Expedited approval pathways in the EU: Reflections on Conditional Marketing Authorisation

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Disclaimer

- These slides outline FJ’s understanding of the present EMA/CHMP approach to CMA applications
- These slides do not represent the views or opinions of EMA, the CHMP or the Swedish MPA

Conditional Marketing Authorisation (CMA)

- "CMA (…) is usually appropriate for *products* where the benefit-risk balance is such that the immediate availability outweighs the limitations of *less comprehensive data than normally required*, i.e. medicines with an established potential to address an *unmet medical need* (UMN)"

Eligibility criteria for CMA

- The disease to be treated is “seriously debilitating or life-threatening” and:
  a) The benefit-risk balance (B/R) of the product is positive
  b) It is likely that the applicant will be able to provide *Comprehensive Data* through *Specific Obligations* (SOB)
  c) An UMN is fulfilled. Requires the establishment of *Major Therapeutic Advantages* (MTA) over available therapies
  d) The benefits to public health of the immediate availability of the medicinal product outweigh the risks inherent in the fact that additional data are still required

What are ”non-comprehensive” data?

- These are: ”less complete than is normally the case at the time of authorisation”
- Non-comprehensiveness may refer to:
  - -The registrational endpoint being an imperfect surrogate of clinical benefit
  - -The limited size of the clinical trial database
  - -The lack of randomised comparative efficacy and safety data
- If comprehensive data are expected post authorisation (through SOB), a CMA may be relevant for the product. Conversion to full approval is anticipated in case SOB succesfully deliver comprehensive data
- If due to the rarity of the disease, comprehensive data are deemed impossible to generate, an approval under ”exceptional circumstances” may be relevant (e.g, Elzonris, Lumoxiti). This is not anticipated to be converted to full approval

Regulatory: CMA compared to US Accelerated Approval (AA)

- CMA is granted for a *medicinal product*
- AA is granted for a *therapeutic indication*
- CMA becomes relevant due to the *non-comprehensiveness* of data. SOB are needed to provide comprehensive data
- AA becomes relevant when efficacy is shown on a *surrogate endpoint*. Confirmatory trials are needed to demonstrate an impact on an endpoint that represents clinical benefit

The application of CMA in oncology

- Most CMA are given to products with initial therapeutic indications for late/last line treatment, where there are no satisfactory treatment options
- In common oncological diagnoses, single arm trial (SAT) data are usually, but not always, considered non-comprehensive
- The comprehensiveness of SAT data may more readily be accepted in rare diseases (e.g, Bavencio, Vitrakvi, Tepmetko, Lytgobi)
- Data from small Randomised Controlled Trials (RCT) with exploratory design may be considered non-comprehensive (e.g. Pixuvri, Polivy, Lartruvo)
- What is deemed to constitute a comprehensive data-package in a treatment indication may be impacted by the progress of science and therapeutics (e.g. Zynyz)

Major Therapeutic Advantage (MTA)

- “Applicants should justify that there exists an UMN (…) or that it is necessary to provide a major improvement over the existing methods”
- “MTA would normally be based on meaningful improvement of efficacy or clinical safety”
- “In exceptional cases, also major improvements to patient care could provide an MTA, e.g (…) if the treatment allows ambulatory treatment instead of treatment in hospital only”
- With regards to *available products with a CMA*, “another medicinal product could potentially address the same UMN’s, provided it is expected, based on appropriate scientific data, that such a product addresses the UMN’s to *a similar* or greater extent than what is understood for the already conditionally authorised product”
- Cross study comparisons are generally required to establish MTA

MTA in oncology - the traditional approach

- If *ORR is evidently higher* than for existing therapies in the treatment niche (usually last line where patients have exhausted established treatment options), an MTA is inferred
- ORR could also be roughly similar to the best therapies, if the new treatment has *a new Mechanism of Action* (no cross resistance anticipated) or if *the safety profile is qualitatively different* from the other treatment (e.g., lack of CRS or peripheral neuropathy)
- If ORR is high, *convenience* may also be cited as an MTA (e.g. oral versus i.v. or treatment holidays versus continuous therapy)

Evolving trends in EU regulation

- Emphasis that the onus is on the applicant to provide the arguments supporting MTA for its product, rather than the CHMP supplying them
- European Public Assessment Reports (EPAR) provide justifications for previous CHMP decisions on MTA. It is recommended that these are studied by applicants
- When the ORR is merely on par with the best fully approved therapies, a novel mechanism of action is not deemed an MTA by default. Arguments/data are required from the applicant to justify major advantages due to a better safety profile or tolerability (in at least some patients?), or due to a lack of cross resistance
- Uncertainties about MTA requirements are increasing

Specific obligations (SOB)

- SOB are instituted to provide a comprehensive data package for the product, post approval of a CMA
- Generally but not always, an RCT is required. Sometimes SAT suffice (e.g., when RCT's are not deemed feasible)
- RCT's are typically but not always performed in an earlier line of treatment than that covered by the CMA
- Relatively often, the SOB is performed in combination with other anticancer agents while the CMA is for monotherapy. Moreover, the dose may differ

The Pixuvri case (2019)

- An anthracycline-like active substance. Received a CMA in 2012 for the treatment of very late line non-Hodgkin lymphoma
- Approval as monotherapy was based on a small RCT showing increased rates of CR and PFS compared to chemotherapy options
- The key SOB was an RCT with superiority design, comparing Pixuvri to gemcitabine, as add-on to rituximab, in earlier line relapsed DLBCL
- The study failed to show a statistically significant benefit on PFS or OS
- Still the CHMP deemed effects ”roughly similar” and replicated, in those patients covered by the original indication
- The CMA was converted to full approval

The Blenrep case (2023)

- An antibody-drug conjugate which fulfilled CMA criteria in 2020
- Indicated *as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy*
- Approval based on a dose comparative trial without a reference control arm
- Patients had relapsed following treatment, where triple refractory and with at least 3 prior therapies
- In 97 patients receiving the registered dose, the ORR was 32% and the median DoR was 11 months
- Toxicities were deemed manageable

Its key SOB failed to provide statistically compelling evidence of an impact on PFS and/or OS

- RCT with superiority design, comparing Blenrep to pomalidomide/dexamethasone
- Included patients with relapsed/refractory myeloma previously treated with at least 2 lines of therapy
- PFS HR: 1.03 (95% CI: 0.72, 1.47)
- OS HR 1.03 (95% CI: 0.74,1.43)
- The ORR/DoR seen at the time of approval was replicated, as was the safety profile

The marketing authorisation for Blenrep was not renewed

- ORR of the magnitude seen with Blenrep in late line myeloma, is understood to represent promising antitumoral *activity*, indicative that the product may have a beneficial effect on PFS or OS. Such an effect would be a measure of *efficacy*
- Thus, (in this case) *activity* is not understood as a measure of clinical benefit
- A demonstrated impact on PFS and/or OS was required to establish *efficacy*
- The SOB proposed by the applicant failed to provide statistically compelling evidence of efficacy, and therefore of clinical benefit
- Thus, the positive B/R was not confirmed by the SOB as required in a CMA

Questions occasioned by the Blenrep decision

- What is the status or clnical value of objective tumour responses:

  -Do these constitute clinical benefit per se? If so, under what conditions (depth/duration of response, nature of the disease treated, efficacy of available therapies)?

  -Or should they rather generally be viewed as an imperfect surrogate for effects on PFS and/or OS?

- What is the relevance of failing to show superiority in an RCT against an active comparator in an earlier treatment line, for B/R in the late line indication?
- If this relevance is questioned, how should comprehensive data be provided after a CMA, in cases where there is no longer equipoise for randomisation in the late line setting, due to the antitumoral activity of the product?