*Dedicated to*

*My deepest gratitude goes to my family who has provided me support throughout my whole life and guided me to reach my objective of life.*

*Thanks Mom & Dad.*

Supervisor: Zakiur Ruhman


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Content: Page No

1. Drug

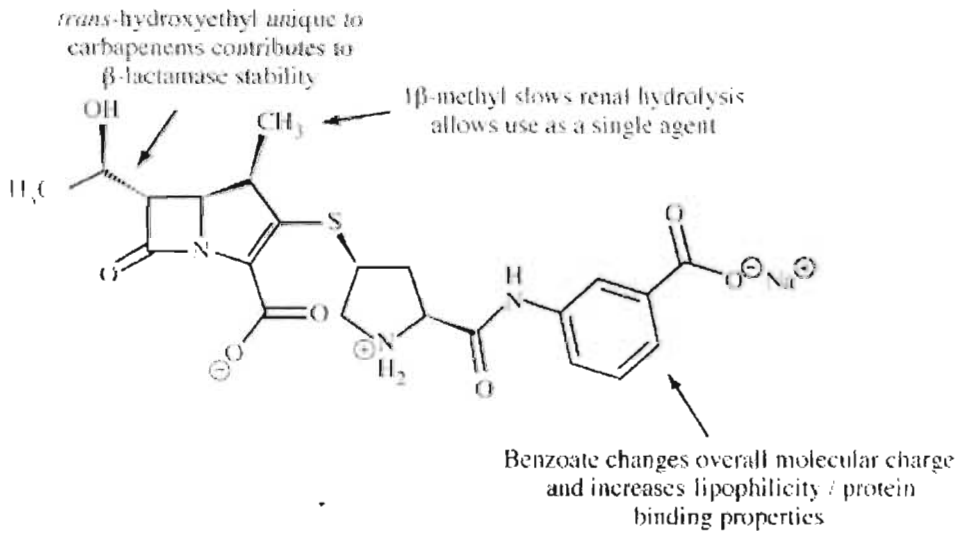
Abstract:

Ertapenem is a sterile, synthetic, parenteral, 1-β methyl-carbapenem that is structurally related to beta-lactam antibiotics. Ertapenem, a Group 1 carbapenem, is most recently introduced into the market and cover both Gram positive and Gram negative pathogens. Here the objective is to find the characteristics of ertapenem in the treatment of complicated infectious diseases and establish demonstrated safety profile and clinical efficacy of ertapenem against complicated diseases. This report is fully based on secondary data which I have collected from many journals, IMS, MIMS, browsing different web sites. From this research it was found that ertapenem shows excellent success in complicated infectious diseases. By doing market strategy regarding IMS data it is assume that if it is launched in the market the total market size will be 31,087,084 within 1-2 years which makes the drug feasible in the market.

# 1. Drug:

## 1.1. Ertapenem description:

Ertapenem is carbapenem compound drug that is recently introduced in the world market. Ertapenem is structurally related to beta-lactam antibiotics. The coverage of ertapenem is its main advantage; it can cover both Gram-positive and Gram-negative aerobic and anaerobic pathogens (Milton L. Hammond, 2004).




The antibacterial efficacy of ertapenem against ß-lactamase-producing organisms are due to the trans-1-hydroxyethyl group in the structure of ertapenem. There is 1ß-methyl substituent in the ertapenem structure which defend the ß-lactam carbonyl group also to reduce dehydropeptidase (DHP)-1 and hydrolysis of ß-lactam, resulting ertapenem to be administered with out a DHP-1 inhibitor.

The molecular weight of the molecule and lipophilicity of the molecule increases through a benzoic acid substituent present at the meta position in the molecule. Ertapenem have a net negative charge due to carboxylic acid moiety, ionized at physiological pH. For this reason, ertapenem is highly protein bound, having extended half life and once daily dosing system.

## 1.2. General information about ertapenem:

U.S Brand Name: Invanz (www.invanz.com).

Pharmacologic category: Antibiotic, Carbapenem (Williams JM, Brands KM, 2005).

Qualitative and quantitative composition: Each vial contains 1.0 g ertapenem equivalent to 1.046 g ertapenem sodium (www.merck.com).

## 1.3. Posology and method of administration:

Adults: The dose of ertapenem is 1 gram (g) given once a day by intravenous route (www.merck.com).

Prophylaxis of surgical site: To prevent surgical site infections, the recommended dosage is 1 g administered as a single intravenous dose (Itani KM, Jensen EH, 2008).

For children: The dose of ertapenem is 15 mg/kg given twice daily patient with 3 months to 12 years of age. (www.medscape.com).

Renal insufficiency: Ertapenem may be used in the treatment of infections in adult patient with renal insufficiency. Dose adjustment may be required for the patients with renal insufficiency (Nix DE, Majumdar AK, 2004).

Administration: Should be infused over a period of 30 minutes. The usual duration of therapy is 3 to 14 days. (www.merck.com).

## 1.4. Pharmacology:

Ertapenem is highly protein bound drug with long half life of 4 hours (Hammond ML, 2004).Ertapenem is excreted (80%) by the kidneys. Ertapenem has in vitro activity against gram-positive and gram-negative aerobic and anaerobic bacteria. Liver is the most predominant organ for metabolism. Ertapenem doses not inhibit the metabolism followed by cytochrome p450 and its isoforms such as 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (www.thedrugmonitor.com).

## 1.5. Mechanism of action:

Ertapenem show its bactericidal activity by the inhibition of cell wall synthesis. Thus ertapenem works against wide range of pathogens. Mechanism of action of ertapenem is similar to penicillin. It is stable to hydrolysis by β-lactamases (www.mims.com). Ertapenem is 1-(beta) methyl-carbapenem that inhibits formation of bacterial cell wall synthesis and causing cell death.

## 1.6. Interaction with other medicinal products:

Ertapenem is advised not to give with probenecid. Because it decrease the renal clearance of ertapenem about 50% (www.oxfordjournals.org). Inhibition of the renal tubular secretion results when ertapenem is given along with probenecid. Probenecid has an effect of ertapenem half life that arise the elimination half life of ertapenem from4.0 hr-4.8 hr and also affect the AUC of ertapenem.

Co-administration of ertapenem with valproic acid is prohibited (Lunde JL, Nelson RE, 2007). Because ertapenem can decrease the serum levels of valproic acid. If ertapenem is co- administered with valproic acid serum level of valproic acid should be monitored.

## 1.7. Ertapenem incase of pregnancy:

Use of ertapenem in case of pregnancy, no well established & adequate data have not been found. Animal studies do not show any harmful effect to pregnant women rather than slightly decreased fetal weights in mice. There is no established data regarding teratogenic effects and fetal harm in animal studies (www.datasheet.com).

## 1.8. Missed dose &Overdose:

In case of missed dose take the dose immediately as remember. If it is almost time for the next dose then take the regular dose in that case. In case of missed dose don't double the dose or not to take extra medicine to cope up the missed dose (www.webmd.com).

## 1.9. Warnings, contraindication and cautions:

In case of ertapenem intramuscular preparation lidocaine is used. Here lidocaine is used as a diluent. Patient's who have hypersensitivity to local anesthetics of the amide type intramuscular administration is contraindicated (Legua P, Lema J, 2002).

Ertapenem is contraindicated to the patients having hypersensitivity to this product or other drugs in the same class (Meropenem, Imipenem, Doripenem).Also contraindicated to the patient having anaphylactic reactions to beta lactam (www.drugs.com).

Ertapenem shows some short of central nervous system side effect (Merck & Co).

Pregnancy Category B. No adequate and well established data not published yet (www.Rxlist.com).

If ertapenem is used for a long duration it may cause overgrowth of non-susceptible organisms (www.merckservices.com).

Sufficient care should be taken when administering ertapenem IM (intramuscular) in order to prevent inadvertent injection into a blood vessel. As it is used to treat complicated infectious diseases so patient should be regularly monitored after ertapenem therapy.

## 1.10. Safety profile of ertapenem:

Ertapenem is a carbapenem compound drug that can cover both Gram positive and Gram negative pathogen with simple dosing system. In a Phase I clinical pharmacology study of ertapenem 41 volunteers received one or more doses of <1 g, another 149 volunteers received one or more doses of 1 g, six volunteers received a single 1.5 g dose, 62 volunteers received one or more doses of 2 g and finally 29 volunteers received one or more doses of 3g (Hedy T, Richard M. Gesser, 2004).

No serious adverse reaction or effects were observed in this clinical trail. Most common side effects were nausea, vomiting, skin rash and headache.

After that phase II and Phase III trials were performed. In this clinical trail 1954 patients received one or more doses of ertapenem 1g, 62 patients received one or more doses of ertapenem 1.5g, 30 patients received one or more doses of ertapenem 2 g, 774 patients received one or more doses of piperacillin–tazobactam 3.375 g and 942 patients received one or more doses of ceftriaxone 1 or 2 g. NO serious side effects were observed in this clinical trail. The side effect in the patient's who received 1.5 or 2g of ertapenem were similar to those who received 1 g of ertapenem.

## 1.11. How to take Ertapenem:

Ertapenem is a broad spectrum antibiotic that is used to treat complicated infectious diseases. In case of intramuscular preparation it is given in to muscle and intravenous preparation given into vein as injection. Doctor, nurse or other health care professional will give this injection only. When ertapenem given into IV, ertapenem must be given slowly and take at least 30 min to complete. As it is broad spectrum antibiotic and used to treat only complicated infectious diseases, so use this medicine after prescribed by the doctor (www.drugs.com).

## 1.12. Pharmacokinetic profile of ertapenem:

### Metabolism:

Liver is the most predominant organ for metabolism. Most of the drugs are metabolize in the liver. Ertapenem does not inhibit drug metabolism by cytochrome P450 and its isoforms 1A2, 2C9, 2C19, 2D6, 2E1, or 3A4 (Nix DE, Majumdar AK, 2004).

### Absorption:

Lidocaine is used to prepare intramuscular preparation of ertapenem. Ertapenem with 1% lidocaine is completely absorbed and ready for therapy. Upon 1g daily intramuscular therapy the mean peak plasma concentration ($C_{max}$) is gain within 2.3 hours ($T_{max}$). Ertapenem may inhibit the absorption of valproic acid from the gastrointestinal tract. So it is advisable not to give ertapenem with valproic acid (www.thedrugmonitor.com).

### Distribution:

Ertapenem is highly bound to human plasma proteins. (Donald G. Musson, Kimberly L. Birk, 2003). Ertapenem is 95% bound to plasma concentration. Average plasma concentration of ertapenem upon 1g doses administration in IV & IM is presented in the table no 1.

Table no.1 Average Plasma Concentrations (mcg/mL)

| Dose/Route | 0.5 hr | 1hr | 2hr | 4hr | 6hr | 8 hr | 12 hr | 18 hr | 24 hr |
|---|---|---|---|---|---|---|---|---|---|
| 1 g IV | 155 | 115 | 83 | 48 | 31 | 20 | 9 | 3 | 1 |
| 1 g IM | 33 | 53 | 67 | 57 | 40 | 27 | 13 | 4 | 2 |

In table 1 plasma concentration of ertapenem in IV & IM upon a single dose administration. Plasma concentration varies on IV & IM administration in different time.

Average plasma concentrations (mcg/mL) of ertapenem in pediatric patients are presented in table no.2

Table no.2 Average Plasma Concentrations (mcg/mL)

| Age | Dose | 0.5h | 1h | 2h | 4h | 6h | 8h | 12h | 24h |
|---|---|---|---|---|---|---|---|---|---|
| **3 to 23 months** | 15 mg/kg | 103.8 | 57.3 | 43.6 | 23.7 | 13.5 | 8.2 | 2.5 | - |
| | 20 mg/kg | 126.8 | 8706 | 58.7 | 28.4 | - | 12 | 3.4 | 0.4 |
| | 40 mg/kg | 199.1 | 144.1 | 95.7 | 58.0 | - | 20.2 | 7.7 | 0.6 |
| **2 to 12 years** | 15 mg/kg | 113.2 | 63.9 | 42.1 | 21.9 | 12.8 | 7.6 | 3.0 | - |
| | 20 mg/kg | 147.6 | 97.6 | 63.2 | 34.5 | - | 12.3 | 4.9 | 0.5 |
| | 40 mg/kg | 214.7 | 152.7 | 96.3 | 55.6 | - | 18.8 | 7.2 | 0.6 |

Here ertapenem is given over 30 min infusion. Dose of ertapenem is 1g once daily. Plasma concentration varies in different time. The volume of distribution of ertapenem in adults is 8 liters (0.11 liter/kg) and 0.2 liter/kg in pediatric patients (www.datasheet.com).

## Elimination:

Kidney, milk, feces are the major route of elimination of drugs. Ertapenem is eliminated primarily via kidney (Wong BK, Sahly Y, 2004). In a clinical trail it was found that upon 1g ertapenem IV administration 80% of the drug eliminated via kidney and 10% via feces and the plasma half life is about 4hours & plasma clearance is 1.8 liter/hr (www.drugmonitor.com).

Estimation of free drug concentration:

$$Cb = n1\ p1k1Cf / 1 + k1Cf + n2\ p2k2Cf$$

Where Cb is the bound concentration, Cf is the concentration of free ertapenem, n1 and n2 are the number of binding sites, p1 and p2 are the concentrations of albumin and k1, K2 are the rate constant for specific and non-specific binding site (Olaf B, Carsten H, 2008).

The free, bound and total (Ct) drug concentrations are expressed as,

$$Ct = Cf + Cb$$

Molecular Weight: 445.45 CAS (www.chinamarket.com).

Experimental Water Solubility: Soluble as sodium salt

Shelf life: 2 years

Special precautions for storage: Do not store above 25°C. Do not freeze solutions of ertapenem

## 1.13. Undesirable effects:

Ertapenem has some Undesirable effects that were found in several clinical trails. In a clinical trail 1954 patients were treated with ertapenem. Most common side effects observed by the patients were nausea, vomiting, infused vein complication, and headache (www.rxlist.com).

Table no.3 Undesirable effects of ertapenem

| | Adverse Events | Ertapenem 1g once daily | Piperacillin/ Tazobactam 3.375gq6h | Ertapenem 1g once daily | Ceftriaxone 1or2 g daily |
|---|---|---|---|---|---|
| Local | Phlebitis | 1.9 | 2.7 | 1.6. | 2.0 |
| | Vein complication | 7.1 | 7.9 | 5.4 | 6.7 |
| Systemic | Fever | 5.0 | 6.6 | 2.3 | 3.4 |
| | Abdominal pain | 3.6 | 4.8 | 4.3 | 3.9 |
| | Oral candidiasis | 0.1 | 1.3 | 1.4 | 1.9 |
| | Nausea | 8.5 | 8.7 | 6.4 | 7.4 |
| | Headache | 5.6 | 5.4 | 6.8 | 6.9 |
| | Erythema | 1.6 | 1.7 | 1.2 | 1.2 |
| | Rash | 2.5 | 3.1 | 2.3 | 1.5 |
| | Pharyngitis | 0.7 | 1.4 | 1.1 | 0.6 |
| | Vomiting | 3.7 | 5.3 | 4.0 | 4.0 |
| | Constipation | 4.0 | 5.4 | 3.3 | 3.1 |
| | Diarrhea | 10.3 | 12.1 | 9.2 | 9.8 |
| | Fever | 5.0 | 6.6 | 2.3 | 3.4 |
| | Hypertension | 1.6 | 1.4 | 0.7 | 1.0 |
| | Hypotension | 2.0 | 1.4 | 1.0 | 1.2 |

Table 3 indicates the local and systemic side effects of ertapenem along with piperacillin/ tazobactam and ceftriaxone. To treat complicated infectious disease ertapenem dosing is 1g once and piperacillin/ tazobactam 3.375g 4 times a day. Here ertapenem shows less side effect than piperacillin/ tazobactam and also shows similar side effect with ceftriaxone 1or2 g daily.

## 1.14. Microbiological Susceptibility of ertapenem:

Table no. 4 Microbiological Susceptibility of ertapenem

| | |
|---|---|
| **Aerobic and facultative gram-positive microorganisms:** | *Staphylococcus aureus* (methicillin susceptible isolates only)<br>*Streptococcus agalactiae*<br>*Streptococcus pneumoniae* (penicillin susceptible isolates only)<br>*Streptococcus pyogenes* |
| **Aerobic and facultative gram-negative microorganisms:** | *Escherichia coli*<br>*Haemophilus influenzae (Beta-lactamase negative isolates only)*<br>*Klebsiella pneumoniae*<br>*Moraxella catarrhalis*<br>*Proteus mirabilis* |
| **Anaerobic microorganisms:** | *Bacteroides fragilis*<br>*Bacteroides distasonis*<br>*Bacteroides ovatus*<br>*Bacteroides thetaiotaomicron*<br>*Bacteroides uniformis*<br>*Clostridium clostridioforme*<br>*Eubacterium lentum*<br>*Peptostreptococcus species*<br>*Porphyromonas asaccharolytica* |
| **Aerobic and facultative gram-positive microorganisms: Microorganisms exhibit an in *vitro* minimum inhibitory concentration** | *Staphylococcus epidermidis* (methicillin susceptible isolates only)<br>*Streptococcus pneumoniae* (penicillin-intermediate isolates only) |
| **Aerobic and facultative gram-negative microorganisms:** | *Citrobacter freundii*<br>*Citrobacter koseri*<br>*Enterobacter aerogenes*<br>*Enterobacter cloacae*<br>*Haemophilus influenzae (Beta-lactamase positive isolates)*<br>*Haemophilus parainfluenzae* |
| **Anaerobic microorganisms:** | *Bacteroides vulgatus*<br>*Clostridium perfringens*<br>*Fusobacterium* spp. |

By observing table no 4, it can easily understandable that ertapenem can cover both Gram positive and Gram negative pathogens along with others.

## 1.15. Ertapenem better than other drugs:

In the structure of ertapenem there are some beneficial features that's why ertapenem is better than other carbapenems and also differs from other drugs belongs in the same class (imipenem, meropenem). In the ertapenem structure there is a benzoic acid substituent present at the meta position in the molecule (Milton L, 2004).This substituent plays a vital role for showing better pharmacological and antibacterial activity of ertapenem. The aromatic ring increases the molecular weight, lipophilicity of the molecule, carboxylic acid moiety and ionized at physiological PH. These make the compound highly plasma protein bound. For example ertapenem is 95% plasma protein bound and imipenem is bound to human serum proteins only 20%. This highly protein binding capacity of ertapenem decrease the rate of free or unbound drug and extend plasma half life. A limiting feature of imipenem that it is rapidly hydrolysis by the enzyme dehydropeptidase. the solution of this problem is its combination with Cilastatin a reversible inhibitor of dehydropeptidase and protects imipenem.

## 1.16. Preparation of ertapenem solution:

### Adults and pediatric patients (13 years of age and older):

### Intravenous administration:

1. Not to mix the ertapenem with other drugs (MERCK & CO, 2003-2007).
2. Use of diluent containing dextrose is prohibited.
3. 1g ertapenem reconstitute with either 10 ml of water for injection, 0.9% Sodium Chloride Injection or Bacteriostatic water for Injection. Then shake well to dissolve and immediately transfer contents of the reconstituted vial to 50 mL of 0.9% Sodium Chloride Injection.
4. Finally complete the infusion within 6 hours of reconstitution.

### Intramuscular administration:

1. 1g vial of ertapenem is reconstituted with 3.2 mL of 1.0% lidocaine HCl injection.
2. Shake vial to form solution.
3. IM solution should be used within 1 hour after preparation.

## Pediatric patients (3 months to 12 years of age):

### Intravenous administration:

1. Not to mix the ertapenem with other drugs (MERCK & CO, 2003-2007)
2. Use of diluent containing dextrose is prohibited.
3. 1g ertapenem reconstitute with either 10 ml of water for injection, 0.9% Sodium Chloride Injection or Bacteriostatic water for Injection.
4. Shake well to dissolve.
5. Based upon 15 mg/kg body weight, withdraw the medicine. Have to consider that volume of the medicine is equal to 15mg /kg and dilute in 0.9% sodium chloride injection to a final concentration of 20 mg or less.
6. Dose must not to exceed 1g /day.

### Intramuscular administration:

1. 1g vial of ertapenem is reconstituted with 3.2 mL of 1.0% lidocaine HCl injection.
2. Based upon 15 mg/kg body weight, withdraw the medicine. Have to consider that volume of the medicine is equal to 15mg /kg and administer to a large muscle mass.

## 1.17 Literature review:

*18.6%*
*Of all deaths*
*Are due to*
*Infectious*
*Diseases*

..... *Ertobex the final solution*

*Rx*

*Ertobex*
*(Ertapenem IV injection)*
*Excellent antibacterial coverage*

## What is Ertobex?

- Preparation of ertapenem(broad spectrum carbapenem antibiotic)
- Available as powder for iv injection or infusion (www.invanz.com)
- 1gm packaging are available
- Commercial box with
  - < Disposable syringe & WFI for compliance
  - < Butterfly needle for convenience

## Very high affinity for penicillin binding proteins

Ertobex (ertapenem) is a highly protein bound drug (Donald G. Musson, Kimberly L. Birk, 2003). Unlike penicillin and cephalosporins, ertapenem binds with the highest affinity for the penicillin-binding proteins resulting lysis of bacterial cell wall.

## Excellent pharmacokinetic profile

- Excellent rate of absorption ( www.thedrugmonitor.com)
- No tendency to accumulate in the body (Wong BK, Sahly Y, 2004)
- Rapid distribution through out the body (Donald G. Musson, Kimberly L. Birk, 2003)
- Good half life (www.invanz.com)

## Favorable safety profile

- less likely cause inflammation at IV site
- pregnancy category B no infant harm has been found

- excellent efficacy in adult patient
- Effective across a broad range of pathogens, disease severities, and patient types
- An important advance because of the excellent efficacy, antimicrobial spectrum, tolerability, and once-daily dosing (www.invanz.com)

## Effective solution for complex infection

- Complicated diabetic foot infection (Chow I, Lemos EV, Einarson TR, 2008)
- Complicated intra-abdominal infection (DiNubile MJ, Friedland IR, 2007)
- Complicated skin/skin structure infection (Gesser RM, McCarroll KA,2004)
- Community-acquired pneumonia (Guillermo Or, Norbert Ve, 2004)
- Complicated urinary tract infection (Wells WG, Woods GL, 2004)
- Acute pelvic infection (Roy S, Higareda I, 2003)

## The versatile antimicrobial agent

Ertobex has coverage against most of the common organisms. It cover both gram+ve and gram-ve organisms including both aerobes and anaerobes.

## When better then meropenem

- 2-4 times more susceptible to most of the staphylococcus aureus, streptococcuc pyogenes.
- More effective against strains of strep.pneumoniae
- Meropenem resistance to pseudomonas aeruginosa strains.
- No need to combine with Cilastatin.

## Used in case of pregnancy

Ertobex has pregnancy category B. Shows no fetal damage in studies.

## Excellent clinical success rate in complicated infectious disease

Ertobex shows excellent clinical efficacy and safety profile in the treatment of complicated infectious diseases. Ertapenem shows high success rate in the treatment of complicated diseases and assumed to be the final solution for all complicated infectious diseases.

# 2. Indication:

Ertapenem is used to treat complicated infectious diseases. For example-

Complicated diabetic foot infection (Chow I, Lemos EV, Einarson TR, 2008).

Complicated intra-abdominal infection (DiNubile MJ, Friedland IR, 2007).

Complicated skin/skin structure infection (Gesser RM, McCarroll KA,2004).

Community-acquired pneumonia (Guillermo Or, Norbert Ve, 2004).

Complicated urinary tract infection (Wells WG, Woods GL, 2004).

Acute pelvic infection (Roy S, Higareda I, 2003).

Disease which is not treated for a long time can be turned to complicated form and that short of disease is called complicated disease. It is called complicated due to containing intricately combined or involved parts, not easy to understand or analyze, associated with other injuries, lesions, or diseases (www.medicaldictionary.com). Ertapenem which is a broad spectrum antibiotic that is used to treat complicated infectious diseases and shows good clinical efficacy and tolerability profile.

# 3. Objective:

The objective of this study is to find out the efficacy and safety profile of ertapenem based on its pharmacological properties, pharmacokinetic data as well as clinical trails. Ertapenem is a 1-β methyl-carbapenem that is structurally related to beta-lactam antibiotics and can cover complicated diseases.

There are many drugs used to treat complicated diseases but here one of the main objective to find out whether ertapenem is superior to cephalosporin's and other carbapenem classes of drug that used to treat complicated infectious diseases be studying its clinical trials, pharmacological parameter and pharmacokinetic data.

Another vital objective is to evaluate the market size of ertapenem. Ertapenem is not yet launch in the Bangladesh. Here study has been made if ertapenem is launch in the market who are the competitors of ertapenem and what will be the total market size of it and finally to find out, if ertapenem is marketed whether it will feasible or not.

# 4. Methodology:

Ertapenem is a carbapenem class drug, only a company marketed this drug so primary data regarding this drug is not available. This report is fully based on secondary data which have been collected from different journals, IMS, and browsing different web sites and finally had to go through books and through the IMS data total market size has been determined and Ms excel was used for this purpose.

# 5. Result and Discussion:

## 5.1. Complicated diabetic foot infections:

Figure: Patient with diabetic foot infection.

Foot ulcers in diabetic patients are due to neuropathy (sensory, motor, and autonomic deficits), ischaemia, or both. With out proper treatment the initial form of disease turn into deeper infectious disease (Dr Peter R, 2005).

Complicated diabetic foot infection develops due to *Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus agalactiae, Streptococcus pyogenes, Klebsiella* pneumoniae, *Proteus mirabilis, B fragilis, Peptostreptococcus species, Porphyromonas asaccharolytica* (www.wikipedia.com).

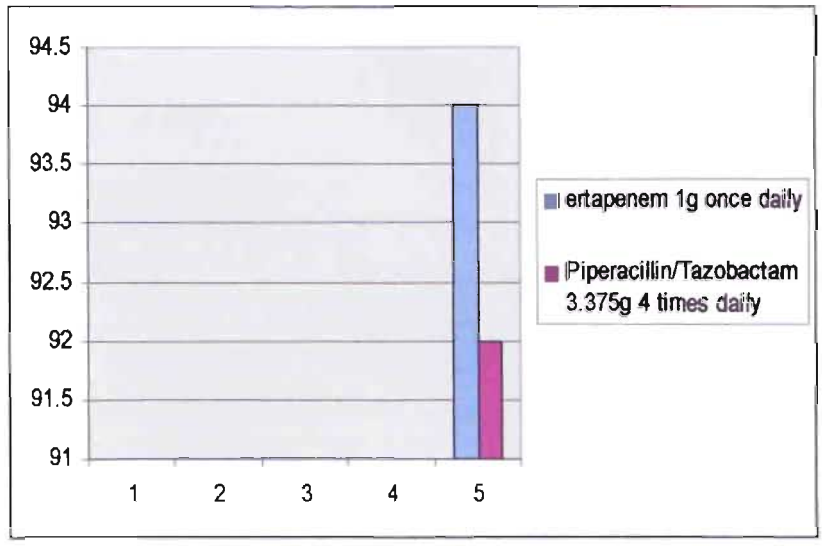
### 5.1.1 Clinical trail in diabetic foot infection:

In a clinical study adults (n=586) with diabetes and a foot infection (moderate-to-severe) and given intravenous therapy. The aim of the study was to find out the efficacy and safety profile of ertapenem versus piperacillin/tazobactam for foot infections (Lipsky BA, Armstrong DG, 2005). Patient treated with ertapenem 1g daily dosing (n=295) or piperacillin/tazobactam 3.375 g every 6 h (n=291) given for a minimum of 5 day, after which oral amoxicillin/clavulanic acid (875/125 mg every 12 h) could be given for up to 23 days. Primary outcome was eexcellent clinical response of ertapenem (cure or improvement).Clinical success rate of ertapenem and piperacillin/tazobactam 94%vs 92%, respectively. Clinical and microbiological outcomes for patients treated with ertapenem were equivalent to those for patients treated with piperacillin/tazobactam.

Ertapenem

## 5.1.2 Efficacy:

In complicated infectious diabetic foot infection ertapenem 1g once daily dose shows better activity than of Piperacillin/Tazobactam 3.375g 4 times daily.




## 5.1.3 Safety profile in case of diabetic foot infection:

Table no.5 Safety profile of ertapenem vs. piperacillin/tazobactam

| Adverse experiences | Ertapenem 1g once daily | Piperacillin/Tazobactam 3.375g 4 times daily |
|---|---|---|
| Diarrhea | 8% | 14% |
| Nausea | 6% | 7% |
| Headache | 4% | 6% |

Upon ertapenem 1g once daily dosing therapy and piperacillin/tazobactam 3.375g 4 times daily therapy, ertapenem shows less side effect than piperacillin/tazobactam which indicates better safety profile of ertapenem.

## 5.1.4 Dosing:

Table no.6 Dosing regimen of ertapenem

| Type of infection | Ertapenem | Piperacillin/Tazobactam |
|---|---|---|
| Complicated diabetic foot infection | 1g once daily | 3.375g 4 times daily |

From table 6 its is easy to understand that in case of Complicated diabetic foot infection ertapenem 1 g once daily therapy is equivalent to piperacillin/tazobactam 3.375g 4times daily therapy.

## 5.2. Complicated urinary tract infections:

Complicated urinary tract infections occur by E coli, including cases with concurrent bacteremia (www.drugs.com).

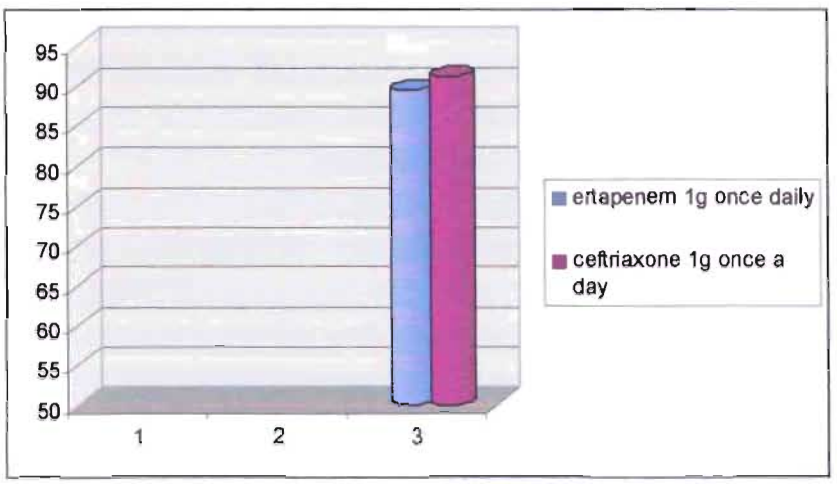
## 5.2.1Clinical trail:

The aim of this clinical trail to evaluate the efficacy and also the safety profile of ertapenem in complicated urinary tract infections.

In this clinical trail, 256 patients in the ertapenem group(1g once a day) and 224 in the ceftriaxone group (1 g once a day) were microbiologically evaluated (Wells WG, Woods GL, 2004). Ninety-six per cent of these patients were switched to oral therapy, usually ciprofloxacin. The median (range) duration of parenteral and total therapy, respectively, was 4 (2-14) days and 13 (14-18) days for ertapenem and 4 (2-14) days and 13 (3-17) days for ceftriaxone. The most common pathogens were Escherichia coli and Klebsiella pneumoniae, which accounted for 64.7% and 9.8% of isolates, respectively. 5-9 days after treatment the efficacy for the patient who received ertapenem was 89.5% and patient who received ceftriaxone was 91.1%. This indicates a favorable microbiological response for both groups and success rate for both groups were similar.

## 5.2.2 Equivalent in efficacy to that of ceftriaxone:

Ertapenem and ceftriaxone both 1 g once daily dosing shows similar success rate in the treatment of complicated urinary tract infections.



## 5.2.3 Dosing:

Table no.7 Dosing regimen of ertapenem

| Type of infection | Ertapenem | Ceftriaxone |
|---|---|---|
| Complicated urinary tract infections | 1g once daily | 1g once a day |

In case of complicated urinary tract infections ertapenem 1g daily dosing is equivalent to ceftriaxone 1g daily therapy.

## 5.3. Community acquired pneumonia:

Patients who have not recently hospitalized can acquire an infection in lung (pneumonia); this disease is called community acquired pneumonia. All stages of people can be affected by community acquired pneumonia.

Most common pathogens responsible for community acquired pneumonia are *Streptococcus pneumoniae*, *Haemophilus influenzae or Moraxella catarrhalis* (www.medscape.com).

### 5.3.1 Ertapenem shows excellent success rates in moderate to severe Community-acquired pneumonia:

The objective of this study is to evaluate the efficacy, safety, and tolerability of ertapenem versus ceftriaxone for the treatment of community-acquired pneumonia in adults(Ortiz-Ruiz G, Caballero-Lopez J, 2002) In a clinical trail 502 patients hospitalized with community-acquired pneumonia were treated with ertapenem or ceftriaxone (for each, 1 g given intravenously once daily). After a minimum of 3 days, therapy could be switched to oral amoxicillin-clavulanate. The median duration of therapy for the clinically evaluable patients was 4 days.

Clinical success rates for ertapenem group was 92.3% and the ceftriaxone group 91.0%.Streptococcus pneumoniae was the most commonly isolated pathogen.

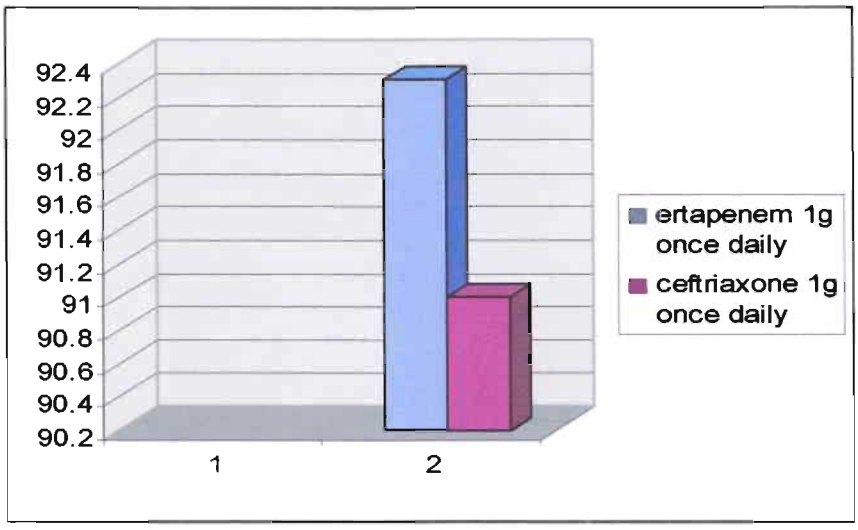
### 5.3.2 Dosing:

Table no.8 Dosing regimen of ertapenem

| Type of infection | Ertapenem | Ceftriaxone |
|---|---|---|
| Community acquired pneumonia | 1g once daily | 1g once a day |

Table no. 8 Ertapenem 1g daily dosing is equivalent to ceftriaxone 1g in CAP.

## 5.3.3 Demonstrated efficacy of ertapenem vs. that of ceftriaxone in community acquired pneumonia:



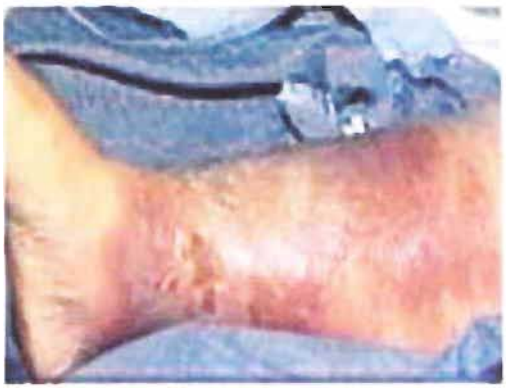

From this clinical study it is easy to understand that ertapenem is highly effective against community acquired pneumonia and in the treatment of community acquired pneumonia ertapenem shows better efficacy than ceftriaxone upon 1g daily dosing.

## 5.4 Complicated skin and skin structure infections:

Infection in the skin structure when untreated for a long time can results to complicated form and that form is called complicated skin and skin structure infection.

*Streptococcus agalactiae*, *Streptococcus pyogenes*, *E coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *B fragilis*, *Peptostreptococcus* species, *Porphyromonas asaccharolytica*, or *Prevotella bivia* are the pathogens responsible for skin and skin structure infections (www.invanz.com).

Figure: Patient with complicated skin and skin structure infection.



### 5.4.1 Clinical trails:

The objective of this study to evaluate efficacy of ertapenem against methicillin-susceptible Staphylococcus aureus in complicated skin/skin structure infections(Ortiz-Ruiz G, Caballero-Lopez J. 2004) versus piperacillin-tazobactam. Staphylococcus aureus is the predominant pathogen in complicated skin/skin structure infections. In this clinical study the efficacy of ertapenem 1 g daily was compared with piperacillin/tazobactam 3.375 g in every 6 hours for treatment of complicated skin/skin structure infections. There were 529 patients in this trial. Therapy duration was 10-21 days. Patient given ertapenem 80.6% and piperacillin-tazobactam 80.9% were cured. Cure rates for both treatment groups were also similar when compared by the severity of infection. Therapy with ertapenem 1 g daily was as effective as piperacillin/tazobactam 3.375 g 4times a day.

## 5.4.2 Efficacy:

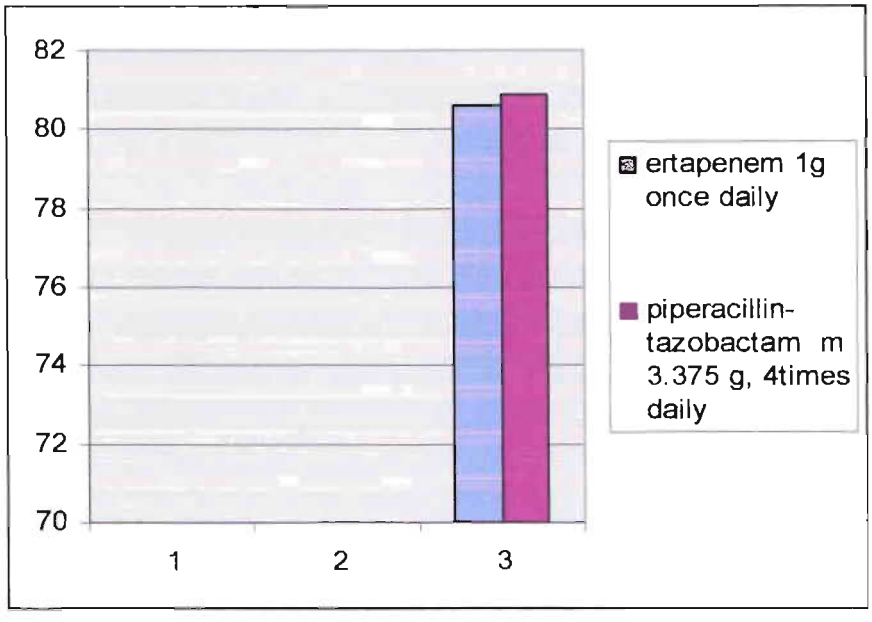



Figure: ertapenem vs. piperacillin/tazobactam in SSTI

From the above figure we can see that upon administration of ertapenem 1g once daily cure rate is 80.6% and piperacillin/tazobactam 3.375 g 4 times a day, cure rate is 80.9%.which show equivalent efficacy of the two drugs.

## 5.4.3 Dosing:

Table no.9 Dosing regimen of ertapenem

| Type of infection | Ertapenem | Piperacillin/Tazobactam |
|---|---|---|
| Complicated skin and skin structure infections | 1g once daily | 3.375g 4 times daily |

Here 1g ertapenem daily dose shows equivalent result to Piperacillin/Tazobactam 3.375g, 4times daily.

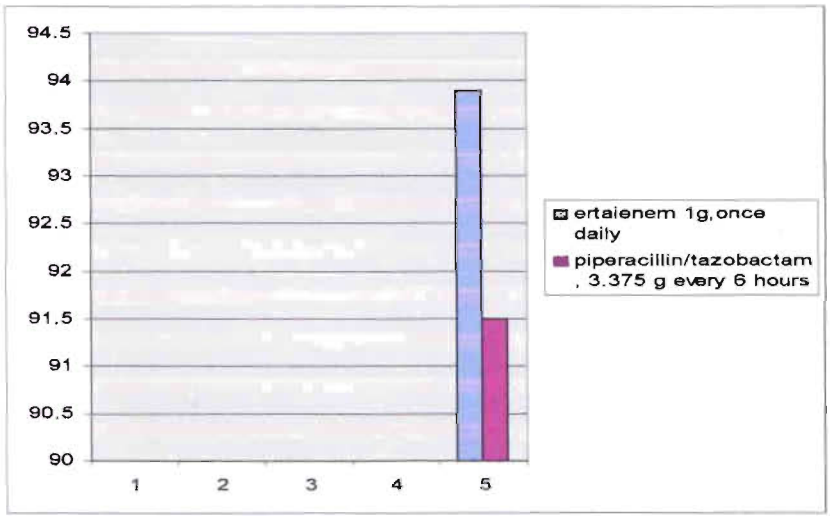
## 5.5 Acute pelvic infections:

The pathogens responsible for acute pelvic infections are to *S agalactiae*, *E coli*, *B fragilis*, *Peptostreptococcus* species, or *P bivia* (www.invanz.com).

### 5.5.1 Ertapenem in acute pelvic infections (clinical trail):

The objective of this study is to compare ertapenem therapy with piperacillin/tazobactam in acute pelvic infections(Roy S, Higareda I, 2003) In this clinical trail 412 women with acute pelvic infection were treated to ertapenem, 1 g once a day, or piperacillin/tazobactam, 3.375 g every 6 hours, both administered intravenously. 163 patients in the ertapenem group and 153 patients in the piperacillin-tazobactam group were clinically evaluated. The duration of therapy was 4.0 days in both treatment groups. The most common single pathogen was Escherichia coli. After 2-4 weeks post therapy, 93.9% of patients who received ertapenem and 91.5% of those who received piperacillin-tazobactam were cured. It indicates that cure rates for both treatment groups were equivalent. From this study, ertapenem was as effective as piperacillin-tazobactam for the treatment of acute pelvic infection, and have equal safety profile.

### 5.5.2 Efficacy profile:




To treat acute pelvic infections 1gm ertapenem once daily dosing shows excellent result rather than or piperacillin/tazobactam 3.375 g 4times daily.

## 5.5.3 Dosing:

Table no.10 Dosing regimen of ertapenem

| Type of infection | Ertapenem | Piperacillin/Tazobactam |
|---|---|---|
| Acute pelvic infection | 1g once daily | 3.375g 4 times daily |

In case of acute pelvic infection ertapenem 1g once daily treatment shows better result than of piperacillin/tazobactam 3.375 g 4times a day.

## 5.6. Complicated intra abdominal infections (IAI):

Complicated intra abdominal infection due to to *Escherichia coli*, *Clostridium clostridioforme*, *Eubacterium lentum*, *Peptostreptococcus spices*, *Bacteroides fragilis*, *B distasonis*, *B ovatus* pathogens.

## 5.6.1 IAI is a major cause of morbidity and mortality:

In general surgery intra abdominal infection is one of the most common infections. On order to manage IAI, Surgery, supportive care, and antibiotic therapy are the key. In a study it was found that incase of 604 patients, morbidity rates 59% and mortality rate of 21% were reported even proper management were taken.

## 5.6.2 Excellent Clinical Efficacy in IAI:

In the treatment of IAI, in clinical trails it was proven that 1 g ertapenem is effective as piperacillin/tazobactam or ceftriaxone plus metronidazole.

.

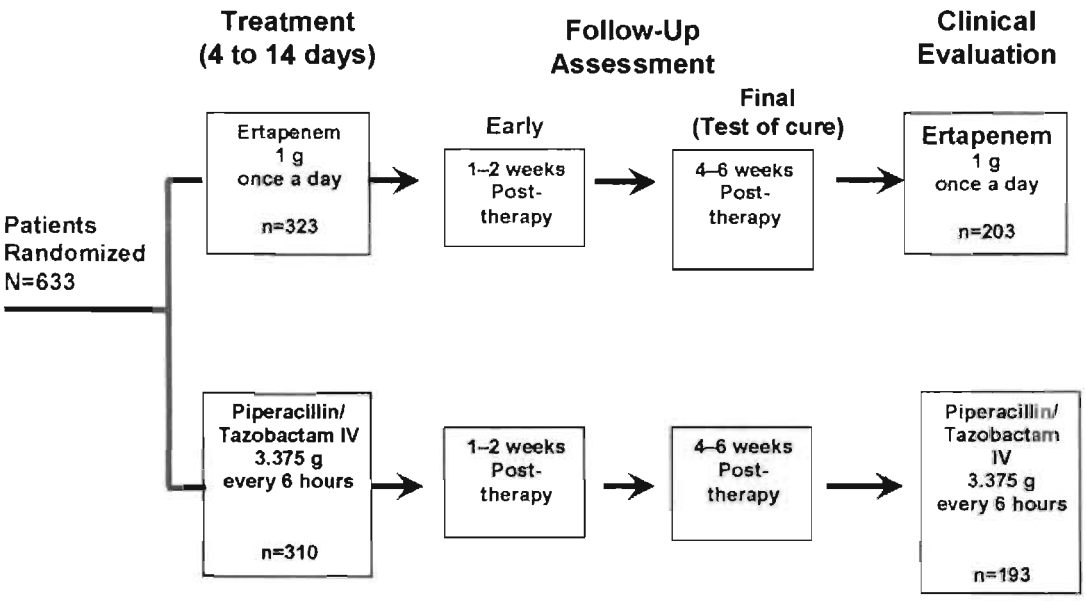
Effective against a wide range of pathogens. and advance because of the excellent efficacy, antimicrobial spectrum, tolerability, and once-daily dosing (Yellin AE, 2002).

| | | | | |
|---|---|---|---|---|
| Ertapenem<br>1g once daily | Vs. | Ceftriaxone 2g once daily<br>Metronidazole<br>500 mg every 8 hours | Or | Piperacillin/tazobactam<br>3.375g every 6hr |

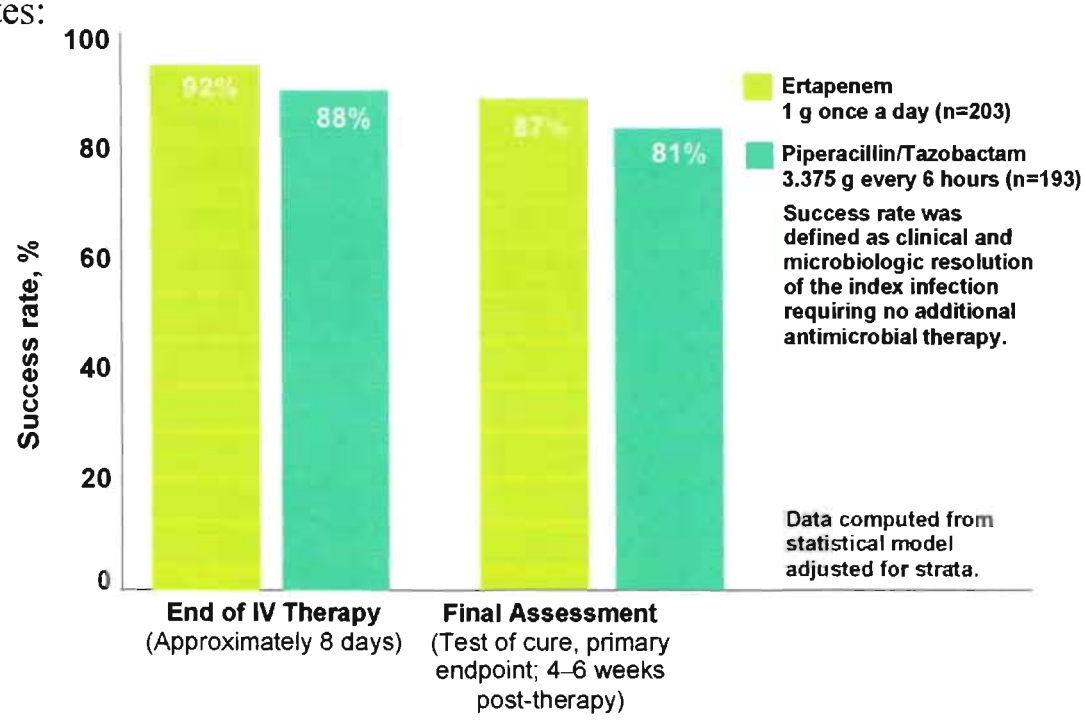
## 5.6.3 Ertapenem shows excellent efficacy in clinical trails:

In order to find or determine the microbiologic efficacy and tolerability of ertapenem 1g daily dosing to patient with intra abdominal infection vs. with piperacillin/tazobactam administered at 3.375 grams every 6 hours. (Solomkin S, Albert E, 2003).

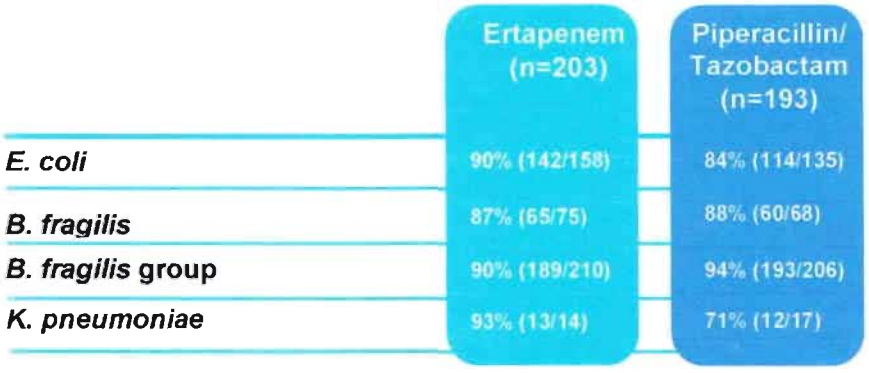
## 5.6.4 Ertapenem vs. Piperacillin/Tazobactam: Study Design:




## 5.6.5 Ertapenem vs. piperacillin/tazobactam: Over 90% success rates:



5.6.6 Ertapenem vs. piperacillin/tazobactam, high microbiologic response rate:




5.6.7 Showed excellent efficacy in microbiologically evaluable subgroup:

Table no.11 Ertapenem in microbiologically evaluable subgroup

| **Infection Site or Process** | **Ertapenem 1 g once a day% (n/N n=203** | **Piperacillin/Tazobactam 3.375 g every 6 hr % (n/N) n=193** |
|---|---|---|
| Colon | 78 (26/36) | 69 (25/36) |
| Small bowel | 69 (25/36) | 73 (8/11) |
| Multiple abscesses | 89 (8/9) | 50 (2/4) |
| Generalized peritonitis | 83 (50/60) | 74 (39/53) |
| Single abscess | 90 (53/59) | 82 (55/67) |

Number of patients with favorable response assessment/Total number of patients with assessment. Success required favorable clinical and microbiological responses.

## 5.6.8 Dosing:

Table no.12 Dosing regimen of ertapenem vs. other drugs in IAI

| Agent | Dose | Dose per day |
|---|---|---|
| Ertapenem | 1g | Once daily |
| Ceftriaxone<br>+<br>Metronidazole | 1–2 g<br><br>7.5 mg/kg | 2<br><br>4 |
| Piperacillin/tazobactam | 3.375 g | 4 |

Ertapenem shows good tolerability profile also excellent clinical trails with single dose treatment. Here I g ertapenem shows better efficacy than of Piperacillin/tazobactam and combination of ceftriaxone & metronidazole in the treatment of complicated intra abdominal infections (Yellin AE, 2002).

1g ertapenem is equivalent to1g ceftriaxone which shows similar efficacy. In case of acute pelvic infections. 1g ertapenem once daily dosing show better clinical result than piperacillin/tazobactam 3.375g 4 times a day. In Community acquired pneumonia 1g ertapenem dosing show better clinical success than ceftriaxone. In complicated infectious diseases ertapenem (1g once daily) shows excellent demonstrated efficacy with minimum side effect and have good clinical trail result.

## 5.7 Overall dosing guideline of ertapenem:

Table no.13 dosing guideline of ertapenem

| Infection | Recommended Dosage | | Recommended Treatment Duration |
|---|---|---|---|
| | Adult Patients | Pediatric Patients (aged 3 months to 12 years) | |
| Complicated intra-abdominal infections | 1 g once daily | 15 mg/kg twice daily | 5 to 14 days |
| Community-acquired pneumonia | 1 g once daily | 15 mg/kg twice daily | 10 to 14 days |
| Complicated skin/skin structure infections | 1 g once daily | 15 mg/kg twice daily | 7 to 14 days |
| Diabetic foot infections | 1 g once daily | 15 mg/kg twice daily | 7 to 14 days |
| Complicated urinary tract infections | 1 g once daily | 15 mg/kg twice daily | 10 to 14 days |
| Acute pelvic infections | 1 g once daily | 15 mg/kg twice daily | 3 to 10 days |
| Prophylaxis of surgical site infection following elective colorectal surgery | Single IV dose—1 g given 1 hr before surgical incision | Not indicated | 1 day |

To treat complicated infectious diseases ertapenem shows better efficacy with simple dosing system, 1 g once daily (www.rxlist.com) for adults and for pediatric patients 15 mg/kg twice daily.

## 5.8 Ertapenem therapy associated with other diseases

Ertapenem is used to treat Complicated diabetic foot infections, Complicated intra-abdominal infections, Complicated skin/skin structure infections, Community-acquired pneumonia, Complicated urinary tract infections. The objective of this study is to evaluate the safety of ertapenem to be used to the patient having other diseases.

Table no 14. Ertapenem associated with other diseases

| Patient profile | Ertapenem | Source |
|---|---|---|
| Patients had a history of surgical intervention | Ertapenem can be given | http://www.ncbi.nlm.nih.gov/sites/entrez |
| Patient suffering from diarrhea | Ertapenem can not given because it is one of the side effects of ertapenem | www.rxlist.com |
| Patient with tuberculosis | No data yet published | - |
| Patient with liver disease | Ertapenem can be used because ertapenem does not inhibit metabolism of cytochrome P450 (CYP) enzyme | http://www.flexyx.com/I/Invanz.html |
| Patient needed urinary catheterization | Ertapenem can be given | http://www.ncbi.nlm.nih.gov/sites/entrez |
| Patient with nervous system disorder | No data yet published | - |
| Patient with diabetics | Its is safe to us ertapenem because one of its use to treat diabetes foot infection | www.invanz.com |
| Patient have epilepsy | May not be able to use, dose adjustment needed if used | http://health.yahoo.com/musculoskeletal-medications/ertapenem/healthwise--d04783a1.html |
| Patient have brain tumor | May not be able to use, dose adjustment needed if used | http://health.yahoo.com/musculoskeletal-medications/ertapenem/healthwise--d04783a1.html |
| hypersensitivity to local anesthetics | Not used | http://www.flexyx.com/I/Invanz.html |

## 5.9 Comparative study of ertapenem to other drugs:

Table no.15 Comparative study of ertapenem with others carbapenem compound drugs

| ria | Imipenem | Meropenem | Doripenem | Ertapenem |
|---|---|---|---|---|
| cation | **Lower respiratory tract infections-** pneumonia and bronchitis as an exacerbation of COPD (chronic obstructive pulmonary disease) caused by *Streptococcus pneumoniae and Haemophilus influenzae*<br><br>**Intra-abdominal infections-** *Enterococcus faecalis; Streptococcus viridans group; Escherichia coli; Klebsiella pneumoniae*<br>**Skin and skin structure infections-** *Staphylococcus, penicillinase-producing strains; Streptococcus pyogenes, Escherichia coli; Enterobacter cloacae; Klebsiella pneumoniae*<br><br>**Gynecologic infections - including postpartum endomyometritis, caused** by Group D streptococcus including *Enterococcus faecalis; Escherichia coli; Klebsiella pneumoniae; Bacteroides intermedius; and Peptostreptococcus species .* | **Skin and Skin Structure Infections-**<br><br>*Staphylococcus aureus , Pseudomonas aeruginosa, Escherichia coli Bacteroides fragili*<br><br>**Intra-abdominal Infections-**<br><br>*streptococci, Escherichia coli, klebsiella pneumoniae, Pseudomonas aeruginosa*<br><br>**Bacterial Meningitis-**<br><br>*Streptococcus pneumoniae, Haemophilus influenzae (β-lactamase and non-β-lactamase-producing isolates), and Neisseria meningitides.*<br><br>**Mixed infections(RTI,UTI,Septicemia)-**<br><br>*E.coli, Staphylococcus pyrogens, Klebsiella pneumoniae. , Proteus mirabilis* | **Complicated Intra-abdominal** Infections- *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Bacteroides caccae, Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Streptococcus intermedius, Streptococcus constellatus*<br>**Complicated Urinary Tract Infections, Including Pyelonephritis** Doripenem (doripenem for injection) is indicated as a single agent for the treatment of complicated urinary tract infections, including pyelonephritis caused by *Escherichia coli.* | **Complicated Intra-abdominal Infections-** *Escherichia coli, Clostridium clostridioforme, Eubacterium lentum, Peptostreptococcus species, Bacteroides fragilis*<br>**Complicated Skin and Skin Structure Infections -** *Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Peptostreptococcus species.*<br>**Community Acquired Pneumonia-** *Streptococcus pneumoniae, Haemophilus influenzae*<br>**Complicated Urinary Tract Infections-** *Escherichia coli*, including cases with *concurrent bacteremia*, or *Klebsiella pneumoniae.*<br>**Acute Pelvic Infections** due to *Streptococcus agalactiae, Escherichia coli, Bacteroides fragilis, Porphyromonas asaccharolytica, Peptostreptococcus species* |

Ertapenem is highly active against wide range of pathogens that have been found in table no.15. It can be used in the treatment of complicated infectious diseases like- Complicated Intra-abdominal Infections, Complicated Skin and Skin Structure Infections, Community Acquired Pneumonia, Complicated Urinary Tract Infections, Acute Pelvic Infections. In table no. 15 comparative study has been made according to the activity of drugs against diseases based on coverage and ertapenem shows wide range of coverage against complicated diseases.

Ertapenem is highly protein bound, long half life and good shelf life which indicates well controlled pharmacokinetic profile of the drug.

Table no.16 comparison based on pharmacokinetic data of drugs

| Criteria | Imipenem | Meropenem | Doripenem | Ertapenem |
|---|---|---|---|---|
| Bioavailability | Not known | 100% | Not known | 90% |
| Half life | 60min | 1 hr | 1 hr | 4 hr |
| Excretion | Not known | Renal (70% unchanged form) | 70%by kidney. Where 15% ring open metabolite (inactive form) & 10% by faces | 80% by kidney & 10% by faces. Of 80% recovered in urine 38% excreted in unchanged form. |
| Metabolism | Renal | Not known | Doripenem is not a substrate for hepatic CYP-450enzyme. | By liver( minor hydrolysis of beta lactum ring , CYP not involved) |
| Protein binding | Not known | 2% | 8% | 85-95% |
| Shelf life | Not known | Not known | Not known | 2 years |
| Penetration to cerebrospinal fluid | Not known | Yes | Not known | Yes |

Ertapenem doesn't accumulate in the body, has pregnancy category B. SO it is a good option for pregnant women, has prophylaxis activity and have FDA approval.

Table no.17 Comparative study based on some additional features

| **Criteria** | **Imipenem** | **Meropenem** | **Doripenem** | **Ertapenem** |
|---|---|---|---|---|
| Accumulation | Not known | No | No | No |
| Prophylaxis activity | Yes | Yes | Yes | Yes |
| Pregnancy category | C | B | B | B |
| Route | IV/IM | IV | IV/IM | IV/IM |
| FDA Approval | Yes | Yes | Yes | Yes |

Table no.18 Comparison based on coverage of ertapenem with its competitors

| Disease | Imipenem | Meropenem | Doripenem | Ertapenem |
|---|---|---|---|---|
| Meningitis | Yes | Yes | No | Yes |
| Complicated UTI infection | Yes | Yes | Yes | Yes |
| Complicated intra abdominal infections | Yes | Yes | Yes | Yes |
| Systemic infections | Yes | Yes | Yes | Yes |
| Complicated SSSI | Yes | Yes | Yes | Yes |
| Septicemia | Yes | No | Yes | Yes |
| Pelvic inflammatory disease | Yes | Yes | No | Yes |
| Nosocomial & community acquired pneumonia | Yes | Yes | Yes | Yes |
| Mixed infections –RTIs | Yes | Yes | Yes | Yes |

## Dosing:

Table no.19 Dosages difference along with other carbapenem compounding drug

| Disease | Dosage of different drugs | | | |
|---|---|---|---|---|
| | **Doripenem** | **Meropenem** | **Ertapenem** | **Imipenem** |
| Complicated intra-abdominal infections | 500mg 3times a day | 1 g in every 8 h | 1g once daily | 500mg- 1g in every 8 h |
| Complicated skin skin structure infection | 500mg 3times a day | 1 g in every 8 h | 1g once daily | 500mg- 1g in every 8 h |
| Community acquired pneumonia | 500mg 3times a day | 1 g in every 8 h | 1g once daily | 500mg- 1g in every 8 h |
| Complicated urinary tract infection | 500mg 3times a day | 1 g in every 8 h | 1g once daily | 500mg- 1g in every 8 h |
| Surgical site infection | 500mg 3times a day | 1 g in every 8 h | 1g once daily | 500mg- 1g in every 8 h |
| Acute pelvic infection | 500mg 3times a day | 1 g in every 8 h | 1g once daily | 500mg- 1g in every 8 h |

Ertapenem is used to treat complicated infectious diseases. One of the main advantages of ertapenem is its simple dosing system. In order to treat complicated infectious diseases ertapenem has 1g once daily dosing system rather than other carbapenem classes of drug.

## 5.11 Product positioning:

Positioning starts with a product. A piece of merchandise, a service, a company, an institution, or even a person….. But positioning is not what you do to a product. Positioning is what you do to the mind of the prospect. That is, you position the product in the mind of the prospect (Philip Kotler, 2003).

### 5.11.1 Gentamicin vs. Ertapenem:

Gentamicin is an aminoglycoside antibiotic, used to treat many types of bacterial infections, particularly those caused by Gram-negative bacteria. Gentamicin is potentially nephrotoxic. Gentamicin is toxic to the sensory cells of the ear Gentamycin is nephrotoxic due to accumulation of tha dose. Gentamicin (Sundin DP, Sandoval R) have pregnancy category D. Neurotoxicity manifested by ototoxicity. Ertapenem does not produce nephrotoxicity and neuro toxicity. Ertapenem has pregnancy category B. ertapenem don't produce ototoxicity.

### 5.11.2 Levofloxacin vs. Ertapenem:

Levofloxacin induce hepatic failure.As with other fluoroquinolones, disturbances of blood glucose. Some fluoroquinolones, including Levofloxacin, (Coban S, Ceydilek B, Ekiz F )have been associated with prolongation of the QT interval.Toxic epidermal necrolysis, coagulation abnormalities and pancytopenia are other possible adverse effect of levofloxacin.Levofloxacin has pregnancy category C

Ertapenem don't hamper hepatic function. Don't cause any disturbances to blood glucose level and have pregnancy category B.

### 5.11.3 Cefpodoxime vs. ertapenem:

**Respiratory side effects**: Asthma, cough, epistaxis, rhinitis, wheezing, bronchitis, dyspnea, pleural effusion, pneumonia, and sinusitis.

Renal side effects: Renal side effects have included increased BUN and creatinine.

Dermatologic side effects: maculopapular rash, diaper rash, fungal dermatitis, acne, exfoliative dermatitis, desquamation, dry skin, hair loss, urticaria.

Nervous system side effect: Impaired concentration, confusion, nightmares, paresthesia, vertigo, tinnitus, hallucination, hyperkinesia, syncope

Hematologic side effects: Lymphocytosis, granulocytosis, basophilia, monocytosis, thrombocytosis, decreased hemoglobin, decreased hematocrit, leukopenia, lymphocytopenia, thrombocythemia, neutropenia

Hepatic side effects: Transient increases in AST, ALT, GGT, alkaline phosphatase, bilirubin and LDH.

Cardiovascular side effects: Congestive heart failure, palpitations, vasodilation, hematoma, migraine, hypertension, and hypotension (www.medicinenet.com).

Metabolic side effects: Dehydration, gout, peripheral edema, hypoglycemia, hypoalbuminemia, hypoproteinemia, hyperkalemia, and hyponatremia

These side effects are not present in Ertapenem.



## Dosing:

Table no.20 Ertapenem dosing vs. Cefotaxime dosing

| **Type of infection** | **Cefpodoxime** | **Ertapenem** |
|---|---|---|
| Community acquired pneumonia | 500 mg orally twice per day. | 1-gram once a day |

## 5.11.4 Cefotaxime vs Ertapenem:

Cardiovascular side effects: Arrhythmia (www.drugs.com).

Dermatologic side effects: Urticaria, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis, and telangiectasia.

Renal side effects: Interstitial nephritis, and transient increases in BUN and creatinine. Reversible fever, azotemia, pyuria.

Hematological side effects: Granulocytopenia, eosinophilia, leukopenia, neutropenia, thrombocytopenia, agranulocytosis, and hemolytic anemia.

Most of these side effects are not present in ertapenem.

## Dosing:

Table no.21 Dosing system of ertapenem vs. Cefotaxime

| **Type of infection** | **Cefotaxime** | **Ertapenem** |
|---|---|---|
| Moderate -severe infections | 1-2 grams every 8 hours | 1-gram once a day |
| Community acquired pneumonia | 200 mg twice per day | 1-gram once a day |

## 5.12 Price Review:

Table no. 22 Price of ertapenem with other drugs

| **Name** | **Strength** | **Dosage Regimen 7days** | **Unit Price** | **Cost per treatment** |
|---|---|---|---|---|
| Invanz | 1 gm/vial | 7 vials | $49.95001 | $349.6500 |
| Merrem | 1 gm/vial | 21 vials | $47.28002 | $992.8800 |
| Primaxin IV | 500 mg/500 mg/vial | 28 vials | $24.67002 | $690.9600 |
| Rocephin and Metronidazole | 2 gm/vial plus 5 mg/mL (100 mL PVC) | 7 vials plus 21 PVC | $67.00002 + $0.14213 | $471.9841 |

Table no 22 indicates that ertapenem 1 g therapy is not very costly than other dugs in the treatment of complicated infectious diseases due to its simple dosing system,1g once daily (Kansas City, Mo.: American College of Clinical Pharmacy).

## 5.13. Market feasibility:

Meropenem, Imipenem (carbapenem compound drug) are already present in the market. The aim of this study is to evaluate that if ertapenem is launched in the market then it will feasible or not.

### Market strategy regarding IMS data

Ertapenem is not yet launched in Bangladesh. So an idea about its market size can be acquired by analyzing its competitor's market size. The market size of different generic is given in the following table.

Table no.23 Yearly market sizes of competitors of ertapenem

| Generic | Yearly market size of ertapenem with its competitors | | | |
|---|---|---|---|---|
| | 2Q-2007 | 2Q-2006 | 2Q-2005 | 2Q-2004 |
| **CEFTRIAXONE** | 924,667,050 | 1,041,445,490 | 732,510,001 | 650,099,214 |
| **CEFTAZIDIME** | 44,557,775 | 52,087,564 | 43,113,440 | 60,190,598 |
| **CEFPIROME** | 3,979,484 | 6,710,434 | 6,867,647 | 0 |
| **CEFEPIME** | 16,199,633 | 19,542,849 | 7,893,492 | 5,352,604 |
| **MEROPENEM** | 17,363,729 | 57,918,600 | 30,798,741 | 6,127,679 |
| **IMIPENEM** | 165,900 | 0 | 0 | 0 |

In order to assume the growth rate of ertapenem, the growth rate of its competitor must be analyzed.

Table no.24 Yearly market growths of competitors of ertapenem

| Generic | Yearly market growth 2Q-2007 | Yearly market growth 2Q-2006 | Yearly market growth 2Q-2005 |
|---|---|---|---|
| **CEFTRIAXONE** | -11 | 42 | 13 |
| **CEFTAZIDIME** | -14 | 21 | -28 |
| **CEFPIROME** | -41 | -2 | |
| **CEFEPIME** | -17 | 148 | 47 |
| **MEROPENEM** | -70 | 88 | 403 |
| **IMIPENEM** | | | |

Growth of Market size of different generic in different year:

Table no.25 Market size of different generic in different year

| Name of the drug | Growth of Market size of different generic in different year | | |
|---|---|---|---|
| | 2004-2005 | 2005-2006 | 2006-2007 |
| CEFTRIAXONE | 13% | 42% | -11% |
| CEFTAZIDIME | -28% | 21% | -14% |
| CEFPIROME | - | -2% | -41% |
| CEFEPIME | 47% | 48% | -17% |
| MEROPENEM | 403% | 88% | -70% |
| IMPENEM | - | - | - |

Total market size and total market growth:

Table no.27 Total market growth

| | 2004 | 2005 | 2006 | 2007 |
|---|---|---|---|---|
| Total market size | 721,770,095 | 821,183,321 | 1,177,704,937 | 1,006,933,571 |
| Total market growth | - | 13.77353075 | 43.41559392 | -14.50035239 |

From 2004 to 2005 ceftriaxone growth was 13%. From 2005to 2006 ceftriaxone growth was 42%. Probably it took the market of cefpirome. From 2006 to 2007 growth was - 11%. It happened because price of all antibiotic decreased by 50%. From 2004 to 2005 ceftazidime growth was –28%. Growth decreased probably because of cefepime and meropenem captured its market. From 2005 to 2006 ceftazidime growth was 21%. Probably it captured the market of cefpirome. From 2006 to 2007 growth was – 14%. From 2006 to 2007 price of product decreased by 50%. There was no growth of cefpirome from 2004 to 2005. From 2005 to 2006 cefpirome growth was –2%. Probably meropenem captured its market and also may be marketing was not good enough. From 2006 to 2007 cefpirome growth was –41%.

From 2006 to 2007 price of product decreased by 50%. From 2004 to 2005 cefepime growth increased by 47%, it happened may be due to cefepime captured ceftazidime's market.from 2005 to 2006 cefepime growth was 148%. It happened probably because it captured cefpirome market. From 2006 to 2007 cefepime growth was – 17%. From 2006 to 2007 price of product decreased by 50%. From 2004 to 2005 meropenem growth was 403%. It happened it captured the market of ceftazidime, ceftriaxone. From 2005 to 2006 meropenem growth was 88%it happened probably it took the market of cefpirome.from 2006 to 2007 meropenem growth decreased by 70%. It happened because from 2006 to 2007 price of product decreased by 50%. Imipenem was launched in market in 2006.

From 2004 to 2005 total market growth was 13.77353%. From 2005 to 2006 the growth increased by 43.41559%. But from 2006 to 2007 market growth was – 14.50035%. It happened because from 2006 to 2007 price of product decreased by 50%.

## 5.14 Ertapenem opportunity:

Ertapenem is a noble carbapenem drug. It can take the market of ceftriaxone, ceftazidime, cefpirome, cefepime, cefotaxime, meropenem, imipenem. From 2004 to 2005 meropenem's (carbapenem drug) growth was 403%. So if ertapenem could be launched in the market it should be profitable.

Ceftriaxone, ceftazidime, cefpirome, cefepime, cefotaxime, meropenem, imipenem. All these are used to treat Community acquired Pneumonia, urinary tract infection, complicated intra-abdominal infections and complicated infectious diseases.

Ceftriaxone is a 3$^{rd}$ generation cephalosporin. From 2004 to 2005 ceftriaxone growth was 13%. From 2005to 2006 ceftriaxone growth was 42%. From 2007, total market size of ceftriaxone was 924,667,050. Ertapenem which is a broad spectrum carbapenem compounding drug if marketed it will taker over 3% of the Ceftriaxone market due to its better pharmacokinetic and pharmacological effect.

Ceftazidime is a 3rd generation cephalosporin. From 2004 to 2005 ceftazidime growth was –28% and from 2005 to 2006 it was 21%. Growth decreased probably because cefepime and meropenem captured its market. Total market size of ceftazidime was 44,557,775 in 2007. So if ertapenem is introduced in the market it will take up more than 4% of the market of Ceftazidime.

Cefpirome is a 4th generation cephalosporin. 2005 to 2006 cefpirome growth was –2%. Probably meropenem and cefepime captured its market. From 2006 to 2007 cefpirome growth was –41%. In 2007 cefpirome market size was 3,979,484. If ertapenem is marketed it will capture 5% the market of cefpirome.

Cefepime growth was 47% in 2004-2005 and from 2005-2006 it was 48% which indicates a huge market size. If ertapenem is marketed with proper marketing it will capture 3% market of Cefepime.

Meropenem is a carbapenem compound drug. It can cover a lot of pathogens. From 2004 to 2005 meropenem growth was 403%. , due to it may be captured the market of ceftazidime, ceftriaxone. From 2005 to 2006 meropenem growth was 88%. In 2007 meropenem market size were 17,363,729 when the price of all antibiotics decrease by 50%.Septicemia coverage of meropenem is not significant enough. So if ertapenem is introduced in the market it will affect the growth rate of meropenem and will capture 5 %market of meropenem.

Another carbapenem compound drug is imipenem that is available in the market. In 2007 total market size of imipenem was 165,900. As it is found that ertapenem shows better pharmacological property than imipenem it will capture 7% market of imipenem.

Ertapenem is a ultra broad spectrum antibiotic with a wide range of coverage and having simple dosage form so if ertapenem is introduced in the market it may capture the market size of many of other cephalosporin's as well as some of carbapenem compound drugs. It is assume that the market size will be 31,087,084 within 1-2 years. If more company introduces ertapenem in the market than that total market size will be huge with in 5 years and also affect the growth rate of other drugs. The price of ertapenem also a vital fact and to be considered as an important factor. If the product is marketed without proper marketing, than the effort given behind this product will not view the success. So proper marketing policy should be implemented to retain it in the market.

## 5.15 SWOT analysis of Ertapenem:

A SWOT analysis is nothing but a strategic planning that involves an assessment of Strengths, Weaknesses, Opportunities, and Threats (www. dictionary.bnet.com). SWOT analysis is used within organizations in the early stages of strategic and marketing planning. In case of problem solving, decision making SWOT analysis is used.

### Strength:

1. Active against pseudomonas ariginosa.
2. Active against community acquired pneumonia.
3. Active against complicated UTIs.
4. Active against Nosocomial pneumonia and early onset VAP.
5. Active against intra abdominal infections
6. Active against systemic infection.
7. Active against septicemia.
8. Active against surgical site infection.
9. Half life is four hour.
10. single dose therapy
11. Pregnancy category B.
12. Only launched by a company. So it will be a pioneer product.
13. Cover both aerobic and anaerobic organisms.
14. Shelf life 2 years.


### Weakness:

1. Pioneer product so pricing has to be justified.
2. Expensive than cephalosporin and penicillin.
3. Has to be given I.V.
4. Has side effect as constipation, headache, vomiting, nausea, diarrhea etc.

## Opportunity:

1. No company has started production of it so pioneer product.
2. Can do business up to 2016 before patent rule becomes applicable.
3. As bacteria are becoming resistant it can be used vastly.
4. It will be a good alternative for meropenem and imipenem.
5. If ertapenem is launched with good marketing policy then it can capture the market size of other drugs.

## Threat:

1. Other companies will start producing it.
2. Doctors who are prescribing meropenem, ertapenem may not like to Prescribe.

# 6. Conclusion:

Ertapenem is a noble carbapenem drug that used to treat complicated infectious diseases. In diabetic foot infection ertapenem shows excellent clinical success rather than piperacillin/tazobactam. In complicated urinary tract infection cure rate of ertapenem is as same as ceftriaxone. In intra abdominal infection ertapenem shows excellent safety profile and efficacy. Clinical success rate is higher with ertapenem in the treatment of community acquired pneumonia. In all cases of complicated infectious diseases ertapenem shows excellent clinical efficacy and also safety profile. By doing market analysis it is assumed that if ertapenem is launched in the market it will be feasible in the market and also profitable and total market size will be 31,087,084 within 1-2 years. If more company launched this product then total market size of ertapenem will be huge and it will affect the market size of other drugs that used to treat complicated infections. Ertapenem can cover both Gram positive and Gram negative pathogens upon 1g once daily administration and via clinical trails it can easily understood that ertapenem has excellent safety profile and clinical efficacy, so if it would launched it will be the final solution of complicated infectious diseases.

## Limitation:

Ertapenem is a new generation carbapenem class of drug which is marketed by a single company. As it is recently launched in the market so not a lot of journal has been published. The availability of clinical trails regarding ertapenem is not rich enough. The report is based on secondary data and market feasibility was based on only six drugs. By observing only 6 drugs it is tough to make a complete assumption of market size of the drug. Not possible to contact with health care professionals or physicians to discuss about the drug. Product positioning was done based on side effects only and finally some websites requires payment for access to get information.

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