EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Keeping up-to-date, regulatory issues

ESCMID Conference on Reviving Old Antibiotics
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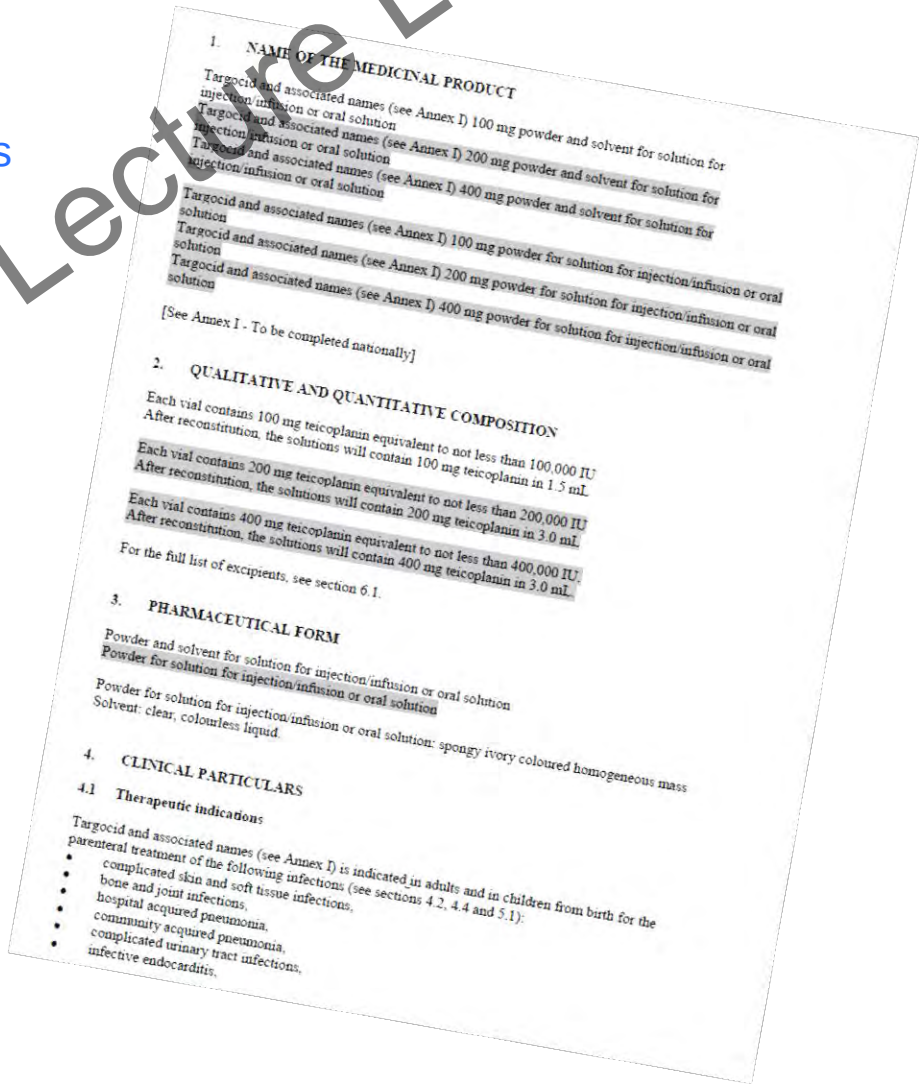
Antimicrobial resistance

- growing European and global health problem;
- MDR bacteria in the EU are associated with 25 000 extra deaths and about 1.5 billion euros extra economic burden per year;
- EMA and its EU and international partners involved in initiatives attempting to limit the development of antimicrobial resistance.

Keeping up-to-date the Product Information (PI) of old antibacterials

The Summary of Product Characteristics (SmPC)

- Legal document approved as a part of the marketing authorisation of each medicine
- Basis of information for EU healthcare professionals on how the medicine should be used
- Updated throughout the lifecycle of the product
- the Patient Leaflet (PL) is accordingly updated.



1. NAME OF THE MEDICINAL PRODUCT

Targocid and associated names (see Annex I) 100 mg powder and solvent for solution for injection/infusion or oral solution
Targocid and associated names (see Annex I) 200 mg powder and solvent for solution for injection/infusion or oral solution
Targocid and associated names (see Annex I) 400 mg powder and solvent for solution for injection/infusion or oral solution
Targocid and associated names (see Annex I) 100 mg powder for solution for injection/infusion or oral solution
Targocid and associated names (see Annex I) 200 mg powder for solution for injection/infusion or oral solution
Targocid and associated names (see Annex I) 400 mg powder for solution for injection/infusion or oral solution

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg teicoplanin equivalent to not less than 100,000 IU
After reconstitution, the solutions will contain 100 mg teicoplanin in 1.5 mL
Each vial contains 200 mg teicoplanin equivalent to not less than 200,000 IU
After reconstitution, the solutions will contain 200 mg teicoplanin in 3.0 mL
Each vial contains 400 mg teicoplanin equivalent to not less than 400,000 IU
After reconstitution, the solutions will contain 400 mg teicoplanin in 3.0 mL

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection/infusion or oral solution
Powder for solution for injection/infusion or oral solution
Powder for solution for injection/infusion or oral solution: spongy ivory coloured homogeneous mass
Solvent: clear, colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Targocid and associated names (see Annex I) is indicated in adults and in children from birth for the parenteral treatment of the following infections (see sections 4.2, 4.4 and 5.1):

- complicated skin and soft tissue infections,
- bone and joint infections,
- hospital acquired pneumonia,
- community acquired pneumonia,
- complicated urinary tract infections,
- infective endocarditis,

Different PI in different EU MSs for old antibacterials- reasons

- different procedures for approving medicines in the EU:
  - centralised procedure
  - mutual recognition procedure, decentralised procedure and purely national procedure
- old antibacterials historically only approved at national level:
  - different interpretations leading to different (wordings of) indications
- change of the regulatory requirements over time

Regulatory tools for keeping up-to-date the PI of old antibacterials across the EU

Referral procedures

•to resolve concerns regarding the safety or efficacy of medicines or benefit-risk balance of a medicine/class of medicines and to harmonise the SmPCs where necessary

•**Legal basis:**

- Directive 2001/83/EC
- Regulation (EC) 726/2004
- New PhV legislation:
  - Regulation (EU) 1235/2010
  - Directive 2010/84/EU

- Types: -"art 30" and "art 31" referrals of particular interest

  -"art 5(3)" for major anti-TB medicines, art 107 (moxifloxacin)

Other procedures: e.g. art 45, art46 of the Paediatric Regulation, etc.

Article 30* referral: the "harmonisation referral"

- triggered when Member States have adopted different decisions over the years for some medicines (e.g. different indications, contraindications or posology) and there is a need to **harmonise** across the EU.

  - article 30(1) referral: divergent decisions adopted by MSs concerning the authorisation, suspension or withdrawal of a particular medicinal product(e.g. different indications, contraindications or posology)
  - *triggered by the EC, a MS, a MAH/Applicant.*
  - article 30(2) referral: initiated for the same reasons when the medicinal product is on the list of the coordination group.

* of Directive 2001/83/EC

List of Article 30 referrals from the coordination group (CMDh)

Proactive harmonisation

- Member States propose each year products for SmPC harmonisation
- CMD(h) lays down a list and forwards it to the EC
- EC, in agreement with EMA, may refer the product

CMD(h) WP (with participation of CMD(h), CHMP, EC, EMA) on SmPC harmonisation

→ Mandate and criteria for selection agreed and published


CMDh

Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

MANDATE, OBJECTIVES AND RULES OF PROCEDURE OF THE WORKING PARTY ON THE HARMONISATION OF SUMMARIES OF PRODUCT CHARACTERISTICS

Doc. Ref.: CMDh/060/2005/Rev.1
March 2014

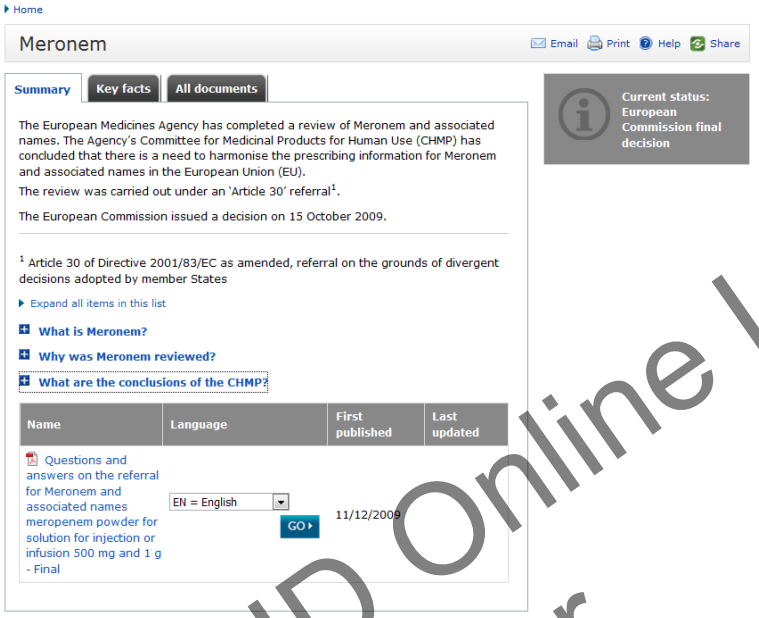
Article 30 referral triggered by the Marketing Authorisation Holder

- **voluntary** triggering of a procedure by the MAH, to harmonise the Product Information of own products.
- the MAH defines the scope of the referral (which presentations, which indications to include).
- the procedure starts with a proposal for a harmonised Product Information submitted by the MAH, to be assessed by the CHMP.

Completed art. 30 referrals for antibacterials

Approved name	INN	Associated names	Opinion date	EC decision date
Augmentin	amoxicillin+clavulanic acid		19.01.2009	19.10.2009
Ciprofloxacin Bayer	ciprofloxacin		24.07.2008	07.10.2008
Meronem	meropenem		23.07.2009	15.10.2009
Tazocin	piperacillin/tazobactam	Tazobac, Tazocel, Tazonac	21.10.2010	21.02.2011
Fortum	ceftazidime	Cefortam,. Glazidin, Panzim, Solvetan	21.10.2010	13.01.2011
Tienam	imipenem/cilastatin	Conet, Imipem, Primaxin, Tenacid, Zienam	06.12.2010	10.03.2011
Tavanic	levofloxacin	Tavanic and associated names	24.05.2012	31.07.2012
Zinacef	cefuroxime sodium	Curocef, Curoxim, Curoxim Monovial, Curoxima, Curoxime, Zinnat, Zinocep, Zinocep Vena	24.05.2012	10.09.2012
Zinnat	cefuroxime axetil	Cefuroxima Solasma, Cefuroxima Allen, Cefuroxima Duncan, Elobact, Nivador, Oraxim, Selan, Tilexim, Zinadol, Zipos, Zoref	24.05.2012	23.08.2012
Targocid	teicoplanin	Targocid, Teicomid	30.05.2013	12.09.2013
Rocephin	ceftriaxone		23.01.2014	21.03.2014

Example of finalised SmPC update: meropenem



Areas harmonised:

- 4.1 therapeutic indications
- 4.2 posology and method of administration
- 4.3. contraindications
- 4.4 special warnings and precautions for use

Harmonisation involves:

- ✓ review of evidence to support efficacy,
- ✓ rewording of older broad indications that are no longer used, to more specific indications in line with current scientific guidelines, where supported by data
- ✓ a review of the posology in all age groups.
- ✓ Section 5.1 (describing the microbiological properties) is also reviewed.

CHMP/IDWP proposal for prioritisation of harmonisation of old antibacterials SmPCs to CMDh (2011)

1. vancomycin	9. erithromycin
2. amoxicillin	10. clindamycin
3. ampicillin	11. rifampicin
4. phenoxymethylpenicillin	12. gentamicin
5. benzylpenicillin	13. tobramycin
6. cefotaxime	14. amikacin
7. azithromycin	15.TMP/SMX
8. clarithromycin	16. metronidazole
17. doxycycline	

Article 31* referral: the "union interest referral"

- triggered when the public health interest of the Union is involved, following specific concerns relating to the **quality, safety or efficacy** of a medicine/class of medicines which is/are on the market in the EU.
- *triggered by the EC, a MS, a MAH/Applicant.*
- Scope can relate to:
  - an individual medicinal product (art 31(1))
  - a range of products or a therapeutic class (art 31(2)).
- Referral type used for norfloxacin (completed) and polymyxins (ongoing)

*of Directive 2001/83/EC

Article 31* referral: Union interest referral

- assessment of safety-related issues:
  - initially conducted by the Pharmacovigilance Risk Assessment Committee (PRAC) and
  - then by the Committee for Medicinal Products for Human Use (CHMP), if the medicine is centrally authorised
  - or, if the medicine was only authorised according to the national procedures, by the Coordination Group for Mutual Recognition and Decentralised Procedures (CMDh).
- referrals other than those for safety-related issues are assessed by the CHMP only.

Article 5(3) referral

- opinions drawn up by the CHMP under Article 5(3) Regulation (EC) No 726/2004 concerning any scientific matter related to the evaluation of medicines for use in humans.
- Triggered by the EMA Executive Director, the European Commission or a Member State.
- This type of referral has been used to review the updated WHO dosing recommendations for the anti-TB medicines used in children
- The outcome is a scientific opinion and is not legally binding

Other procedures

- Art 107i referral: triggered when a MS/EC consider that urgent action is necessary because of a **safety issue** related to a medicine/class of medicines.
  - e.g. consideration for suspension/revocation of the MA for a medicine, prohibition of supply of a medicine or refusing a renewal
- Art 45. and 46 of the Paediatric Regulation
  - allow for a PI update

Keeping up-to-date-role of the emerging science

- new data generated by the academic community of great importance
- additional data on efficacy, PK and PK/PD of old antibacterials needed to allow answers to important questions
  - Exposure response relationships, determine PD target, study emergence of resistance
- EMA fully supportive of on-going work

Regulatory issues in updating the PI of old antibacterials (I)

- number of procedures/year limited: capacity of the EU regulatory network
- availability and quality of data varies
  - historical reasons: differences in enrolment in CTs, different requirements
  - different levels of participation from industry
- art 30 procedures only address divergences, no new data can added to the PI
  → potential need for additional procedures→ additional burden

Regulatory issues in updating the PI of old antibacterials (II)

- some procedures are only confined to the originator
  - difficulties in ensuring harmonisation of PI for all generics
- other procedures do not lead to legally binding outcomes

NOTE: PI update cannot and should not replace treatment guidelines and antibiotic stewardship

Conclusions

- The PI update of „old" antibacterials: an important regulatory activity
- ensures that updated information is provided for all EU healthcare professionals
- opportunity to modernise the product information
- efforts/initiatives to generate new supportive data are welcomed
- should not replace treatment guidelines/antibiotic stewardship
- prioritisation of the exercise is key, in view of the limited resources.
- in particular the harmonisation of SmPCs by referrals should continue and should be strengthened

BACK-UP SLIDES

Article 30

1.If two or more applications submitted in accordance with Articles 8, 10, 10a, 10b, 10c and 11 have been made for marketing authorisation for a particular medicinal product, and if Member States have adopted divergent decisions concerning the authorisation of the medicinal product or its suspension or revocation, a Member State, the Commission or the applicant or the marketing authorisation holder may refer the matter to the Committee for Medicinal Products for Human Use, hereinafter referred to as"the Committee", for the application of the procedure laid down in Articles 32, 33 and 34.

Article 30

2. In order to promote harmonisation of authorisations for medicinal products authorised in the Community, Member States shall, each year, forward to the coordination group a list of medicinal products for which a harmonised summary of product characteristics should be drawn up. The coordination group shall lay down a list taking into account the proposals from all Member States and shall forward this list to the Commission. The Commission or a Member State, in agreement with the Agency and taking into account the views of interested parties, may refer these products to the Committee in accordance with paragraph 1.

Article 31

1. The Member States, the Commission, the applicant or the marketing authorisation holder shall, in specific cases where the interests of the Union are involved, refer the matter to the Committee for application of the procedure laid down in Articles 32, 33 and 34 before any decision is reached on an application for a marketing authorisation or on the suspension or revocation of a marketing authorisation, or on any other variation of the marketing authorisation which appears necessary.

Article 31

2. Where the referral results from the evaluation of data relating to pharmacovigilance of an authorised medicinal product, the matter shall be referred to the Pharmacovigilance Risk Assessment Committee and Article 107j(2) may be applied. The Pharmacovigilance Risk Assessment Committee shall issue a recommendation according to the procedure laid down in Article 32.

The final recommendation shall be forwarded to the Committee for Medicinal Products for Human Use or to the coordination group, as appropriate, and the procedure laid down in Article 107k shall apply.

However, where urgent action is considered necessary, the procedure laid down in Articles 107i to 107k shall apply.