2009-2011

Update to the EU Guideline on Antibacterial Agents

Current guidance

- Note for Guidance on evaluation of medicinal products indicated for treatment of bacterial infections

  CPMP/EWP/558/95 rev 1; 2004

- Replaced 1997 version and a separate section 5.1 guidance document

- Includes microbiology, PK/PD, clinical development and sections of the SPC

Revision started 2009

5 years experience indicated need to:

- Clarify position on some issues
- Establish a position on some issues
- Modify position on some issues

Antibacterial agents 1997-2010
* since 2004

- Daptomycin *
- Telithromycin
- Tigecycline *
- Ertapenem
- Doripenem *

MRP

- Levofloxacin
- Cefditoren
- Linezolid
- Moxifloxacin
- Synercid

- Oritavancin *
- Dalbavancin *
- Telavancin *
- Ceftobiprole *
- Iclaprim *
- Gemifloxacin *
- Garenoxacin *
- Trovafloxacin

MRP

- Cefdinir
- Grepafloxacin
- Gatifloxacin

Revision Plan

- Concept paper adopted Feb 2009
- Release for consultation Feb 2010
- Consultation extended from August to November 2010 due to planned WS
- Finalisation during 2011 (2Q)

Content of Presentations

- What does the current draft say on the topic ?
- Rationale for current draft ?
- Comments received ?
- Updated proposal (if appropriate)

Non-inferiority studies

- Accepted for all indications for which superiority studies not feasible or not considered necessary
- Patient selection criteria and choice of comparator critically important
- Primary endpoint = clinical and/or microbiological outcome at TOC

Non-inferiority studies

- It is preferred that each clinical indication for use is supported by at least two randomised and controlled studies
- The provision of a single pivotal study may be acceptable if this has been conducted in accordance with applicable CHMP guidance
- The choice of non-inferiority margin requires particular attention in accordance with the available CHMP guidance

HAP/VAP – example

DORI-09 HAP/early VAP
Expected cure rate ~ 65% according to piptazobactam NP studies

DORI-10 VAP
Expected cure rate ~ 60% based on previous imipenem studies

Both studies pre-defined a NI margin -20%

ACTUAL lower bound 95% CI in both studies and both co-primary populations were all within -10%

APPROVED FOR:
- ***Nosocomial pneumonia, including ventilator-associated pneumonia***

cSSTI – example

9801 Daptomycin vs. vancomycin or SSP

9901 Daptomycin vs. vancomycin or SSP

The primary efficacy endpoint was clinical outcome at TOC in CE and MITT populations

The pre-defined NI margin was 10% for both studies

ACTUAL lower bound 95% CI in both studies and both co-primary populations were all within -9%

Comments received

- Request to specify the acceptable NI margins (e.g. cSSTI, CAP, HAP/VAP, cUTI, IAI)
- Request to provide more detailed guidance on patient selection criteria
- Request to re-consider pre-approval requirements (study size; single study)
- How to meet different regulatory expectations using same studies?

NI studies - future

- State that same studies can be used to satisfy more than one regulatory body
- Specify single primary endpoint for protocol that would lead to the largest sample size
- Develop separate SAPs for each agency
- Will further discuss developing an addendum with indication-specific guidance

Superiority studies - issues

- NI studies unreliable if active treatment not consistently superior to placebo in a defined patient population/subset
- Results cannot establish that test agent would be superior to placebo if compared
- Constancy is also an issue i.e. historical data vs. no treatment/placebo might not give the same results if repeated in 2009

Superiority studies - 2004

- Superiority vs placebo expected in infections with high spontaneous cure rates
- Justify absence of superiority study
- Third (active treatment) arm preferred
- No mention of superiority vs an active control
- CHMP objected to AECB and ABS based on NI only

Superiority studies - 2010

- In such cases superiority study expected
  e.g. AMS, AECB, OM, some topical uses

- If vs. placebo inclusion of a third (active comparator) arm is preferred
  [Not necessary to show NI vs. comparator]

- If vs. active comparator then superiority vs. active based on a clinical endpoint *demonstrating benefit* sufficient

Comments received

- Superiority vs. active comparator rather than placebo is welcomed as an option
- Request for specific examples
- Possible situations in which superiority cannot be demonstrated for any variable
- Sub-populations exist in which NI could and should be acceptable

Superiority studies - future

- Recognition that placebo control design not acceptable in some sub-populations
- Still paucity of consistent data to indicate and define these sub-populations
- Leave open possibility that sponsor may provide adequate evidence to support selection of a NI margin applicable to a well-defined population

Rare infections/pathogens – 2004

Possible licensure based on "limited data" for agents shown to be clinically active against:

- ***Problematic resistant organisms***
- ***Difficult to treat and/or rare infections***
- ***Infections with few treatment options***

Advice from EU Regulators should be sought

Rare infections/pathogens - 2010

- No clinical data possible *OR*
- Very limited clinical data possible
- Data may be collected during a (large) indication-specific study and/or a (smaller) targeted study

Rare infections/pathogens -2010

- Adequately powered RCT not possible
- Randomisation step always preferred
- The justification for a randomised study planned with lower than standard levels of statistical power must include comment on the prevalence of the infection and on the statistical performance characteristics of the trial (e.g. Type I and Type II errors to investigate an effect size of interest)

Rare infections/pathogens - 2010

- Aim for 10-20 cases per treatment group
- < 10 per group may be acceptable if very rare
- Pool data across studies in single indication if same or very similar design and population
- *For very rare pathogens it may be appropriate to conduct studies in which patients with clinically confirmed infections due to these organisms are enrolled regardless of the site of the infection*

Rare infections/pathogens Comments

- Pool data across indications if same body site (e.g. CAP/HAP; IAI/Pelvic) or across all sites?
- Unqualified pathogen-specific indications?
- Supplement indication-specific NI study with study of rare pathogens vs. OBT (low power) including wide range of infection types?
- No licensed OBT patients default to test agent in a parallel non-comparative arm?

Rare infections/pathogens – 2004

Clinical efficacy against MDR organisms:

If activity of new agent is unaffected:

no need to search for organisms of the species with this/these types of resistance in clinical trials

If activity affected but efficacy still expected:

at least limited clinical data should be sought

Rare infections/pathogens – 2010

In-vitro activity unaffected by R-mechanism(s) to other agent(s) or affected but efficacy still expected (e.g. animal models, PK/PD):

..patients harbouring multidrug-resistant pathogens are more likely to have already received other agents and to have underlying conditions that complicate the clinical course so that clinical and microbiological success rates may be lower and more variable

At least limited clinical data should be sought

“Problematic” indications

Indications discussed 2010 include:

- **Bacteraemia**
- **Febrile neutropenia**
- **Catheter-related infections**
- **Eradication of carriage**

Bacteraemia

- Defined as the isolation from blood culture(s) of one or more species likely to be responsible for or contributing to the clinical signs and symptoms of infection

- A qualified indication for:

  treatment of bacteraemia when occurring in association with [type of infection ± restriction to specific pathogens]

  might be considered on provision of a sufficient number of cases

Bacteraemia

- Unqualified implies can treat any underlying infection focus and associated with any pathogen

- Qualification by pathogen still implies treatment of any underlying infection focus

Recent Example – Art 30

- The current draft guidance suggests that an indication for use in bacteraemia ± qualification by species might be possible once an agent has been approved for a wide range of indications

- This statement was re-considered w.r.t. CHMP decision on 3 parallel Art 30 applications completed in late 2010

Recent Example – Art 30

Adults and adolescents

- Severe pneumonia including hospital-acquired and ventilator-associated pneumonia
- Complicated urinary tract infections (including pyelonephritis)
- Complicated intra-abdominal infections
- Complicated skin and soft tissue infections (including diabetic foot infections)

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Tazocin may be used in the management of neutropenic patients with fever suspected to be due to a bacterial infection.

Bacteraemia - comments

- Few based on current wording
- More concern regarding guidance re catheter-related infection and eradication of carriage

Eradication of carriage

- Indications that relate to the reduction or eradication of a pathogen from a specified body site are not acceptable unless the microbiological findings were shown to result in a measurable clinical outcome
- Require a placebo-controlled study (unless usage has become widely accepted as SOC)
- Use of published data to substantiate link between eradication and clinical benefit not acceptable (with one exception)

Eradication of carriage

- Fully validated microbiological techniques must be used to detect and quantify pathogens (may need pilot study)
- Need to define reduction in or eradication of carriage (cfu/mL and duration) as well as failure to eradicate and relapse/re-infection
- May be appropriate to use very sensitive detection methods (such as PCR) in addition to culture and to type organisms

Eradication of carriage - comment

- Comments seem to have come from only 2 sources directly involved in developing agents intended for elimination of carriage
- Request that elimination of carriage is *per se* viewed as a clinical benefit meriting an indication for use
- Propose taking into account reduction in cross-infection but no proposal to provide data to support such claims

Section 5.1 – remove table

- Current table with classification of target pathogens according to expected susceptibility has caused many problems

- One SmPC for 30 countries
- AR is frequently pocketed; data unreliable
- Classification in terms of likely R Rates is meaningless to the individual prescriber and his local working environment

- Continue to highlight possible R problems in descriptive paragraphs regularly updated

Demonstration of clinical efficacy by pathogen

- Removing the table removes the asterisk system
- New section specific to clinical efficacy against specific pathogens, listed by indication
- Optional section to describe other very relevant species S *in vitro* but insufficient clinical data
- Optional section to describe inherently resistant species (e.g. unexpected gaps in spectrum)
- No description of studies (details in EPAR) UNLESS there is a problem that needs to be highlighted

Plans for finalisation

- IDWP will discuss comments received in writing and heard during this WS
- Aim to finalise main guidance by end 2Q 2011 for adoption by CHMP
- Will discuss possible need for an indication-specific addendum and its content
- Will draft a Concept Paper if this is agreed to be the next step (with BS WP input)