ACUTE DIARRHOEA AND RACECADOTRIL

Racecadotril specifically targets the uncontrolled secretory processes that underlie acute diarrhea, reducing stool output and diarrhea duration.
OVERVIEW OF DIGESTIVE SYSTEM
DIGESTIVE SYSTEM – ANATOMY

• Functions:
  - Movement of food
  - Secretion of digestive juice followed by digestion of food
  - Absorption of water and various electrolytes

**Alimentary canal:**
- mouth, pharynx, oesophagus, stomach, small intestine, large intestine ending at anus

**Accessory organs:**
- tongue, teeth, salivary glands, liver,
- biliary tract, pancreas

SECRETORY PROCESSES OCCUR AT THE VILLI

- The intestinal lumen consists of small finger-like projections called villi. The walls of the villi are made up of enterocytes with microvilli on their edges. In the intestines, water absorption takes place at the tip of the villi whereas secretion occurs in the crypts.
**DAILY FLUID EXCHANGES**

- **Fluid ingested**: 1.5 L/day
- **Fluid excreted**: 0.2 L/day
- **Gastrointestinal secretions**: (7 L/day)

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FLUID AND ELECTROLYTE BALANCE & DIARRHOEA
ENKEPHALINS ARE ESSENTIAL IN REGULATING WATER AND ELECTROLYTE SECRETION

DIARRHOEA IS CAUSED BY HYPERSECRETION OF WATER

• Passage of abnormally liquid or unformed stools at an increased frequency
• Stool weight >200 g/day
• Diarrhoea is not:
  – Frequent passage of formed stools
  – Passage of loose, "pasty" stools by breastfed babies

PATHOPHYSIOLOGY OF ACUTE DIARRHEA

DIARRHOEAL RISK – SIGNS OF DEHYDRATION


AETIOLOGY OF INFECTIOUS DIARRHOEA

**Developed Countries**
- Virus 70% (Rotavirus 40%)
- Bacteria 10-20%
- Protozoa <10%

**Developing Countries**
- Virus 35% (Rotavirus 15-20%)
- Bacteria 50-60%

**Enteropathogenic E. coli** 25%
- *Campylobacter jejuni* 10-18%
- *Shigella* species 5%
- *Salmonella* species 5%

2. Cooke M. *S Afr J Clin Nutr* 2010;23(1) Supplement:S42-S46
BURDEN OF DIARRHOEA
Acute gastroenteritis is generally defined as a decrease in the consistency of stools (loose or liquid) and/or an increase in the frequency of evacuations (typically ≥ 3 in 24 hours), with or without fever or vomiting. However, a change in stool consistency versus previous stool consistency is more indicative of diarrhea than stool number, particularly in the first months of life. Acute diarrhea typically lasts less than 7 days and not longer than 14 days.
## DIARRHOEA: GLOBAL PREVALENCE AND BURDEN

<table>
<thead>
<tr>
<th>Segment</th>
<th>Prevalence/Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developing world</td>
<td>2.5 million deaths/ year</td>
</tr>
<tr>
<td>In USA</td>
<td>200 to 300 million new cases in US annually with a health expenditure of 23 million dollars/year</td>
</tr>
<tr>
<td>Infants / children (&lt;5 years)</td>
<td>~1.5 billion episodes and 3 million deaths /year</td>
</tr>
<tr>
<td>In Europe (in children &lt;3 years)</td>
<td>0.5 to 1.9 episodes/child/year</td>
</tr>
<tr>
<td>Elderly</td>
<td>Associated with significant morbidity and quality of life</td>
</tr>
<tr>
<td></td>
<td>9.1 % prevalence rate (according to Rome criteria)</td>
</tr>
<tr>
<td>Viral aetiology</td>
<td>&gt;70% of infectious diarrhoea: 600,000 to 800,000 deaths annually (Rota virus)</td>
</tr>
<tr>
<td>Bacterial aetiology</td>
<td>1.5%-5.6% of cases</td>
</tr>
<tr>
<td>Amoebic aetiology</td>
<td>50 million people resulting in 40 000 deaths per year (Entamoeba histolytica)</td>
</tr>
<tr>
<td>Traveller’s diarrhoea</td>
<td>30% to 40% of travellers visiting developing countries</td>
</tr>
<tr>
<td>Drug-related</td>
<td>7% of drugs adverse effects manifest as diarrhoea</td>
</tr>
</tbody>
</table>

*a The true prevalence is underestimated due to misdiagnosis and lack of medical or hospital attention sought by patients.

# Causative Agents in Diarrhea

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Viruses</th>
<th>Parasites</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Diarrheagenic Escherichia coli</em></td>
<td>Rotavirus</td>
<td><strong>Protozoan</strong></td>
</tr>
<tr>
<td><em>Campylobacter jejuni</em></td>
<td>Norovirus (calicivirus)</td>
<td><em>Cryptosporidium parvum</em></td>
</tr>
<tr>
<td><em>Vibrio cholerae O1</em></td>
<td>Adenovirus (serotype 40/41)</td>
<td><em>Giardia intestinalis</em></td>
</tr>
<tr>
<td><em>V. cholerae</em> O139*</td>
<td>Astrovirus</td>
<td><em>Microsporida</em></td>
</tr>
<tr>
<td><em>Shigella species</em></td>
<td>Cytomegalovirus*</td>
<td><em>Entamoeba histolytica</em></td>
</tr>
<tr>
<td><em>V. parahaemolyticus</em></td>
<td></td>
<td><em>Isospora belli</em></td>
</tr>
<tr>
<td><em>Bacteroides fragilis</em></td>
<td></td>
<td><em>Cyclospora cayetanensis</em></td>
</tr>
<tr>
<td><em>C. coli</em></td>
<td></td>
<td><em>Dientamoeba fragilis</em></td>
</tr>
<tr>
<td><em>C. upsaliensis</em></td>
<td></td>
<td><em>Blastocystis hominis</em></td>
</tr>
<tr>
<td><em>Nontyphoidal Salmonellae</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Clostridium difficile</em></td>
<td></td>
<td><strong>Helminths</strong></td>
</tr>
<tr>
<td><em>Yersinia enterocolitica</em></td>
<td></td>
<td><em>Strongyloides stercoralis</em></td>
</tr>
<tr>
<td><em>Y. pseudotuberculosis</em></td>
<td></td>
<td><em>Angiostrongylus costaricensis</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Schistosoma mansoni, S. japonicum</em></td>
</tr>
</tbody>
</table>

* These agents are no longer reported in the Indian subcontinent.
PREVENTION AND THE EVOLVING CLINICAL APPROACHES TO MANAGE DIARRHOEA
Preventive Measures

USE OF ANTI-MICROBIAL AND ANTI-DIARRHOEAL DRUGS: WHO 2005

Anti-microbial Drugs
• Should not be used routinely
  – All clinical episodes might not respond to anti-microbials (ETEC)
  – Difficult to differentiate the clinical episodes which might respond (rotavirus)
  – For selection of appropriate antibiotic: Information regarding sensitivity of the causative agent is usually unknown
  – Incurs additional cost to the treatment
  – Risk of adverse reaction increases
  – Enhances development of resistant bacteria
• Used only for the treatment of children with
  – Bloody diarrhoea (probable shigellosis)
  – Suspected cholera with severe dehydration
  – Non intestinal infections and pneumonia

AntiPROTOzoal drugs
• Are rarely indicated

Anti-diarrhoeal drugs and anti-emetics
• No practical benefits in children with acute or persistent diarrhoea
• Do not prevent dehydration
• Do not improve nutritional status
• Dangerous, sometimes fatal side effects
• Not used in children below 5 years

### Table 2 Episodes of diarrhea can be classified into three categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Clinical manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute diarrhea</td>
<td>Presence of three or more abnormally loose or watery stools in the preceding 24 h</td>
</tr>
<tr>
<td>Dysentery</td>
<td>Presence of visible blood in stools</td>
</tr>
<tr>
<td>Persistent diarrhea</td>
<td>Acutely starting episode of diarrhea lasting more than 14 days</td>
</tr>
</tbody>
</table>

WGO – Acute diarrhea practice guidelines 2012.
1. WGO. World Gastroenterology Organisation practice guideline; Acute Diarrhea. 2012.
## INCUBATION PERIOD AND LIKELY CAUSES OF DIARRHEA

<table>
<thead>
<tr>
<th>Incubation period</th>
<th>Likely causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6 h</td>
<td>Preformed toxin of <em>S. aureus</em> and <em>Bacillus cereus</em></td>
</tr>
<tr>
<td>6–24 h</td>
<td>Preformed toxin of <em>C. perfringens</em> and <em>B. cereus</em></td>
</tr>
<tr>
<td>16–72 h</td>
<td><em>Noroviruses, ETEC, Vibrio, Salmonella</em>&lt;br&gt;<strong>Shigella, Campylobacter, Yersinia</strong>&lt;br&gt;<strong>Shiga toxin–producing E. coli, Giardia</strong>&lt;br&gt;<strong>Cyclospora, Cryptosporidium</strong></td>
</tr>
</tbody>
</table>
CLINICAL APPROACH – ADULTS WITH ACUTE DIARRHOEA (WGO 2008)

Initial Assessment
- Dehydration
- Duration (>1 day)
- Inflammation

Symptomatic Treatment
- Rehydration
- Treatment of symptoms

Subsequent Management
- Epidemiological clues
- Clinical Clues: bloody diarrhoea, abdominal pain, dysentery, wasting, faecal inflammation

Microbiological Analysis of Faeces

Specific Antibiotic Therapy

WGO, World Gastroenterology Organisation.

THERAPEUTIC APPROACHES
TREATMENT OF ACUTE DIARRHOEA – BASED ON DEGREE OF DEHYDRATION (WGO 2008)

**Children**

≥2 of the following signs:
- Lethargy or unconsciousness
- Sunken eyes
- Unable to drink or poor drinking
- Skin pinch goes back very slowly

Severe Dehydration

≥2 of the following signs:
- Restless, irritable
- Sunken eyes
- Drinks eagerly, thirsty
- Skin pinch goes back slowly

Mild Dehydration

- Well alert
- Normal eyes
- Normal drinking
- Skin pinch goes back slowly

No Dehydration

**Adults**

- Pulse rate > 90
- Postural and supine hypotension
- Absence of palpable pulse
- Dry tongue and sunken eyeballs

Dehydration

WGO, World Gastroenterology Organisation.

CURRENT THERAPEUTIC OPTIONS FOR DIARRHOEA

Diarrhoea Therapy Options

Motility inhibitors
- Loperamide
- Atropine

Adsorbents
- Diosmectite
- Bismuth

Probiotics
- Saccharomyces boulardii
- Lactobacillus acidophilus
- Lactobacillus bifidus
- Enterococcus faecalis
- Bacillus clausii

Anti-infectives
- Ciprofloxacin
- Rifaximin
- Nifuroxazide
- Ofloxacin
- Tinidazole

Others
- Racecadotril
- Creosote
- Geranium robertianum
- Phellodendron
- Glycyrrhiza glabra

Vaccines
- RV1
- RV5

Anti-infectives
- Ciprofloxacin
- Nifuroxazide
- Ofloxacin
- Tinidazole

Others
- Racecadotril
- Creosote
- Geranium robertianum
- Phellodendron
- Glycyrrhiza glabra

Vaccines
- RV1
- RV5

6. Xifaxan (rifaximin) [prescribing information]. Salix Pharmaceuticals.
## ANTI-DIARRHOEAL DRUGS, WGO 2008 & 2012

### Anti-motility agents

**Loperamide:**
- Agent of choice for adults (4-6 mg/day; 2-4 mg/day for children aged >8 years)
- Inhibits intestinal peristalsis
- Used for mild to moderate traveller's diarrhoea
- Avoided in febrile patients and contraindicated in abdominal pain
- Not recommended in children aged below 2 years

### Anti-secretory agents

**Bismuth subsalicylate:**
- Alleviate stool output in children
- Alleviate symptoms of diarrhoea, nausea
- Alleviate abdominal pain in traveler's diarrhoea

**Racecadotril:**
- Enkephalinase inhibitor
- Has antisecretory activity
- Authorised for use in children in many countries
- Used in children with diarrhoea, not in adults with cholera

### Adsorbents

**Kaolin pectin, attapulgite, activated charcoal**
- Efficacy not proved in acute adult diarrhoea

---

“Racecadotril, a specific enkephalinase inhibitor that prevents degradation of the endogenous antisecretory peptide neurotransmitter enkephalins that inhibit cyclic nucleotide secretory pathways without effect on gut motility” (103)
ANTI-MOTILITY OR ANTI-PERISTALTIC DRUGS ESPHGAN GUIDELINES (2008 and 2014)

- Loperamide
  - Opioid receptor agonist
  - Reduces intestinal lumen motility
  - Used for the short-term symptomatic relief of acute diarrhoea in adults
  - Should not be used for the management of AGE in infants and young children

2014: 9.3.2 Antimotility or Antiperistaltic Drugs (Loperamide)
Loperamide is not recommended in the management of AGE in children (II, B) (strong recommendation, very low quality evidence).

2. Guarino et al. JPGN 2014; 59:132-152
• Racecadotril (acetorphan)
  – Exhibits pharmacological action by inhibiting enkephalinase
  – Decreases the secretion of water and electrolytes in the GIT
  – May be considered in the management of AGE
  – Used to treat children with severe watery diarrhoea as an adjunct to ORT
  – Reduces stool output, intake of ORS and duration of diarrhoea

2. Guarino et al. JPGN 2014; 59:132-152
ANTIMICROBIAL THERAPY IN CHILDREN AND ADULTS

• In Children
  – Antibiotic agent recommended only under specific conditions
  • Septicaemia
  • Bloody diarrhoea
  • Younger than 6 months with salmonella
  • Cholera with severe dehydration
  • Non-intestinal/extra-intestinal infections
  • Malnourished/immunocompromised
  • Clostridium difficile-associated pseudomembranous enterocolitis
  – Children who travelled abroad: based on specialist advice
  – Antiprotozoal drug for Giardia or Entamoeba histolytica infections
  – Dosage of drug to depend on body weight

• In Adults
  – Treatment to be weighed against
    • Drug cost
    • Risk of adverse reaction
    • Risk of eradication of normal intestinal flora
    • Induction of Shiga toxin production
    • Development of drug resistance

“Anti-infective therapy should not be given to the vast majority of otherwise healthy children with acute gastroenteritis (Vb, D)”

(ESPGHAN recommendation)

Antimicrobial agents are recommended only for the treatment of specific causes of diarrhoea or under special conditions.

<table>
<thead>
<tr>
<th>Disease</th>
<th>1st choice</th>
<th>2nd choice</th>
<th>3rd choice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cholera</strong></td>
<td>Doxycycline</td>
<td>Tetracycline</td>
<td>Azithromycin or Ciprofloxacin</td>
</tr>
<tr>
<td>Adults:</td>
<td>300 mg once or 500 mg 4 times a day x 3 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Shigellosis</strong></td>
<td>Ciprofloxacin</td>
<td>Pivmecillinam or Ceftriaxone</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Children:</td>
<td>15 mg/kg 2 times a day x 3 days Adults: 500 mg 2 times a day x 3 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Amoebiasis</strong></td>
<td>Metronidazole</td>
<td>Ciprofloxacin or Pivmecillinam</td>
<td></td>
</tr>
<tr>
<td>Children:</td>
<td>10 kg/kg 3 times a day x 5 days* Adults: 750 mg 3 times a day x 5 days*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Giardiasis</strong></td>
<td>Metronidazole</td>
<td>Pivmecillinam or Ceftriaxone</td>
<td>Azithromycin</td>
</tr>
<tr>
<td>Children:</td>
<td>5 mg/kg 3 times a day x 5 days Adults: 250 mg 3 times a day x 5 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Campylobacter</strong></td>
<td>Azithromycin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*10 days for severe disease

RACECADOTRIL – OVERVIEW
EFFICACY & SAFETY
NORMAL SECRETORY PROCESS
Regulated by neurotransmitters, the enkephalins, and by an enzyme enkephalinase

BASELINE STATE
• Enkephalins bring about a reduction in the level of AMPc
• As a consequence, a reduction in hydroelectrolytic secretion in the lumen of the small intestine
• Enkephalinase causes an increase in the level of AMPc and therefore of secretion: by inactivating enkaphalins

HYPERSECRETION
• In diarrhoea, viral/bacterial toxins and prostaglandins lead to breakdown of enkephalins by enkephalinase
• Massive increase in the level of AMPc
• Hydroelectrolytic secretion in the lumen of the small intestine

NORMALISATION
Racecadotril:
• Powerful and selective inhibitor of enkephalinase,
• Prolongs the antisecretory action of enkephalins
• Opposes the intestinal hypersecretion of water and electrolytes

Selective inhibitor of enkephalinase that decreases intestinal hypersecretion
RACECADOTRIL or racecadotril is indicated in the symptomatic treatment of acute diarrhoea in adults, children and infants older than 3 months.

It is available as:
- 100 mg hard capsule
- 10 mg and 30 mg granules for oral suspension

2. Racecadotril 100 mg local approved leaflet
RAPID ABSORPTION OF RACECADOTRIL AND 8-HOUR ANTISECRETORY EFFECT

- Rapid onset of enkephalinase inhibition after conversion of racecadotril to thiorphan
- RACECADOTRIL can be given without regard to meals

1. Racecadotril 100 mg local approved leaflet
RACECADOTRIL – FAVOURABLE DISTRIBUTION PROFILE

• Moderate distribution of thiorphan into bodily tissues – no accumulation

• Although RACECADOTRIL passes the blood-brain barrier:
  – It is rapidly and completely converted to hydrophilic thiorphan, which cannot pass the blood-brain barrier
  – Thus entry to the brain and thereby possibility of CNS adverse effects is precluded

• Thiorphan is highly protein bound (90%) – does not affect protein binding of other drugs

1. Racecadotril 100 mg local approved leaflet
• Angiotensin converting enzyme inhibitors (ACE-inhibitors), such as captopril, enalapril, lisinopril, fosinopril, perindopril, ramipril are known to induce angioedema. This risk could be increased in presence of racecadotril.

• Thiorphan converted to inactive metabolites

• No accumulation after repeated administration

• Pharmacokinetics of racecadotril not altered by other medications used in treating diarrhoea (loperamide, nifuroxazide)

• In vitro data indicate that racecadotril/thiorphan and the 4 major inactive metabolites do not inhibit/induce the CYP enzymes isoforms (3A family 2A6, 2B6, 2C9/2C19, 1A family, 2E1) and UGTs conjugating enzymes to an extent that would be clinically relevant.
EXCRETION IS PRIMARILY RENAL

- Primarily eliminated renally as inactive metabolites
- In hepatic failure, $T_{\text{max}}$ and $T_{\frac{1}{2}}$ remain similar and $C_{\text{max}}$ and AUC are reduced as compared to healthy subjects
- In severe renal failure, $C_{\text{max}}$ is reduced, $T_{\frac{1}{2}}$ and AUC are increased as compared to healthy subjects
- Similar pharmacokinetics in adults and children
- No dosage adjustment is required in the elderly
PHARMACODYNAMIC PROPERTIES OF RACECADOTRIL

• Thiorphan, the active metabolite of RACECADOTRIL is associated with:
  – Pure intestinal antisecretory effect
  – Reduced hypersecretion but not basal secretion
  – No effect on intestinal transit
  – No abdominal distension
  – Inhibition of enkephalinase, an enzyme responsible for breakdown of enkephalins and thus prolong their antisecretory effect
  – Mechanism of action discussed in detail in up-coming slides
HYPERSECRETION RESULTS FROM REDUCED ENKEPHALIN ACTIVITY DURING INFECTIOUS DIARRHOEA

RACECADOTRIL NORMALISES SECRETION BY PRESERVING ENKEPHALIN ACTIVITY

Enkephalins

Delta receptor

K⁺, H₂O, Na⁺, Cl⁻

c-AMP

Toxic peptides from viruses / bacteria

Racecadotril

Enkephalinase

**RACECADOTRIL – THERAPEUTIC INDICATIONS**

- **Adults**
  - Symptomatic treatment of acute diarrhoea. If causal treatment of acute diarrhea is possible, racecadotril can be co-administered.

- **Children**
  - Complementary symptomatic treatment of acute diarrhoea in infants (older than 3 months) and children together with oral rehydration (ORS). If causal treatment of acute diarrhea is possible, racecadotril can be co-administered.
WEIGHT- BASED DOSING IN INFANTS AND CHILDREN

• Administration via the oral route, together with oral rehydration
• The recommended dose is determined according to body weight: 1.5mg/kg per dose (corresponding to 1 to 2 sachets), three times daily at regular intervals:
  - in infant less than 9 kg: one 10mg sachet 3 times daily
  - in infant from 9kg to 13kg: two 10mg sachets 3 times daily
  - in children from 13kg to 27kg: one 30mg sachet 3 times daily
  - in children of more than 27kg: two 30mg sachets 3 times daily

Due to the presence of sucrose, RACECADOTRIL is contraindicated in patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption syndrome or sucraseisomaltase insufficiency.
## WEIGHT-BASED DOSING IN INFANTS AND CHILDREN

<table>
<thead>
<tr>
<th>Age</th>
<th>3-9 months</th>
<th>9-30 months</th>
<th>30 months-9 years</th>
<th>+ 9 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose (mg TID)</strong></td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td><strong>Sachets / Dose</strong></td>
<td>1 x 10 mg sachet ‘infants’ TID</td>
<td>2 x 10 mg sachets ‘infants’ TID</td>
<td>1 x 30 mg sachet ‘children’ TID</td>
<td>2 x 30 mg sachets ‘children’ TID</td>
</tr>
</tbody>
</table>

**RACECADOTRIL** granules are contraindicated in patients with fructose intolerance, glucose malabsorption syndrome and saccharase-isomaltase deficiency

1. Racecadotril 100 mg local approved leaflet
Posology and method of administration

For oral use.
The usual daily dose is determined according to body weight on the basis of 1.5 mg/kg per administration, with an initial administration followed by three administrations in the course of the day.

*In practice:*

Number of sachet(s) per administration according to the infant’s body weight:

From 1 month to 9 months (less than 9 kg): 1 sachet per administration.

From 9 months to 30 months (about 9 to 13 kg): 2 sachets per administration.

1. Racecadotril 100 mg local approved leaflet
WEIGHT-BASED DOSING IN CHILDREN – Racecadotril 30 mg

Posology and method of administration
For oral use.
The usual daily dose is determined according to body weight on the basis of 1.5 mg/kg per administration, with an initial administration followed by three administrations in the course of the day.

In practice:
Number of sachet(s) per administration according to the child’s body weight:
From 30 months to 9 years (approximately 13 to 27 kg): 1 sachet per administration.
Over 9 years (approximately over 27 kg): 2 sachets per administration.

1. Racecadotril 100 mg local approved leaflet
DOSING IN ADULTS – Racecadotril 100 mg Adults

• Administration via the oral route
• One capsule initially regardless of the time of day. Then, one capsule three times daily preferably before the main meals.
• Treatment should be continued until two normal stools are recorded.
• Treatment should not exceed 7 days
• Long-term treatment with racecadotril is not recommended.

Posology and method of administration
For oral use.
Adults: In the treatment of acute diarrhoea, one capsule initially regardless of the time of day, and then one capsule before the three main meals. The treatment should not be continued for more than 7 days. The administration of Hidrasec does not dispense with the need for rehydration, if this is necessary.
CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Patients who have reported angioedema with angiotensin converting enzyme inhibitors (such as captopril, enalapril, lisinopril, perindopril, ramipril) should not take racecadotril.
SPECIAL WARNINGS AND PRECAUTIONS FOR USE

• The administration does not modify the usual rehydration regimens.

• Presence of bloody or purulent stools and fever may indicate presence of invasive bacteria as a reason for diarrhoea or the presence of other severe disease, warranting causal (e.g. antibiotic) treatment or further investigation. Racacadotril may be given concomitantly with antibiotics in case of acute diarrhoea with a bacterial cause as a complementary treatment.

• Use of racecadotril in antibiotic-associated diarrhoea and chronic diarrhoea is not recommended due to insufficient data.

• Product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

• Occurrence of skin reactions has been reported with the use of the product.

1. Racecadotril 100 mg local approved leaflet
UNDESIRABLE EFFECTS – 100mg capsule

• Nervous system disorders: Common: headache. (common: ≥1/100 to < 1/10).

• Skin and subcutaneous tissue disorders: Uncommon: rash, erythema. (uncommon: ≥ 1/1000 to < 1/100), Unknown: erythema multiforme, tongue oedema, face oedema, lip oedema, eyelid oedema, angioedema, urticaria, erythema nodosum, rash papular, prurigo, pruritus, toxic skin eruption.

1. Racecadotril 100 mg local approved leaflet
Racecadotril does not produce abdominal distension. During its clinical development, racecadotril produced secondary constipation at a rate comparable to placebo.

When administered via the oral route, its activity is exclusively peripheral, with no effects on the central nervous system.
UNMET NEEDS
THE IDEAL TREATMENT FOR ACUTE DIARRHOEA

- Inhibits fluid secretion by intestinal mucosa
- Prevents dehydration and malnutrition
- Reduces the duration and severity of diarrhoea
- Has a rapid onset of action
- Limited constipating effects
- High therapeutic index
- Minimal central nervous system effects
- Low abuse potential

Racecadotril was developed specifically with these characteristics in mind

UNMET NEEDS IN THE MANAGEMENT OF ACUTE DIARRHOEA

• Rational mode of action (resolve the underlying cause of acute diarrhoea)
• High efficacy rates (stool output)
• Fast onset of action
• Good tolerability and safety profile in children and infants
• Good synergy with oral rehydration therapy (ORT)
• License for use in children and small infants

CLINICAL ADVANTAGES OF RACECADOTRIL

RACECADOTRIL: PRODUCT HIGHLIGHTS

• Novel mode of action
• Rapid onset of action
• High efficacy rates
• Tolerability and safety profile similar to placebo
• Positive endorsement in paediatric guidelines (ESPHGAN & Canadian guidelines (level I))

ESPGHAN- ESPID, European Society for Paediatric Gastroenterology, Hepatology, and Nutrition/European Society for Paediatric Infectious Diseases
KEY CLINICAL TRIALS – META-ANALYSIS PEDIATRIC FORMULATION
OBJECTIVE
To study the efficacy of racecadotril in infants and children with acute gastroenteritis compared to placebo from Individual Patient Raw Data (IPD).

Meta-analysis of 9 RCTs (1384 randomised patients)
- Individual Patient raw Data of RCTs were used for analysis
- At least racecadotril and placebo were randomised in RCTs
- Male and female, infants and children from 1 month to 15 years old
- Outcomes
  - Duration of diarrhoea
  - Number of diarrhoeic stools
  - Inpatients - stool output during the first 48 hrs.
  - Outpatients - Total number of diarrhoeic stools until recovery

Lehert P. et al., *Dig Liver Dis.* 2011; S43(9):707-713.
## RESULTS OF INDIVIDUAL STUDIES AND META-ANALYSIS ON RESPONDER PROPORTION: Lehert P et al., 2011

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Weight</th>
<th>Risk Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Events</strong></td>
<td><strong>Total</strong></td>
<td><strong>Events</strong></td>
<td><strong>Total</strong></td>
<td><strong>Weight</strong></td>
</tr>
<tr>
<td>Cezard-01</td>
<td>61</td>
<td>89</td>
<td>31</td>
<td>83</td>
</tr>
<tr>
<td>SalazarLindo-00</td>
<td>47</td>
<td>68</td>
<td>28</td>
<td>67</td>
</tr>
<tr>
<td>Savitha-05</td>
<td>21</td>
<td>30</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>Gutierrez1-10</td>
<td>60</td>
<td>135</td>
<td>18</td>
<td>135</td>
</tr>
<tr>
<td>Cojocaru-02</td>
<td>27</td>
<td>81</td>
<td>11</td>
<td>83</td>
</tr>
<tr>
<td>Santos-09</td>
<td>35</td>
<td>88</td>
<td>23</td>
<td>91</td>
</tr>
<tr>
<td>Alvarez-09</td>
<td>19</td>
<td>84</td>
<td>12</td>
<td>86</td>
</tr>
<tr>
<td>Melendez-07</td>
<td>19</td>
<td>25</td>
<td>13</td>
<td>25</td>
</tr>
<tr>
<td>Gutierrez2-10</td>
<td>63</td>
<td>92</td>
<td>23</td>
<td>92</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>692</strong></td>
<td><strong>692</strong></td>
<td><strong>100%</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Total events 352 168**

**Heterogeneity: \( \chi^2 = 13.06, \text{df} = 8 (P=0.11); I^2 = 39\% \)**

**Test for overall effect: Z=9.39 (P<0.00001)**

* Response defined as diarrhoea duration < 2 days

---

1. Lehert P. et al., *Dig Liver Dis.* 2011; S43(9):707-713.
**META-ANALYSIS RESULTS: Lehert P et al., 2011**

- Highly significant predictors were dehydration level and rotavirus infection

<table>
<thead>
<tr>
<th>Results</th>
<th>Placebo</th>
<th>Racecadotril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea duration after inclusion (Median days) $P&lt;0.001$</td>
<td>2.81</td>
<td>1.75</td>
</tr>
<tr>
<td>Responders (patients with duration of diarrhoea &lt;2 days) RR=1.98</td>
<td>25.8%</td>
<td>50.3%</td>
</tr>
<tr>
<td>Need for i.v. rehydration (3 studies on out-patients) $P&lt;0.05$</td>
<td>12/37</td>
<td>4/35</td>
</tr>
</tbody>
</table>

1. Lehert P. et al., *Dig Liver Dis.* 2011; S43(9):707-713.
KEY CLINICAL TRIALS IN ADULTS
## SUMMARY OF LIST OF STUDIES IN ADULTS

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Type</th>
<th>Inclusion</th>
<th>N (RAC/Cont)</th>
<th>Primary Efficacy</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baumer et al., 1992</td>
<td>Multicentre, double-blind, randomised, placebo-controlled, parallel-group study in France</td>
<td>Acute diarrhoea of presumed infectious origin Patients aged &gt;18 years</td>
<td>96/98</td>
<td>Duration of diarrhoea</td>
<td>RAC 200 mg, then 100 mg after each unformed stool x 10 days or resolution Placebo for 10 days or until resolution</td>
</tr>
<tr>
<td>Hamza et al., 1999</td>
<td>Multicentre, double-blind, randomised, placebo-controlled study in Tunisia</td>
<td>Acute diarrhoea of presumed infectious origin Patients aged &gt;18 years</td>
<td>32/38 (ITT)</td>
<td>Stool weight on day 1</td>
<td>RAC 100 mg TID x 6 days, or until recovery Placebo</td>
</tr>
<tr>
<td>Rogé et al., 1993</td>
<td>Single-centre, double-blind, randomised, parallel-group study in France</td>
<td>Acute diarrhoea of presumed infectious origin Patients aged &gt;18 years</td>
<td>37/32</td>
<td>Duration of diarrhoea</td>
<td>RAC 200 mg, then 200 mg in 12 h. Then 100 mg TID x 7 days or resolution LOP 2.66 mg, then 2.66 mg in 12 h. Thereafter 1.33 mg TID x 7 days or until resolution</td>
</tr>
<tr>
<td>Vetel et al., 1999</td>
<td>Multicentre, randomised, double-blind, double-placebo, active controlled study in France</td>
<td>Outpatients with acute diarrhoea Patients aged &gt;18 years</td>
<td>77/70 (ITT)</td>
<td>Number of diarrhoeic stools passed until recovery</td>
<td>RAC 100 mg PO TID x 7 days, or until recovery LOP 2 mg PO after each diarrheic stool</td>
</tr>
<tr>
<td>Prado et al., 2002</td>
<td>Multicentre, multinational, single-blind, randomised trial</td>
<td>Acute watery diarrhoea of presumed infectious origin Patients aged &gt;18 years</td>
<td>473/471 (ITT)</td>
<td>Duration of diarrhoea</td>
<td>RAC 100 mg PO TID until recovery LOP 2 mg PO TID until recovery</td>
</tr>
<tr>
<td>Wang et al., 2005</td>
<td>Multicentre, randomised, single-blind controlled study in Taiwan</td>
<td>Acute diarrhoea of presumed infectious origin Patients aged &gt;18 years</td>
<td>31/31 (ITT)</td>
<td>Duration of diarrhoea from first treatment to recovery</td>
<td>RAC 100 mg PO TID until recovery LOP 2 mg PO TID until recovery</td>
</tr>
<tr>
<td>Gallelli et al., 2010</td>
<td>Multicentre, randomised, double-blind, loperamide-controlled study in Italy</td>
<td>Elderly patients with acute diarrhoea Patients aged 73-96 years</td>
<td>30/31 (ITT)</td>
<td>Duration of diarrhoea</td>
<td>RAC 100 mg TID LOP 4 mg followed by 2 mg after each unformed stool</td>
</tr>
</tbody>
</table>

**RAC=Racecadotril; ITT=Intent To Treat; TID= Thrice a day; PO=Per Oral; LOP=Loperamide;**

EFFECTS OF ACETORPHAN, AN ENKEPHALINASE INHIBITOR, ON EXPERIMENTAL AND ACUTE DIARRHEA: Baumer et al., 1992

STUDY OBJECTIVE
To compare the efficacy, safety and tolerability of racecadotril and placebo in adult patients with acute watery diarrhoea

STUDY DESIGN
Double-blind, randomised, placebo-controlled, parallel group study

Patients
96
Racecadotril (Acetorphan)

98
Placebo (Lactose)

Total: 194

INCLUSION CRITERIA
• More than 3 stools in the last 24 hours
• Onset of diarrhoea-less than 5 days

EFFICACY AND TOLERABILITY RESULTS: Baumer et al., 1992

Frequency of Adverse Events (Number of Patients)

<table>
<thead>
<tr>
<th>Event</th>
<th>Racecadotril (Acetorphan) (96)</th>
<th>Placebo (98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Thirstiness</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Vertigo</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Constipation</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

TOLERANCE
Frequency and nature of adverse events were similar in both groups

RAC: Racecadotril
TOLERABILITY RESULTS: Baumer et al., 1992

RACECADOTRIL VS PLACEBO IN THE TREATMENT OF ACUTE DIARRHOEA IN ADULTS: Hamza et al., 1999

STUDY OBJECTIVE
To compare the efficacy and tolerability of racecadotril and placebo in adult patients with acute diarrhoea

STUDY DESIGN
Two-centre, double-blind, parallel group randomised study

Patients

Racecadotril

Placebo

Total: 70

INCLUSION CRITERIA
- Age: >18 years
- Suffering from acute diarrhoea
- >3 loose stools in the last 24 hours
- Onset of diarrhoea: less than 5 days

EFFICACY RESULTS: Hamza et al., 1999

Mean stool weight during the first 24 hours under treatment

<table>
<thead>
<tr>
<th>Stool weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Racecadotril: 355±35g</td>
</tr>
<tr>
<td>Placebo: 499±46g</td>
</tr>
</tbody>
</table>

\[ P = 0.025 \]

TOLERABILITY AND SAFETY RESULTS: Hamza et al., 1999

<table>
<thead>
<tr>
<th>TOLERABILITY AND SAFETY</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Percentage of patients suffering from adverse events on day 4</td>
</tr>
<tr>
<td>• Racecadotril: 3.1%</td>
</tr>
<tr>
<td>• Placebo: 5.3%</td>
</tr>
<tr>
<td>• Percentage of patients suffering from abdominal distension on day 4</td>
</tr>
<tr>
<td>• Racecadotril: 5.6%</td>
</tr>
<tr>
<td>• Placebo: 18.2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADVERSE EVENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Racecadotril Group: Dizziness and malaise: 1 patient</td>
</tr>
<tr>
<td>Placebo group: Moderate backache: 1 patient</td>
</tr>
<tr>
<td>Placebo group: Abdominal distension: 1 patient</td>
</tr>
</tbody>
</table>

CONCLUSION

• Good tolerability of racecadotril vs. placebo
• Rapid efficacy in acute diarrhoea in adults

THE ENKEPHALINASE INHIBITOR, ACETORPHAN, IN ACUTE DIARRHOEA: A DOUBLE-BLIND, CONTROLLED CLINICAL TRIAL VERSUS LOPERAMIDE: Roge et al., 1993

STUDY OBJECTIVE
To compare the clinical efficacy and tolerability of racecadotril and loperamide in adult patients with acute diarrhoea

STUDY DESIGN
Single centre, double-blind, randomised, active-controlled, parallel-group study

Study period: Up to 7 days or until resolution

Patients

37

Racecadotril

INCLUSION CRITERIA
• Age: >18 years
• Acute diarrhoea of presumed infectious origin
• >2 liquid stools in 24 hours
• Onset of diarrhoea: less than 5 days

32

Loperamide

Total: 69

### EFFICACY AND TOLERABILITY RESULTS: Roge et al., 1993

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Racecadotril</th>
<th>Loperamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Delay of diarrhoea resolution</td>
<td>2.2 ± 0.2 days</td>
<td>2.3 ± 0.2 days (NS)</td>
</tr>
<tr>
<td>• Cumulative recovery on day 2</td>
<td>59.3%</td>
<td>50.0% (NS)</td>
</tr>
<tr>
<td>• Duration of abdominal distension</td>
<td>1.1 ± 0.2 days</td>
<td>1.8 ± 0.3 days (P&lt;0.05)</td>
</tr>
<tr>
<td>• Abdominal distension for &gt; 1 day</td>
<td>27%</td>
<td>50% (P&lt;0.05)</td>
</tr>
<tr>
<td>• Abdominal pain for &gt; 1 day</td>
<td>40.5%</td>
<td>59.4% (NS)</td>
</tr>
<tr>
<td>• Constipation after diarrhoea resolution</td>
<td>8.1%</td>
<td>31.3% (P&lt;0.02)</td>
</tr>
<tr>
<td>• Duration of treatment</td>
<td>3.0 ± 0.2 days</td>
<td>4.4 ± 0.3 days (P&lt;0.0001)</td>
</tr>
</tbody>
</table>

NS: Not Significant

COMPARISON OF RACECADOTRIL AND LOPERAMIDE IN ADULTS WITH ACUTE DIARRHOEA: Vetel et al., 1999

STUDY OBJECTIVE
To compare the efficacy, safety and tolerability of racecadotril and loperamide in adult patients with acute diarrhoea.

STUDY DESIGN
Double-blind, randomised, double-placebo controlled, parallel group study.

INCLUSION CRITERIA
- Age: >18 years
- Suffering from acute diarrhoea
- >3 loose stools for a minimum of 24 hours and a maximum of 5 days
- Onset of diarrhoea-less than 5 days

Patients
- Racecadotril: 82
- Loperamide: 75
- Total: 157

EFFICACY RESULTS: Vetel et al., 1999

Efficacy: similar

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Racecadotril</th>
<th>Loperamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of diarrhoea</td>
<td>14.9 ±2.0h</td>
<td>13.7±2.2h</td>
</tr>
<tr>
<td>Number of stools</td>
<td>3.5±0.5</td>
<td>2.9±0.4</td>
</tr>
<tr>
<td>Efficacy on visual analogue scale</td>
<td>83.7±2.1</td>
<td>82.2±2.3</td>
</tr>
</tbody>
</table>

Both the groups had similar efficacy

TOLERABILITY RESULTS: Vetel et al., 1999

Tolerance: better

- As effective as loperamide in treating acute diarrhoea
- Less likely to be associated with adverse events like constipation

Criteria | Racecadotril | Loperamide |
---|---|---|
Incidence of adverse events | 7.4% | 12% |
Rebound constipation | 9.8% | 18.7% |
Mean duration of constipation | 1.3±0.1 | 1.6±0.1 |

A MULTINATIONAL COMPARISON OF RACECADOTRIL AND LOPERAMIDE IN THE TREATMENT OF ACUTE WATERY DIARRHOEA IN ADULTS: Prado et al., 2002

STUDY OBJECTIVE
To compare the clinical efficacy and tolerability of racecadotril and loperamide in adult patients with acute diarrhoea

STUDY DESIGN
Multicentre, multi-national, single-blind, randomised, parallel-group comparative study

Patients

Racecadotril

473

Placebo

472

Total: 945

INCLUSION CRITERIA
• Age: ≥18 years
• 3 or more watery stools, with no visible blood, in the last 24 hours
• Onset of diarrhoea of presumed infectious origin, of at least 24 hours and less than 5 days

EFFICACY RESULTS: Prado et al., 2002

Rapid onset of action upon diarrhoea (International study)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Racecadotril</th>
<th>Loperamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Clinical Response (%)</td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td>Duration of Diarrhoea (hours)</td>
<td>55</td>
<td>55</td>
</tr>
</tbody>
</table>

**TOLERABILITY RESULTS AND CONCLUSION: Prado et al., 2002**

- **Racecadotril**: Safe, efficacious and tolerable in the treatment of acute diarrhoea in adults.
- Achieved a higher clinical success rate than loperamide.
- Adverse events: less constipation and a rapid resolution of abdominal distension and pain.

### Total Adverse Events
- **RAC**: 14.2%
- **LOP**: 23.9%
- \( P = 0.001 \)

<table>
<thead>
<tr>
<th>Adverse Event (by preferred term)</th>
<th>Racecadotril (n=473)</th>
<th>Loperamide (n=472)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>16 (3.4%)</td>
<td>59 (12.5%)</td>
</tr>
<tr>
<td>Abdomen enlarged</td>
<td>8 (1.7%)</td>
<td>29 (6.1%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>4 (0.8%)</td>
<td>11 (2.3%)</td>
</tr>
<tr>
<td>Headache</td>
<td>10 (2.1%)</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (0.2%)</td>
<td>9 (1.9%)</td>
</tr>
</tbody>
</table>

RAC: Racecadotril  
LOP: Loperamide  

STUDY OBJECTIVE
To study the efficacy, tolerability, and safety of racecadotril and loperamide in elderly patients with acute diarrhoea

STUDY DESIGN
Randomised, prospective, double-blind, parallel group study

Patients

100 mg Racecadotril

30

INCLUSION CRITERIA
• Adults with acute diarrhoea, without signs of severe dehydration and bacterial infection
• ≥ 3 watery stools in 24 hours

2.0 mg Loperamide

31

Total: 61

EFFICACY RESULTS: RACECADOTRIL VS LOPERAMIDE: Galleli et al., 2010

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Racecadotril</th>
<th>Loperamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean total stool output before recovery (hours)</td>
<td>120±27 g/kg</td>
<td>150±39 g/kg</td>
</tr>
</tbody>
</table>

### TOLERABILITY AND SAFETY RESULTS: RACECADOTRIL VS LOPERAMIDE - Gallelli et al., 2010

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Racecadotril (% number of patients)</th>
<th>Loperamide (% number of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurrence of adverse events</td>
<td>12%</td>
<td>60%</td>
</tr>
<tr>
<td>Nausea</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>Constipation</td>
<td>15%</td>
<td>60%</td>
</tr>
</tbody>
</table>

Racecadotril is more effective and tolerable than loperamide

---

RACECADOTRIL EFFICACY IN THE SYMPTOMATIC TREATMENT OF ADULT ACUTE DIARRHOEA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Vetel et al., International Journal of Clinical Medicine, 2014;5:361-375.
OBJECTIVE
To examine whether Racecadotril (RC) reduces diarrhoea duration, assessing the efficacy of RC for the symptomatic treatment of acute diarrhoea in adults

Systematic review of randomised controlled trials (RCTs) performed in adults suffering from acute diarrhoea using RC as one treatment arm
- Twelve randomised trials (2619 patients) met the inclusion criteria
- Main efficacy endpoint was diarrhoea duration (DD) defined as time to recovery compared between groups
- Constipation proportion was the main safety endpoint, evaluated between treatments by the Relative Risks (RR)


STUDY DESIGN
Systematic Review
All RCTs, double-blind or single blind studies exclusively using a random-effect meta-analytic model

INCLUSION CRITERIA
- Age: >18 years
- Male and female
- Suffering from acute diarrhoea, any cause except cholera, healthy volunteers, paediatric patients, patients with chronic HIV-related diarrhoea, or due to anti-cancerous chemotherapy

INTERVENTION
- RC
- Adult formulation, without dosage restriction

OUTCOMES
- DD from treatment onset to the last unformed stools
- Safety, in particular treatment related constipation adverse effect


Details of the 12 RCTs used for the meta-analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Control group</th>
<th>Design</th>
<th>ITT sample size</th>
<th>PP sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RC</td>
<td>ITT Control</td>
<td>PP Control</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RC</td>
<td>ITT Control</td>
<td>PP Control</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baumer P</td>
<td>Placebo</td>
<td>DB</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>Hamza H</td>
<td>Placebo</td>
<td>DB</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Vetel JM (multidose)*</td>
<td>Placebo</td>
<td>DB</td>
<td>173</td>
<td>173</td>
</tr>
<tr>
<td>Moraes E</td>
<td>Sb = Saccharomyces bouardii</td>
<td>SB</td>
<td>207</td>
<td>175</td>
</tr>
<tr>
<td>Coffin B &amp; Rampal P*</td>
<td>Placebo</td>
<td>DB</td>
<td>86</td>
<td>83</td>
</tr>
<tr>
<td>Rogé J</td>
<td>Loperamide</td>
<td>DB</td>
<td>40</td>
<td>37</td>
</tr>
<tr>
<td>Vetel JM</td>
<td>Loperamide</td>
<td>DB</td>
<td>82</td>
<td>77</td>
</tr>
<tr>
<td>Prado D</td>
<td>Loperamide</td>
<td>SB</td>
<td>473</td>
<td>473</td>
</tr>
<tr>
<td>Coulden S*</td>
<td>Loperamide</td>
<td>SB</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Lin Sanren SB006*</td>
<td>Loperamide</td>
<td>SB</td>
<td>112</td>
<td>111</td>
</tr>
<tr>
<td>Wang HH</td>
<td>Loperamide</td>
<td>SB</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Gallelli L</td>
<td>Loperamide</td>
<td>DB</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td><strong>All studies (n = 12)</strong></td>
<td></td>
<td></td>
<td>1422</td>
<td>1378</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1295</td>
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Results: Diarrhoea duration forest plot – comparison of RC versus placebo

- 65% more patients were observed to recover in the RC group compared with placebo (HR = 1.65 [1.38 - 1.97], p < 0.00001)

**Results:** Constipation occurrences forest plot – comparison of RC versus placebo

- Constipation was similar between RC and placebo arms (RR = 0.95 [0.24 - 3.68], p = 0.97)

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Study limitations:

• RC dose differed between studies and sometime from the SmPC
• The definition of constipation was not homogeneous among studies as there is no universal definition of constipation

Conclusions:

• Compared to placebo, RC is characterised by a clinically relevant earlier remission of diarrhoea in adults experiencing acute diarrhoea.

• When RC was compared to loperamide, diarrhoea duration was similar, but significantly fewer secondary constipation adverse effects were observed.

THANK YOU