SUMMARY OF PRODUCT CHARACTERISTIC

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Cephalexin For Oral Suspension USP 125mg/5ml
(Cephalexin For Oral Suspension USP 125mg/5ml)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains:
Cephalexin Monohydrate USP
Eq. to Anhydrous Cephalexin 125 mg

3. PHARMACEUTICAL FORM

Dry Powder for Oral Suspension.
White granular powder filled in white HDPE bottle.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cefalexin is indicated in the treatment of the following infections: Respiratory tract infections; otitis media; skin and soft tissue infections; bone and joint infections; genito-urinary infections, including acute prostatitis and dental infections.

Cefalexin is active against the following organisms in vitro: β-haemolytic streptococci; staphylococci, including coagulase-positive, coagulase-negative and penicillinase-producing strains; Streptococcus pneumoniae; Escherichia coli; Proteus mirabilis; Klebsiella species, Haemophilus influenza; Branhamella catarrhalis.

Most strains of enterococci (Streptococcus faecalis) and a few strains of staphylococci are resistant to cefalexin. Cefalexin is inactive against most strains of enterobacter, morganella morganii, pr. Vulgaris, colstridium difficule, and the following species: legionella, campylobacter, pseudomonas or herellea species. When tested by in vitro methods, staphylococci exhibit cross-resistance between cefalexin and methicillin-type antibiotics.

4.2 Posology and Method of Administration

Posology

Adults:

1-4 g daily in divided doses; most infections will respond to a dosage of 500 mg every 8 hours.

For skin and soft tissue infections, streptococcal pharyngitis and mild, uncomplicated urinary tract infections, the usual dosage is 250 mg every 6 hours, or 500 mg every 12 hours.

More severe infections, or those caused by less susceptible organisms may need larger doses.

If daily doses greater than 4g are required other parenteral cephalosporins, in appropriate doses, should be considered.

Elderly and patients with impaired renal function:

As for adults although dosage should be reduced to a daily maximum of 500mg if renal function is severely impaired (glomerular filtration rate < 10ml/min).

Children

The recommended daily dosage for children is 25-50 mg/kg (10-20mg/lb) in divided doses.

For skin, soft tissue infections, streptococcal pharyngitis and mild, uncomplicated urinary tract infections, the total daily dose may be divided and administered every 12 hours.

For most infections, the following is suggested:

Children under 5 years : 125mg every 8 hours

Children 5 years and over: : 250 mg every 8 hours.

In severe infections, the dosage may be doubled.

In the therapy of otitis media, clinical studies have shown that a dosage of

75-100 mg/kg/day in 4 divided doses is required.

In the treatment of β-haemolytic streptococcal infections, a therapeutic dose

should be administered for at least 10 days.

Route of administration

Oral

4.3 Contra-indications

Cephalexin is contra-indicated in patients with known allergy to the cephalosporin group of antibiotics.
Cephalexin should be given cautiously to patients who have show hypersensitivity to other drugs. Cephalosporins should be given with caution to penicillin-sensitive patients, as there is some evidence of partial crossallergenicity between the penicillins and the cephalosporins. Patients have had severe reactions (including anaphylaxis) to both drugs.
Cephalexin is contraindicated in patients with acute porphyria.

4.4 Special Warnings and Special Precautions for Use

Before instituting therapy with cephalexin, every effort should be made to determine whether the patient has had previous hypersensitivity reactions to the cephalosporins, penicillins or other drugs. Cephalexin should be given cautiously to penicillin-sensitive patients. There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and cephalosporins. Patients have had severe reactions (including anaphylaxis) to both drugs.

If an allergic reaction to Cephalexin occurs the drug should be discontinued and the patient treated with the appropriate agents. Prolonged use of Cephalexin may result in the over growth of non-susceptible organisms. Careful observation of the patient is essential. If super infection occurs during therapy, appropriate measures should be taken.

Pseudomembranous colitis has been reported with virtually all broad spectrum antibiotics, including macrolides, semisynthetic penicillins and cephalosporins. It is important, therefore, to consider its diagnosis in patients who develop diarrhoea in association with the use of antibiotics.Such colitis may range in severity from mild to life-threatening. Mild cases of

pseudo membranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, appropriate measures should be taken.

Cephalexin should be administered with caution in the presence of markedly impaired renal function. Careful clinical and laboratory studies should be made because safe dosage may be lower than that usually recommended.

Positive direct Coombs' tests have been reported during treatment with cephalosporin antibiotics, In haematological studies, or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side, or in Coombs' testing of new-borns whose mothers have received cephalosporin antibiotics before parturition, it should be recognised that a positive Coombs' test may be due to the drug.

A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions or with copper sulphate test tablets.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

Acute generalized exanthematous pustulosis (AGEP) has been reported in association with cefalexin treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, cefalexin should be withdrawn immediately and an alternative treatment considered. Most of these reactions occurred most likely in the first week during treatment.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Probenecid causes reduced excretion of cefalexin leading to increased plasma concentration. Cephalosporins may have an increased risk of nephrotoxicity in the presence of amphotericin, loop diuretics, aminoglycosides, capreomycin or vancomycin.

In a single study of 12 healthy subjects given single 500mg doses of cefalexin and metformin, plasma metformin Cmax and AUC increased by an average of 34% and 24%, respectively, and metformin renal clearance decreased by an average of 14%. No side-effects were reported in the 12 healthy subjects in this study. No information is available about the interaction of cefalexin and metformin following multiple dose administration. The clinical significance of this study is unclear, particularly as no cases of “lactic acidosis” have been reported in association with concomitant metformin and cefalexin treatment.

Hypokalaemia has been described in patient taking cytotoxic drugs for leukaemia when they were given gentamicin and cephalexin.

4.6 Pregnancy and Lactation

Pregnancy: Although laboratory and clinical studies have shown no evidence of teratogenicity, caution should be exercised when prescribing for the pregnant patient.

Breastfeeding: The excretion of cefalexin in human breast milk increased up to 4 hours following a 500mg dose. The drug reached a maximum level of 4 micrograms/ml then decreased gradually and had disappeared 8 hours after administration. Caution should be exercised when cefalexin is administered to a nursing woman, possible effects to the infant include modification of bowel flora.

4.7 Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable Effects

Gastro-intestinal: Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely. The most frequent side-effect has been diarrhoea. It was very rarely severe enough to warrant cessation of therapy. Dyspepsia and abdominal pain have also occurred.

Hypersensitivity: Allergic reactions have been observed in the form of rash, urticaria, angioedema, and rarely erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. These reactions usually subside upon discontinuation of the drug, although in some cases supportive therapy may be necessary. Anaphylaxis has also been reported.

Haemic and Lymphatic System: Eosinophilia, neutropenia, thrombocytopenia, haemolytic anaemia and positive Coombs' tests have been reported.

Hepatic: As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Skin and subcutaneous tissue disorders:

Not known – Acute generalised exanthematous pustulosis (AGEP)

Other: These have included genital and anal pruritus, genital candidiasis, vaginitis and vaginal discharge, dizziness, fatigue, headache, agitation, confusion, hallucinations, fever, arthralgia, arthritis and joint disorder. Hyperactivity, nervousness, sleep disturbances and hypertonia have also been reported. Reversible interstitial nephritis has been reported rarely and toxic epidermal necrolysis have been observed rarely. Slight elevations of AST and ALT have been observed.

4.9 Overdose

Symptoms of overdosage may include nausea, vomiting, epigastric distress, diarrhoea and haematuria.

In the event of severe overdosage, general supportive care is recommended including close clinical and laboratory monitoring of haematological, renal and hepatic functions and coagulation status until the patient is stable. Forced diuresis, peritoneal dialysis, haemodialysis, or charcoal haemoperfusion have not been established as beneficial for an overdose of cefalexin. It would be extremely unlikely that one of these procedures would be indicated.

Unless 5 – 10 times the normal total daily dose has been ingested, gastro-intestinal decontamination should not be necessary.

There have been reports of haematuria without impairment of renal function in children accidentally ingesting more than 3.5g of cefalexin in a day. Treatment has been supportive (fluids) and no sequelae have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: Antibacterials for systemic use, first-generation cephalosporins,

ATC code: J01DB01.

In-vitro tests demonstrate that the Cephalosporins are bactericidal because of their inhibition of cell-wall synthesis.

Cephalexin is active against the following organisms in vitro:

Beta-haemolytic streptococci

Staphylococci, including coagulase-positive, coagulase-negative and penicillinase-producing strains.

Streptococcus pneumoniae

Escherichia coli

Proteus mirabilis

Klebsiella species

Haemophilus influenzae

Branhamella catarrhalis

Most strains of enterococci (*Streptococcus faecalis*) and a few strains of *staphylococci* are resistant to Cephalexin. It is not active against most strains of *Enterobacter species*, *Morganella morganii* and *Pr. vulgaris.* It has no activity against *Pseudomonas* or *Herellea species* or *Acinetobacter calcoaceticus*. Penicillin-resistant *Steptococcus pneumonia* is usually cross-resistant to beta-lactam antibiotics. When tested by in-vitro methods, staphylococci exhibit cross-resistance between Cephalexin and methicillin-type antibiotics.

5.2 Pharmacokinetic Properties

Absorption

Human pharmacology - Cephalexin is acid stable and may be given without regard to meals.

It is rapidly absorbed after oral administration. Following doses of 250 mg, 500 mg and 1 g, average peak serum levels of approximately 9, 18 and 32 mg/L respectively were obtained at 1 hour. Measurable levels were present 6 hours after administration.

Cephalexin is almost completely absorbed from the gastro-intestinal tract, and 75-100% is rapidly excreted in active form in the urine. Absorption is slightly reduced if the drug is administered with food. The half-life is approximately 60 minutes in patients with normal renal function. Haemodialysis and peritoneal dialysis will remove Cephalexin from the blood.

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Comparative pharmacokinetics of cefadroxil, cefaclor, cephalexin and cephradine in infants and children

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The pharmacokinetics of cefadroxil, cephalexin, cephradine and cefaclor were studied in infants and children. The effects of a cow or infant milk feed upon absorption were also investigated. The serum half-lives of cephalexin and cephradine were similar (about 1 h); the cefaclor half-life was about 0·6 h and cefadroxil about 1·5 h. Because of the slower rate of absorption and elimination, the bioavailability of cefadroxil was about twice that of cefaclor and 75% greater than that of cephradine or cephalexin.

The absorption of cefadroxil and cefaclor was not affected by the ingestion of milk but the peak serum concentrations and AUCs of cephalexin and cephradine were reduced after such a feed.

Vergleichende Pharmakokinetik von vier Oralcephalosporinen bei Säuglingen und Kindern

Bei 137 Säuglingen und Kindern wurde das pharmakokinetische Verhalten von Cefadroxil, Cefaclor, Cephalexin und Cephradin untersucht. Ebenfalls untersucht wurde, wie die Resorption dieser oralen Cephalosporine bei gleichzeitiger Gabe von Milch beeinflußt wird.

Die Serumeliminationshalbwertszeiten von Cephalexin und Cephradin waren ähnlich (ca. 1 Stunde). Die Halbwertszeiten von Cefaclor und Cefadroxil lagen bei 0,6 bzw. 1,5 Stunden. Aufgrund seiner langsameren Elimination war die biologische Verfügbarkeit von Cefadroxil, gemessen an der Fläche unter der Serumspiegelkurve, ungefähr doppelt so groß wie diejenige von Cefaclor und um 75% größer als diejenige von Cephradin bzw. Cephalexin.

Die Aufnahme von Cefadroxil und Cefaclor aus dem Gastrointestinaltrakt wurde bei gleichzeitiger Verabreichung von Milch nicht beeinflußt. Demgegenüber nahmen Serumpeak und Fläche unter der Serumspiegelkurve ab, wenn Cephalexin und Cephradin zusammen mit der Milch gegeben wurden.

At present there are four orally administered cephalosporins – cefadroxil, cephalexin, cefaclor and cephradine – approved and marketed for use in infants and children. The spectrum of antibacterial activity of cefadroxil, cephalexin and cephradine are similar. Cefaclor is more active than the others against both β-lactamase positive and negative strains of *Haemophilus influenzae* and certain strains of Gram-negative enteric bacilli (Bill & Washington, 1977).

Since these agents have potential usefulness for the treatment of a variety of infectious conditions in infants and young children, this study was undertaken to determine the pharmacokinetic properties of these antimicrobials in paediatric patients. Additionally, the studies were designed to evaluate the effect of concomitant drug and milk ingestion on bioavailability.

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0305-7453/82/10B027+05 $03.00/0

Materials and methods

The studies were conducted in the outpatient clinic of Children's Medical Center, Dallas, Texas. Infants and children with impetigo, pharyngitis, urinary-tract infections and otitis media (receiving only cefaclor) were eligible for study. The decision to initiate antimicrobial therapy was made independent of the investigators. The parents of each patient were informed of the nature of the study and written parental consent was obtained prior to starting.

Cefadroxil monohydrate, cefaclor and cephradine Most children were studied twice: once while fasting and once when the antibiotic was given with 4 ounces of cow's or powdered milk. All the patients were at least 2 months old. Blood samples were obtained at 0·5, 1, 2, 4 and 6 h after the dose through a heparinised wing-tip needle inserted into a peripheral vein.

The concentrations of the various drugs in serum and urine were assayed by an agar-disk diffusion micromethod (Simon & Yin, 1970) using *Sarcina lutea* (ATCC 9341) as the test organism. The samples and standards were diluted identically either in pooled serum, for measurement of serum concentrations, or in 10% pooled serum-phosphate-buffered saline (pH 6·0) for urine samples.

Regression line analysis of the log serum concentrations of the drugs against time was calculated by the method of least mean squares. The serum half-life was calculated. The area under the serum-concentration/time curve (AUC), expressed as milligrams per litre per hour was determined by the trapezoidal method (Ritschel, 1976).

Data were analysed by using the Student *t* test and Bartlett's test for equal variance. (Zar, 1974). When significant differences were found, the two tests were compared using the Mann–Whitney U-test (Zar, 1974). Differences in values were considered significant if the *P* value was less than 0·05.

Cefadroxil. Seventeen children, 13 months to 11 years of age (mean age, 4·9 years), were studied. After ingestion of 15 mg/kg doses of cefadroxil suspension, mean peak serum levels 13·7 and 11·0 mg/l were obtained at 1 h in fasting and non-fasting children, respectively. The serum concentrations at 2, 4 and 6 h were not substantially affected by co-administration of milk or infant feed. All children had measurable antimicrobial activity 6 h after the dose; the concentrations ranged from 0·28 to 2·6 mg/l. Mean serum half-life times ranged from 1·3 to 1·5 hours and AUC values were 41 and 39 mg/l.h in fasting and non-fasting patients, respectively.

Twenty-eight other children, 4 years, 6 months to 13 years of age (mean age, 7·5 years) received cefadroxil in suspension or capsule form. Fifteen children received capsules in dosages that ranged from 12 to 18·9 mg/kg (mean 14·1 mg/kg) and 13 subjects were administered cefadroxil suspension in a dose of 15 mg/kg. Although there was no significant difference in the peak serum concentrations between the two study groups, there were significant differences in the serum values between the two groups at $\frac{1}{2}$, 4 and 6 h, irrespective of whether they had been fed. Children who received cefadroxil in suspension form had higher serum concentrations at $\frac{1}{2}$ h, whereas those given capsules had higher values at 4 and 6 h after ingestion. This is most likely the result of delayed gastrointestinal absorption of drug when ingested in capsular form.

		No. of patients studied	Dose (mg/kg)	Concentrations of drug in serum (mg/l) at time (h) after dose					Serum half-life (min)	Area under the curve (mg/l. h)
				0·5	1	2	4	6		
Cephradine	Fasting	15	15	21·3	12·6	4·8	0·79	0·15	48	29
	Fed	16	15	9·9	9·4	5·6	1·2	0·31	60	23
Cefaclor	Fasting	10	15	13·1	11·5	3·8	0·4	0·6	36	20
	Fed	14	15	10·9	7·5	3·6	0·7	0·2	46	18
Cefadroxil										
(a) Suspension	Fasting	16	15	11·0	13·7	10·5	3·0	1·1	80	41
	Fed	17	15	7·4	11·0	10·7	3·4	1·2	90	39
(b) Capsules	Fasting	14	12–18	2·3	12·2	12·4	5·2	1·6	84	44
	Fed	15	12–18	1·5	7·8	11·6	5·5	2·3	102	43

Cefaclor. Fourteen children, 4 months to 4 years of age (mean age, 18·6 months), received 15 mg/kg doses of cefaclor monohydrate suspension. Mean peak concentrations of 13·1 and 10·9 mg/l occurred in serum at 30 min in fasting and non-fasting children, respectively. The average concentrations 6 h after the dose were 0·6 mg/l in fasting patients and 0·2 mg/l in those who received drug and milk concomitantly. The serum half-lives and AUCs were not significantly different between fasting and non-fasting children.

Cephradine. Sixteen children, 13 months to 8 years 3 months (mean age 3·5 years), received 15 mg/kg doses of cephradine suspension. Mean peak serum concentrations of 21·3 and 9·9 mg/l were attained at 0·5 h in fasting and non-fasting children, respectively. The difference between these values is statistically significant. There were no significant differences in the serum concentrations at 1 and 2 h after the dose for fasting and non-fasting patients. However, the serum concentrations were significantly higher at 4 and 6 h in children who received drug and milk concomitantly. Serum half-life values were similar in the two study groups; however, the mean AUC was 26% (29 mg/l . h) larger in fasting than non-fasting patients (23 mg/l . h).

Concentrations in urine

Urine samples were obtained randomly from all patients during the 6 h study periods. Twenty-six other patients received a single 30 mg/kg dose of cefadroxil as part of a therapeutic efficacy study. The concentrations of the various drugs in urine are shown in Table II. Each of the four drugs was present in high concentrations in urine during the 6 h study interval (Table II). Between 4 and 6 h after the dose the mean concentrations of cephradine (1177 mg/l) and cephalexin (1217 mg/l) were similar while that of cefaclor

Table II. Urinary concentrations of four oral cephalosporins

Drug	Dose (mg/kg)	Concentrations of drug in urine (mg/l) at time (h) after dose				
		0–2	2–4	4–6	6–12	12–24
Cefaclor	15	1870 (815–5280)	720 (310–1312)	540 (56–860)	341 (0–1860)	—
Cefadroxil	15	1700 (765–2225)	2620 (424–8000)	1840 (750–2930)	2303* (110–4600)	149* (1·6–670)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	—	—
Cephradine	15	2420 (1000–4810)	3933 (460–8760)	1177 (28–3720)	—	—

* After 30 mg/kg doses.
( ) Range of values.

was approximately one-half of the latter two drugs. By contrast, the mean concentration of cefadroxil was more than threefold larger than that of cefaclor. At 24 h following the dose all but one patient had measurable concentrations of drug in their urine; concentrations ranged from 0 to 68 mg/l (mean, 16 mg/l). Cefadroxil was detectable in 11 of 13 (85%) of urine samples that were obtained at 24 h following ingestion of a 30 mg/kg dose.

Discussion

The results of these pharmacokinetic studies indicate that cefadroxil and cefaclor, the newest of the oral cephalosporins, have different pharmacokinetic properties than their predecessors, cephalexin and cephradine. Each of the four drugs is rapidly absorbed after oral administration; however, cefadroxil and cefaclor are not significantly affected by the concomitant ingestion of milk and infant feed. Co-administration of milk with cephalexin or cephradine substantially reduces the peak serum concentrations and area under the curve values. The half-life of cefaclor in serum is similar to that of cephalexin and cephradine; the half-life of cefadroxil is 50 to 90% longer than that for the other three drugs. Because of its slower absorption from the gastrointestinal tract, the bioavailability of cefadroxil is approximately twice that of cefaclor and as great as 75% or larger than that for cephalexin and cephradine.

All of the oral cephalosporins are excreted in the urine in concentations that greatly exceed the minimal inhibitory and bactericidal concentrations for most urinary pathogens. Because of its prolonged half-life, cefadroxil persists in urine for many hours after administration. Twenty-five of 26 patients who received 30 mg/kg doses of cefadroxil had measurable concentrations of drug in their urine at 24 h after the dose.

References

Bill, N. J. & Washington, J. A. (1977). Comparison of *in-vitro* activity of cephalexin, cephradine and cefaclor. *Antimicrobial Agents and Chemotherapy* **11**, 470–4.

Simon, H. J. & Yin, E. J. (1970). Microbioassay of antimicrobial agents. *Applied Microbiology* **19**, 573–9.

Ritschel, W. A. (1976). *Handbook of Basic Pharmacokinetics*, pp. 235–43. Drug Intelligence Publications, Inc. Hamilton, 111.

Zar, G. (1974). *Biostatistical Statistical Analysis.* Prentice Hall, Englewood Cliffs, N.J.

Distribution

Peak blood levels are achieved one hour after administration, and therapeutic levels are maintained for 6-8 hours. Approximately 80% of the active drug is excreted in the urine within 6 hours. No accumulation is seen with dosages above the therapeutic maximum of 4 g/day.

The half-Life may be increased in neonates due to their renal immaturity, but there is no accumulation when given at up to 50 mg/kg/day.

Elimination

Cephalexin is excreted in the urine by glomerular filtration and tubular secretion. Studies showed that over 90% of the drug was excreted unchanged in the urine within 8 hours. During this period peak urine concentrations following the 250 mg, 500 mg and 1g doses were approximately 1000, 2200 and 5000 mg/l respectively.

5.3 Preclinical Safety Data

The daily oral administration of Cephalexin to rats in doses of 250 or 500 mg/kg prior to and during pregnancy, or to rats and mice during the period of organogenesis only, had no adverse effect on fertility, foetal viability, foetal weight, or litter size.

Cephalexin showed no enhanced toxicity in weanling and newborn rats as compared with adult animals. The oral LD50 of Cephalexin in rats is 5,000 mg/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Xanthan Gum	USP
Sodium Benzoate	USP
Aerosil	USP
Colour Sunset Yellow FCF	IH
Flavour Strawberry	IH
Pharma Grade Sugar	USP

6.2 Incompatibilities

None Known

6.3 Shelf Life

36 Months

6.4 Special Precautions for Storage

Store protected from light at a temperature not exceeding 30°C.

6.5 Nature and Contents of Container

100ml glass bottle packed in a unit carton along with leaflet.

6.6 Special precautions for disposal

Reconstitution

Cephalexin For Oral Suspension USP 125 mg/5 mL has to be reconstituted by the addition of water and shaking until all the granules have dispersed. The reconstituted syrup/mixture can be kept for 14 days below 25° C. Any unused syrup/mixture should be discarded.

7. MARKETING AUTHORISATION HOLDER

Scott-Edil Advance Research Laboratories & Education Limited.
Hill Top Ind. Area, Bhatoli Kalan,
Baddi-173205, Himachal Pradesh, INDIA

8. MARKETING AUTHORISATION NUMBER

07080/08326/NMR/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Feb 4, 2022

10. DATE OF REVISION OF THE TEXT

Not Applicable