cure of IMI during the dry period in a herd of Jersey cows (Texas) dried with Orbenin-DC compared to cows dried with Spectramast DC at dry-off. Additionally, yield of fat-corrected milk and reproductive performance up to 100 days postpartum of cows treated with Orbenin-DC was not different compared with cows treated with Spectramast DC. Dairy producers may choose to use Orbenin-DC or Spectramst DC for dry-cow therapy with no clinical differences to udder health, productive and reproductive performance in the next lactation. In conclusion, Orbenin-DC is an efficacious and economical dry tube choice for dairy producers who want to select a product with zero milk and meat withhold after a 28-day dry period.

REFERENCES

1. Arruda, A. G., Godden S., Rapnicki P., Gorden P., Timms L., Aly S.S., Lehenbauer T.W., and Champagne J. 2013. Randomized noninferiority clinical trial evaluating three commercial dry cow mastitis preparations: I. Quarter-level outcomes. *J Dairy Sci.* 96:4419-4435.
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5. Reyher, K.K. and Dohoo, I. R. Diagnosing intramammary infections: Evaluation of composite milk samples to detect intramammary infections. 2011. *J. Dairy Sci.* 94:3387–3396.

WARNINGS: For use in dry cows only. Do not use within four weeks (28 days) of calving. Treated animals must not be slaughtered for food purposes within 4 weeks (28 days) of treatment.

F-27865909

Orbenin-DC®

(benzathine cloxacillin)

DRY COW (VACA SECA)

Intramammary Infusion
(Infusión intramamaria)

LONG ACTING FORMULA
(FÓRMULA DE LARGA ACCIÓN)

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Orbenin-DC (benzathine cloxacillin) is a stable, nonirritating suspension of benzathine cloxacillin containing the equivalent of 500 mg of cloxacillin per disposable syringe. Orbenin-DC is manufactured by a nonsterilizing process.

Benzathine cloxacillin is a semisynthetic penicillin derived from the penicillin nucleus, 6-amino-penicillanic acid. Benzathine cloxacillin is the benzathine salt of 6-[3-(2-chlorophenyl)-5-methylisoxazolyl-4-carboxamido] penicillanic acid.

The low solubility of Orbenin-DC results in an extended period of activity. Therefore, directions for use should be followed explicitly.

ACTION: Benzathine cloxacillin is bactericidal in action against susceptible organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. It is active against gram-positive organisms associated with mastitis such as *Staphylococcus aureus* and *Streptococcus agalactiae* and, because of its resistance to penicillinase, penicillin G-resistant staphylococci which may be the cause of mastitis.

Appropriate laboratory tests should be conducted, including *in vitro* culturing and susceptibility tests on pretreatment milk samples collected aseptically.

SUSCEPTIBILITY TEST: The Kirby-Bauer* procedure, utilizing antibiotic susceptibility disks, is a quantitative method that may be adapted to determining the sensitivity of bacteria in milk to Orbenin-DC.

For testing the effectiveness of Orbenin-DC in milk, follow the Kirby-Bauer procedure using the 1 mcg **oxacillin** susceptibility disk. Zone diameters for interpreting susceptibility are:

Resistant	Intermediate	Susceptible
≤ 10 mm	11–12 mm	≥ 13 mm

* Bauer AW, Kirby WMM, Sherris JC, *et al*: Antibiotic testing by a standardized single disk method, *Am J Clin Path* 45:493, 1966. Standardized Disk Susceptibility Test, Federal Register 37:20527–29, 1972.

INDICATIONS: Orbenin-DC is indicated in the treatment and prophylaxis of bovine mastitis in nonlactating cows due to *Staphylococcus aureus* and *Streptococcus agalactiae.*

CONTRAINDICATIONS: Because benzathine cloxacillin is relatively insoluble, Orbenin-DC's activity will be prolonged. Therefore, Orbenin-DC should not be used for the occasional cow which may have a dry period of less than 4 weeks. This precaution will avoid residues in the milk following removal of the colostrum.

WARNINGS: For use in dry cows only. Do not use within 4 weeks (28 days) of calving. Treated animals must not be slaughtered for food purposes within 4 weeks (28 days) of treatment.

PRECAUTION: Because it is a derivative of 6-amino-penicillanic acid, Orbenin-DC has the potential for producing allergic reactions. Such reactions are rare; however, should they occur, the subject should be treated with the usual agents (antihistamines, pressor amines).

DOSAGE AND ADMINISTRATION: At the last milking of lactation, milk the cow out normally. Clean and disinfect the teats with alcohol swabs provided in the carton, and infuse 1 syringe of Orbenin-DC, which has been warmed to room temperature, into each quarter. Do not milk out. The cow may be milked as usual when she calves.

The extent of subclinical and latent mastitis in a herd is frequently greater than suspected. In untreated herds a significant buildup of subclinical mastitis may occur during the dry period, which results in clinical severity after a few lactations. The adverse influence of subclinical mastitis on milk yield, the risk of cross-infection, and the chance of clinical mastitis flare-up make it necessary to treat the matter as a herd problem. Clinical studies have proven the value of treating all the cows in heavily infected herds as they are dried off. When the herd infection has been reduced, it may be desirable to be more selective in treating infected quarters.

Each carton contains 12 alcohol swabs to facilitate proper cleaning and disinfecting of the teat orifice.

HOW SUPPLIED: Orbenin-DC is supplied in cartons of 12 single-dose syringes with 12 alcohol swabs. Each disposable syringe contains 500 mg of cloxacillin as the benzathine salt in 7.5 g of suitable base.

Do Not Store Above 24°C (75°F)

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NADA #55-069, Approved by FDA

Manufactured by:
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Syracuse, NY 13201

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Orbenin-DC®
(benzathine cloxacillin)

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