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)

The views expressed in this presentation are primarily those of the author and do not necessarily express those of the BfArM, nor of the EMA

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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 treartment and maintenance of remission“ or „induction and maintanance“
      - or Dosing instructions differentiate between induction and maintenance
      - Older licenses with indication: Acute treatment of CD
    - Children: Licensed for 6-18 year olds

„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

  Usually „historical“ national licenses only
  - 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 predni
  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 inteolerance“

„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)

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

Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis (2008):

- 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

- 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

- **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

- 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

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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?

Thank you for your attention!