EMA workshop on the development of new medicinal products for the treatment of ulcerative colitis and Crohn’s disease

Overview of authorised medicines for IBD in Europe - previous regulatory positions

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(No conflicts of interest)

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Regulatory situation in Europe:

- **Products licensed via centralised procedure**
  - Marketing authorisation by EU commission, valid for all EU-member countries plus EEC countries NO, IS and LIE

- **Products licensed via decentralised/mutual recognition procedure**
  - Marketing authorisation led by one country, all other MSs (only) comment on the assessment
  - Results in national marketing authorisations, which are similar in the MSs involved
  - Choice of MSs involved by applicant

- **Products licensed on national level only**
  - „Historical products“
Mesalazine (and associated products):

- Licensed via DCP/MRP

- Products:
  - Brands: Pentasa, Claversal, Asacol, Salofalk, Mezavant
    (e.g. in Germany: 156 registered products)
  - Oral formulations:
    - Tablets, granules,
  - Rectal formulations
    - Suppositories, rectal foam, rectal suspension/enemas
  - Indication(s)
    - Rectal formulations:
      - Treatment of acute left-sided UC
        (restricted to the rectum for supps.; partly restricted to „mild to moderate“)
    - Oral formulations:
      - „Mild to moderate UC“,
      - Partly „acute treatment and maintenance of remission“ or „induction and maintenance“
      - or Dosing instructions differentiate between induction and maintenance
      - Older licenses with indication: Acute treatment of CD
  - Children: Licensed for 6-18 year olds
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„Mesalazine-associated products“:
- Licensed via DCP/MRP and/or national only:
- Products: (oral forms only)
  - Olsalazine
    - Acute treatment of UC and maintenance of remission
  - Balsalazide
    - Treatment of mild to moderate UC and maintenance of remission
- Sulfasalazine:
  - Acute treatment of UC and maintenance of remission;
  - acute treatment of mild to moderate CD when the colon is involved
Corticosteroids:

- **Substances:**
  - Prednisone
  - Prednisolone
  - Methylprednisolone
  - Budesonide
  - Beclomethasone

- **Pharmaceutical forms:**
  - Oral: Tablets (IR and MR), granulate
  - Rectal: Enemas, Foams
  - Intravenous

- **Indications:**
  - UC and CD („global“), or acute treatment of UC and CD (for the „historicals“)
  - Rectal forms: acute UC (partly left-sided, proctosigmoiditis, etc.)
  - Budesonide: Entocort and Budenofalk: CD („mild to moderate“, „involvement of ileum and ascending colon“)
    Cortiment MMX: „Induction of remission in mild to moderate UC when treatment with mesalazine is not sufficient“

- **Children:**
  - Dosing instructions for children usually included for prednisone
  - No paediatric use for budesonide
**Immunosuppressants/Immunomodulators:**

**Thiopurines: Azathioprine**
- Indication: Moderate to severe UC and CD
- Mercaptopurine: Not licensed (DE and UK)

**Methotrexate:**
- Licensing status variable across countries
- One i.v. form approved for “mild to moderately severe CD in combination with corticosteroids when thiopurines are not effective or in case of intolerance”

**„Other immunosuppressants“ – Usually not licensed for any IBD indication**
- Cyclosporine
- Tacrolimus
- Mydophenolate mofetil
- Cyclophosphamide
- 6-Thioguanine (recently licensed in NL; MRP awaited; maintenance of remission in CD and UC in pat. intolerant or not responding to AZA and 6-MP)

**Others:**
- Generally not licensed
- Antibiotics
- Probiotics (one license for „maintenance of remission of UC“ for Mutaflor in DE)
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Biologicals:
- Licensed via centralised procedure
  („compulsory scope“ of using centralised procedure for substances using biotechnological processes)
- **Products:**
  - TNF-α antibodies:
    - Infliximab (Remicade; +biosimilars)
    - Adalimumab (Humira)
    - Golimumab (Simponi)
  - Integrin antibodies
    - Vedolizumab (Entyvio)
- **Indications:**
  - Second (third) line in moderate to severe disease
  - „Treatment of...“ (no specification on induction or maintenance)
- **Children:**
  - Infliximab for UC and CD,
  - Adalimumab for CD, all others: adults only

Not licensed in EU: Certolizumab-pegol, Natalizumab

• Patient characteristics/In- and exclusion criteria
  – Patients classified based on Montreal classification:
    – Proctitis/Left sided/extensive UC
    – Mild/moderate/severe
    – Special situations: Refractory disease; steroid dependency
  – Histological diagnosis required
  – Crohn, indeterminate, ischaemic, microscopic, infectious colitis should be excluded
  – Define level of treatment (first/second/third line), define failed therapy

• Aims of therapy – Potential indications (“claims”):
  – Treatment of active disease: Remission: Rem. to be achieved within 4-8 wk, and maintained for further 4 wk.
  – Maintenance treatment: Keep remission in remission Include those in remission only, keep in remission for 52 wks.
  – Both need confirmation in separate studies

• Study design
  - Randomised placebo- and active controlled studies
  - At least two studies
  - Induction and maintenance of remission in different trials
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• UC guideline (continued):

  • Endpoints: Should reflect disease activity
    – Clinical activity indices mentioned (incl. missing validation) but none recommended
    – Preferable to use those including signs and symptoms
    – Endoscopic evaluation may be part of the index but is not mandatory
    – Remission definition depends on index used
      - should include normalisation of stool frequency, lack of urgency and no blood in stool
    – Secondary endpoints:
      – Individual components of index, endoscopy, histology, biomarkers

  • Choice of comparator
    – Depends on setting claimed (first, second, third line; induction or maintenance; extent of disease)
    – Placebo not acceptable for first line moderate and severe disease; in all other circumstances recommended

  • Special situations/populations
    – Steroid refractory/dependent population:
    – Acute severe first line indication
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• Guideline on the development of new medicinal products for the treatment of Crohn’s Disease (2009):
  
  • Patient characteristics/in- and exclusion criteria
    – Characterisation regarding phenotype, duration, activity, localisation etc. necessary
    – Disease activity at least 220 on CDAI
    – Diagnosis must be documented by recent visualisation (e.g. radiology, (capsule)) endoscopy, and histology
    – Failed prior therapies should be taken into account
  
  • Definition of Disease stages/potential claims
    – Reflection of Montreal/Vienna classification
    – Potential Claims/Duration of trials:
      – Treatment of active disease/Induction of remission (4-8 weeks)
      – Maintenance of remission/prevention of relapse (52 weeks)
      – Treatment of fistulising disease (no duration given)
      – Claims for steroid sparing, endoscopic remission, treatment of obstruction are not part of indication but may be included in prescribing information in other sections
  
  • Study design
    – Randomised double-blind parallel group studies
    – Induction and maintenance trials may be studied in separate or combined trials, but re-randomisation is mandatory
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- CD guideline (continued):

  - Endpoints
    - Primary: An ideal endpoint does not exist, CDAI recommended. Remission is CDAI<150
    - Secondary: Response (reduction of at least 100 pts. CDAI), biomarkers, endoscopy, QoL, steroid sparing, reduction in surgical procedures
  
  - Choice of comparator
    - For first line indication active control should be included; placebo recommended unless aimed at superiority
    - In the “add-on” setting, placebo is recommended
    - For steroid and immunosuppressive refractory CD, comparison with anti-TNF is recommended.

- Special populations
  - Steroid dependent population
    - Withdrawal of steroids accepted as objective
  - Fistulising Disease:
    - Applicable to chronic, non-suppurative fistulas
    - Objectives/Endpoints:
      » Fistula closure (primary endpoint), secondary endpoints
      » Active comparator (antibiotics) recommended
EMA IBD workshop – Proposed revision of UC and CD guidelines

Concept paper on revision of the two guidelines (2014)

- Problems identified:
  - Definition of endpoints – morphological endpoints may reflect long-term outcome better
    - “Mucosal healing” – how to define it
    - Combination with other components (clinical, biomarkers)
  
- Paediatrics: Current guideline only includes general comments. Clarification needed for:
  - Extrapolation from adults to children
  - Design of studies in children (placebo?)

- General study design:
  - Do we still need the strict separation between induction and maintenance?
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Thank you for your attention!