

**HEXASOL- oxytetracycline, flunixin meglumine injection, solution
Norbrook Laboratories Limited**

**Hexasol™ Injection
(oxytetracycline and flunixin meglumine)**

ANTIBIOTIC/NON-STEROIDAL ANTI-INFLAMMATORY DRUG (NSAID)

Each mL contains 300 mg of oxytetracycline base as amphoteric oxytetracycline and 20 mg of flunixin as flunixin meglumine.

For intramuscular or subcutaneous use in beef and non-lactating dairy cattle, calves and yearlings.

Not for use in female dairy cattle 20 months of age or older, bulls intended for breeding, and calves intended to be processed for veal.

Read entire package insert carefully before using this product.

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

DESCRIPTION:

Hexasol™ Injection is a sterile, pre-constituted solution of the broad-spectrum antibiotic oxytetracycline dihydrate and the non-steroidal anti-inflammatory drug (NSAID) flunixin meglumine. Each mL contains 300 mg of oxytetracycline base as amphoteric oxytetracycline; 20 mg of flunixin base as flunixin meglumine, 40% (v/v) glycerol formal, 10% (v/v) polyethylene glycol 200, 2.7% (w/v) magnesium oxide, 0.4% (w/v) sodium formaldehyde sulphoxylate (as a preservative) and monoethanolamine (as required to adjust pH).

INDICATIONS:

For the treatment of bacterial pneumonia associated with *Pasteurella* spp. and for the control of associated pyrexia in beef and non-lactating dairy cattle.

DOSAGE AND ADMINISTRATION:

Administer Hexasol Injection once as an intramuscular or subcutaneous injection of 1 mL per 22 lb body weight (13.6 mg oxytetracycline and 0.9 mg flunixin per lb BW). Do not administer more than 10 mL per injection site (1 to 2 mL per site in small calves). Hexasol Injection is recommended where retreatment of calves and yearlings is impractical due to husbandry conditions, such as cattle on range, or where their repeated restraint is inadvisable.

Animal weight (lb)	Number of mL or cc
100	4.5
200	9.0
300	13.6
400	18.1
500	22.6
600	27.2
700	31.7
800	36.3
900	40.8

1000	45.3
1100	49.8
1200	54.4

CONTRAINDICATIONS:

Do not use in animals showing hypersensitivity to either flunixin meglumine or oxytetracycline.

WARNINGS AND PRECAUTIONS:

Withdrawal Periods and Residue Warnings

Residue Warnings: Discontinue treatment at least 21 days prior to slaughter of cattle. Do not use in female dairy cattle 20 months of age or older. Use in this class of cattle may cause milk residues. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal. Use of dosages other than those indicated may result in residue violations.

Exceeding the highest recommended level of drug per pound of bodyweight per day, administering more than the recommended number of treatments, and/or exceeding 10 mL intramuscularly or subcutaneously per injection site in beef cattle and non-lactating dairy cattle may result in antibiotic residues beyond the withdrawal time.

Antibacterial Warnings

Use of antibacterial drugs in the absence of a susceptible bacterial infection is unlikely to provide benefit to treated animals and may increase the risk of the development of drug-resistant pathogenic bacteria.

As with all antibiotic preparations, use of this drug may result in overgrowth of non-susceptible organisms, including fungi. The absence of a favorable response following treatment or the development of new signs or symptoms may suggest an overgrowth of non-susceptible organisms. If superinfections occur, the use of this product should be discontinued and appropriate specific therapy should be instituted. Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving Hexasol Injection in conjunction with penicillin.

User Safety Warnings

Not for use in humans. Keep out of reach of children.

The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information. To obtain an MSDS contact Norbrook at 1-866-591-5777.

Animal Safety Warnings and Precautions

At the first sign of any adverse reaction, discontinue use of the product. Some of the reactions may be attributable either to anaphylaxis (an allergic reaction) or to cardiovascular collapse of unknown cause.

Shortly after injection, treated animals may have transient hemoglobinuria resulting in darkened urine. Intramuscular injection in the rump area may cause mild temporary lameness associated with swelling at the injection site.

As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal and hepatic toxicity. Sensitivity to drug-associated adverse effects varies with the individual patient. Patients at greatest risk for adverse events are those that are dehydrated, on diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease

in patients with underlying or pre-existing disease that has not been previously diagnosed. Since many NSAIDs possess the potential to produce gastrointestinal ulceration, concomitant use of Hexasol Injection with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided or closely monitored.

Flunixin is a cyclo-oxygenase inhibitory NSAID, and as with others in this class, adverse effects may occur with its use. The most frequently reported adverse effects have been gastrointestinal signs. Events involving suspected renal, hematologic, neurologic, dermatologic, and hepatic effects have also been reported for other drugs in this class.

Not for use in animals intended for breeding purposes. The effects of oxytetracycline and flunixin on bovine reproductive performance, pregnancy, and lactation have not been determined. NSAIDs are known to have potential effects on both parturition and the estrous cycle. There may be a delay in the onset of estrus if flunixin is administered during the prostaglandin phase of the estrous cycle. The effects of flunixin on imminent parturition have not been evaluated in a controlled study. NSAIDs are known to have the potential to delay parturition through a tocolytic effect.

Other Warnings

Hexasol Injection, when administered as directed, may induce a transient reaction at the site of injection and underlying tissues that may result in trim loss of edible tissue at slaughter.

ADVERSE REACTIONS:

At the first sign of any adverse reaction, discontinue use of the product. Reports of adverse reactions associated with oxytetracycline administration include injection site swelling, restlessness, ataxia, trembling, swelling of eyelids, ears, muzzle, anus and vulva (or scrotum and sheath in males), respiratory abnormalities (labored breathing), frothing at the mouth, collapse and possibly death. Some of these reactions may be attributed either to anaphylaxis (an allergic reaction) or to cardiovascular collapse of unknown cause. After flunixin administration in cattle, anaphylactic-like reactions have been reported, some of which have been fatal, primarily following intravenous use.

CONTACT INFORMATION:

For technical assistance, contact Norbrook at 1-866-591-5777. To report suspected adverse drug events, contact Norbrook at 1-866-591-5777 or FDA at 1-888-FDA-VETS.

CLINICAL PHARMACOLOGY:

Oxytetracycline is derived from the metabolic activity of the actinomycete, *Streptomyces rimosus*. Oxytetracycline is an antimicrobial agent that is effective in the treatment of a wide range of diseases caused by susceptible Gram-positive and Gram-negative bacteria. The antibiotic activity of oxytetracycline is not appreciably diminished in the presence of body fluids, serum or exudates. Studies have shown that the half-life of oxytetracycline in blood following intramuscular treatment with Hexasol at 5 mg per pound of bodyweight is approximately 23 hours in cattle. Studies have shown when Hexasol Injection is administered once intramuscularly or subcutaneously to cattle at 13.6 mg per pound of bodyweight, blood oxytetracycline concentration of greater than 0.2 µg/mL have been observed for at least 7 to 8 days.

Flunixin meglumine is a weak acid ($pK_a=5.82$)¹ which exhibits a high degree of plasma protein binding (approximately 99%).² However, free (unbound) drug appears to readily partition into body tissues (V_{ss} predictions range from 297 to 782 mL/kg).²⁻⁵ Total body water is approximately equal to 570 mL/kg).⁶ In cattle, elimination occurs primarily through biliary excretion.⁷ This may, at least in part, explain the presence of multiple peaks in the blood concentration/time profile following IV administration.²

In healthy cattle, total body clearance of flunixin has been reported to range from 90 to 151 mL/kg/hr.²⁻⁵

These studies also report a large discrepancy between the volume of distribution at steady state (V_{ss}) and the volume of distribution associated with the terminal elimination phase (V_B). This discrepancy appears to be attributable to extended drug elimination from a deep compartment.⁸ The terminal half-life following IV injection has been shown to vary from 3.14 to 8.12 hours.²⁻⁵ Although the average depletion half-life of flunixin following IV administration is less than that following intramuscular and subcutaneous Hexasol Injection, a range of terminal elimination half-life values similar to those reported above are observed following subcutaneous and intramuscular injection. The absolute bioavailability of the flunixin component of Hexasol Injection is 83% when administered via the intramuscular or subcutaneous routes of administration.

Flunixin persists in inflammatory tissues⁹ and is associated with anti-inflammatory properties which extend well beyond the period associated with detectable plasma drug concentrations.⁴⁻⁹ These observations account for the counterclockwise hysteresis associated with flunixin's pharmacokinetic/pharmacodynamic relationships.¹⁰ Therefore, prediction of drug concentrations based upon the estimated plasma terminal elimination half-life will likely underestimate both the duration of drug action and the concentration of drug remaining at the site of activity.

ANIMAL SAFETY:

A randomized negative-controlled target animal safety study was conducted in 3- to 5-month-old calves to evaluate the effects of Hexasol Injection when administered to cattle intramuscularly at 1X, 3X, and 5X the labeled dose every 3 days for 3 treatments (3X the labeled duration). Hexasol Injection produced no drug-related adverse effects at the labeled dose. In separate injection site studies, intramuscular or subcutaneous injection of Hexasol Injection resulted in transient inflammation, including signs of discomfort, swelling, and/or hardness.

EFFECTIVENESS:

The effectiveness of Hexasol Injection for the control of pyrexia associated with bovine respiratory disease was demonstrated in a US multi-location study. Crossbred beef calves were enrolled if they had an abnormal respiratory score and/or an abnormal attitude score and a rectal temperature of $\geq 104.5^{\circ}\text{F}$. Calves were randomly assigned and treated with either Hexasol Injection (13.6 mg oxytetracycline/lb BW and 0.9 mg flunixin/lb BW), Tetradure (oxytetracycline, NADA 141-143, 13.6 mg oxytetracycline/lb BW) or saline as a single subcutaneous (SC) injection in the neck at 1 mL/22 lb BW at enrollment (Hour 0). At 6 hours ± 1 hour, there was a clinically relevant decrease in mean rectal temperature in the Hexasol Injection-treated group. The decrease in mean rectal temperature in the Hexasol Injection-treated group compared to the saline-treated group and in the Hexasol Injection-treated group compared to the Tetradure-treated group was statistically significant ($p < 0.0001$).

HOW SUPPLIED:

Hexasol Injection is available in 100 mL, 250 mL and 500 mL vials containing 300 mg oxytetracycline and 20 mg flunixin meglumine per mL.

STORAGE:

Store at 59° to 86°F (15° to 30°C)

REFERENCES

1. Johansson M, Anler EL. Gas chromatographic analysis of flunixin in equine urine after extractive methylation. *J Chromatogr*. 1988; 427:55-66
2. Odensvik K, Johansson M. High-performance liquid chromatography method for determination of flunixin in bovine plasma and pharmacokinetics after single and repeated doses of the drug. *Am J Vet Res*.

- Res.* 1995; 56:489-495.
3. Anderson KL, Neff-Davis CA, Davis LE, Bass VD. Pharmacokinetics of flunixin meglumine in lactating cattle after single and multiple intramuscular and intravenous administrations. *Am J Vet Res.* 1990;51:1464-1467
 4. Odensvik K. Pharmacokinetics of flunixin and its effect on prostaglandin F₂ metabolite concentrations after oral and intravenous administration in heifers. *J Vet Pharmacol Ther.* 1995;18:254-259.
 5. Hardee GE, Smith JA, Harris SJ. Pharmacokinetics of flunixin meglumine in the cow. *Res Vet Sci.* 1985;39:110-112
 6. Ruckebusch Y, Phaneuf LP, Dunlop R. Physiology of Small and Large Animals. Chapter 2: "Body Fluid Compartments," Philadelphia, Pa: B.C. Decker, 1991:8-18
 7. Kopcha M, Ahl AS. Experimental uses of flunixin meglumine and phenylbutazone in food-producing animals. *J Am Vet Med Assoc.* 1989;194:45-49
 8. Wagner JG. Significance of ratios of different volumes of distribution in pharmacokinetics. *Biopharm & Drug Dispos.* 1983;4:263-270
 9. Lees P, Higgins AJ. Flunixin Inhibits prostaglandin E2 production in equine inflammation. *Res Vet Sci.* 1984;37: 347-349
 10. Landoni MF, Cunningham FM, Lees P. Determination of pharmacokinetics and pharmacodynamics of flunixin in calves by use of pharmacokinetic/pharmacodynamic modeling. *Am J Vet Res.* 1995;56:786-794.

Restricted Drug (California) - Use Only As Directed.

NADA 141-312, Approved By FDA

Made in the UK.

Norbrook Laboratories Limited

Newry, BT35 6PU, Co. Down, Northern Ireland U.S. Patent No. 6,479,473

™ Hexasol is a registered trademark of Norbrook Laboratories Limited

REVISION DATE - September 2010

012670I01



Principal Display Panel – 500 mL Label

NDC 55529-016-05

Hexasol™ Injection

(oxytetracycline and flunixin meglumine)

300 mg oxytetracycline and 20 mg flunixin per mL

ANTIBIOTIC/NON-STEROIDAL

ANTI-INFLAMMATORY

DRUG (NSAID)

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian. For intramuscular or subcutaneous use in beef and non-lactating dairy cattle, calves and yearlings for the treatment of bacterial pneumonia and pyrexia associated with *Pasteurella* spp.

Not for use in female dairy cattle 20 months of age or older, bulls intended for breeding, and calves intended to be processed for veal.

NADA 141-312, Approved By FDA

500 mL

Norbrook®

INDICATIONS

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Hexasol™ (oxytetracycline and flunixin) Injection is a sterile preconstituted solution of the broad-spectrum antibiotic oxytetracycline and the NSAID flunixin meglumine. Each mL contains 300 mg of oxytetracycline base as amphoteric oxytetracycline; 20 mg of flunixin base as flunixin meglumine; 2.7% w/v magnesium oxide; 40% v/v glycerol formal; 10% w/v polyethylene glycol; and 0.4% w/v sodium formaldehyde sulphoxylate (as a preservative), monoethanolamine (as required to adjust pH).

WARNINGS AND PRECAUTIONS:

Withdrawal Periods and Residue Warnings

Residue Warnings: Discontinue treatment at least 21 days prior to slaughter of cattle. Do not use in female dairy cattle 20 months of age or older. Use in this class of cattle may cause milk residues. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal. Use of dosages other than those indicated may result in residue violations.



1193

NDC 55529-016-05

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Before using this drug, read package insert for complete product information.

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Restricted Drug (California) - Use Only As Directed.

Made in the UK.

Norbrook Laboratories Limited
Newry, BT35 6PU, Co. Down,
Northern Ireland

U.S. Patent No. 6,479,473

REVISION DATE: September 2010



Lot No.:

Exp. Date:

Principal Display Panel – 500 mL Carton

NDC 55529-016-05

Hexasol™ Injection

(oxytetracycline and flunixin meglumine)

300 mg oxytetracycline and 20 mg flunixin per mL

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DRUG (NSAID)

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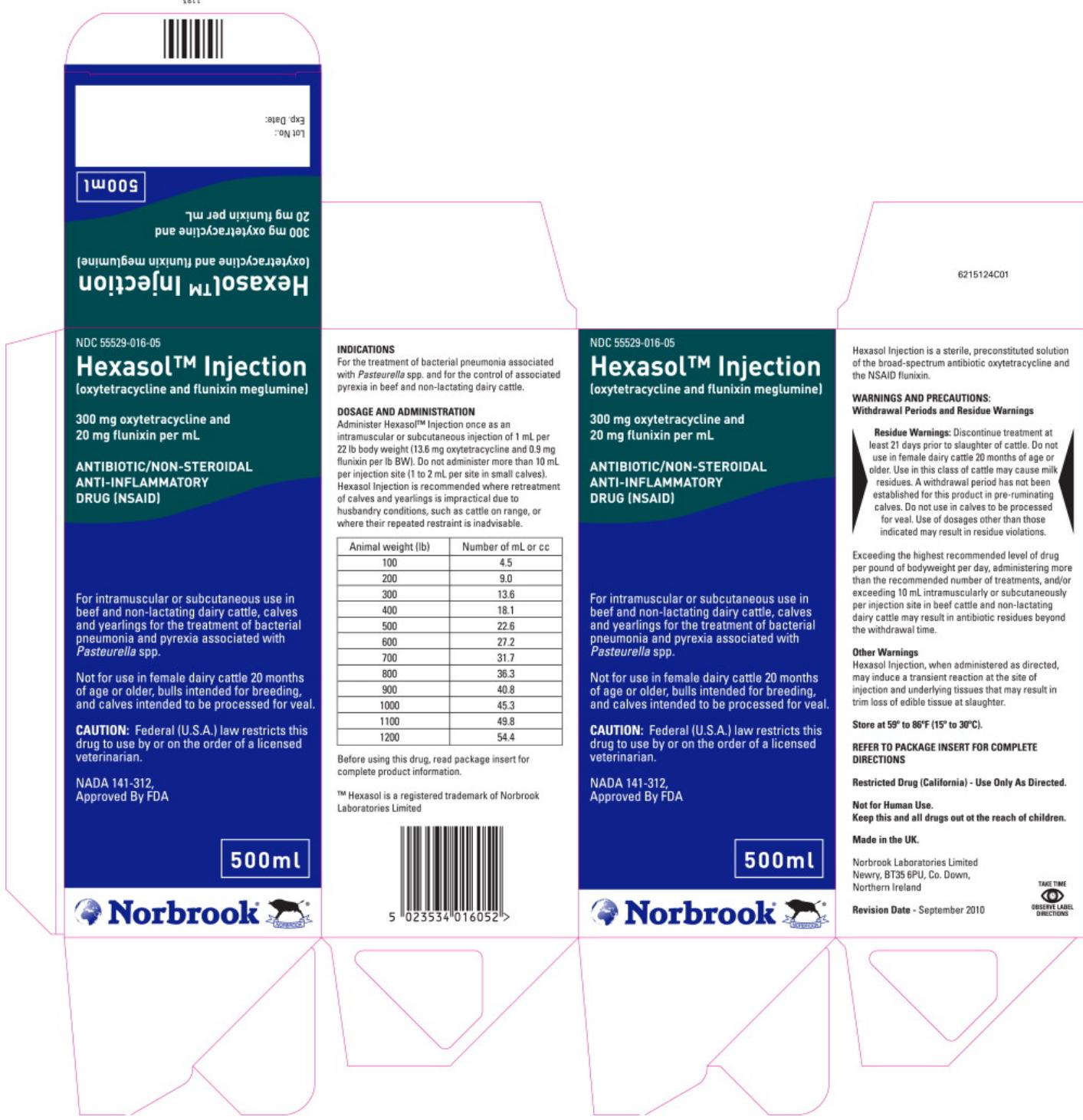
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NADA 141-312, Approved By FDA

500 mL

Norbrook®



HEXASOL

oxytetracycline, flunixin meglumine injection, solution

Product Information

Product Type	PREScription ANIMAL DRUG	Item Code (Source)	NDC:55529-016
Route of Administration	INTRAMUSCULAR, SUBCUTANEOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
oxytetracycline (UNII: X20I9EN955) (oxytetracycline - UNII:X20I9EN955)	oxytetracycline	300 mg in 1 mL
flunixin meglumine (UNII: 8Y3JK0JW3U) (flunixin - UNII:356IB1O400)	flunixin meglumine	20 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
glycerol formal (UNII: 3L7GR2604E)	
polyethylene glycol (UNII: 3WJQ0SDW1A)	
magnesium oxide (UNII: 3A3U0GI71G)	
sodium formaldehyde sulfoxylate (UNII: X4ZGP7K714)	
water (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55529-016-02	1 in 1 CARTON		
1		100 mL in 1 VIAL, GLASS		
2	NDC:55529-016-04	1 in 1 CARTON		
2		250 mL in 1 VIAL, GLASS		
3	NDC:55529-016-05	1 in 1 CARTON		
3		500 mL in 1 VIAL, GLASS		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NADA	NADA141312	11/30/2010	

Labeler - Norbrook Laboratories Limited (214580029)

Establishment

Name	Address	ID/FEI	Business Operations
Armagh Road		232880554	MANUFACTURE, ANALYSIS

Establishment

Name	Address	ID/FEI	Business Operations
Carnbane Industrial Estate		211218325	MANUFACTURE

Revised: 11/2010

Norbrook Laboratories Limited