EMA regulatory perspective on long-acting HBV treatments

HBV Forum 10 meeting

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Definition and types of modified release formulations

- Formulations where **the rate and/or site of the release** of the **active ingredient** is **different** from **that of the immediate dose form**
- Achieved by **special formulation design** or **manufacturing methods**
- **Several modified release formulations** including delayed release dosage forms, multiphasic release dosage forms, multiple- or single unit formulations, intramuscular/ subcutaneous depot formulations and transdermal drug delivery systems (TDDS)

Prolonged release dosage forms:

Sustained release of the **active substance** compared to that of an immediate release dosage form.

EMA Guideline on the pharmacokinetic and clinical evaluation of modified release forms

Purpose:

- **Define studies** necessary to investigate the **efficacy, safety, biopharmaceutic and pharmacokinetic properties** of modified release formulation
- General principles for **designing, conducting and evaluating** such studies
- **Types** and **number of studies** dependent on
  a. the **intrinsic properties** of the active substance,
  b. the **route of administration**,
  c. the **type of delivery system** and
  d. the **intended therapeutic indications**

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Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms

Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (europa.eu)

EMA Guideline on the pharmacokinetic and clinical evaluation of modified release forms

- **Three circumstances** in which a **modified release (MR) formulation** might be developed
- **Separate guidance** and **standards** are required for each of the
  1. Applications for **modified release forms** of **new chemical entities** (NCE)
  2. Application for a **modified release formulation** of an **authorised drug** with a **formulation with a different release rate** (e.g. immediate release formulation)
  3. **Abridged applications** for **modified release forms** referring to a **marketed modified release form**, e.g. applications according to Article 10(1) or 10(3)

Rational for development

- Should be based on a **well-defined clinical need** (e.g. improvement of patient compliance and/or safety) and on an **integration** of **physiological, pharmacodynamic** and **pharmacokinetic considerations**.
- Dossier must provide a **complete justification** of:
  - The **physical form** of the modified release device and the **mechanism of the release form**;
  - The **choice of the dosage form**, defining the ***in vitro*** and ***in vivo*** **performance** of the product;
  - The **choice of active substance contents per unit** of the dosage form;
  - The **clinical rational for the new dosage form**, particularly in relation to the **proposed indications** and **posology** including conditions of administration and optimal use

Application for a modified release formulation of a drug that is authorised in a formulation with a different release rate

Aim:

- To reach a **similar total exposure (AUC)** of the active substance as for the immediate release formulation
- **Not necessitate** the **same nominal doses** given
- In general **MR-formulations** are **not bioequivalent** to their immediate release form
- **PK-data** alone may **not be sufficient** to evaluate **if the B/R ratio of MR is similar** to the immediate release form
- **Additional clinical** data will be required unless scientifically justified

IMPORTANT:

The applicant **has to prove** that:

- The **benefit** of the **new formulation outweigh its potential risk**
- That the **benefit/risk is similar** to the **authorised formulation** with a different release rate.

Application for a modified release formulation of a drug that is authorised in a formulation with a different release rate

- New formulation should be characterised in **single-and multiple dose pharmacokinetic**, **pharmacodynamic** and **clinical efficacy** and **safety studies**
- **Additional studies** may be needed, e.g. characterisation of the **metabolic profile** in case of **different route of administration**
- **Toxicological, pharmacological** or **clinical tests** to **define the intrinsic properties** of the active substance are **not required** → similar total systemic exposure of active substances/metabolites for the two formulations
- **Market immediate release product** of the same active substance should sever as **reference product**
- **Final marketed formulation** should be **used in PK and clinical studies**, unless it can be justified that differences between study formulation and final market formulation do **not affect release characteristics and bioavailability**

Required pharmacokinetic characterisation of MR formulations

Characteristic of MR formulation	Meassures and outcomes
Rate and extent of absorption	• Use of **relevant pharmacokinetic parameters** in comparison to immediate release formulation • **Demonstration** that the MR formulation has the **claimed release characteristics**
Fluctuations in drug concentrations at steady state studied following repeated dosing	• **Only similar** or **less fluctuation** as immediate release formulation are **acceptable** • Inform about **dose instruction** for **switching from immediate formulation to MR** (and vice versa) to **maintain ss concentrations** during the switch
Inter-subject variability in pharmacokinetics arising from the drug formulation	• Comparison between modified and immediate release formulation • **No excess of variability** of MR compared to immediate release allowed
Dose proportionality	• Dose proportionality for **different strengths / doses** of the modified release formulations should be adequately addressed • Evaluated by **single dose study** or in case of **drug accumulation: multiple dose study** • **Comparison of PK** parameters **after dose adjustment**
Factors affecting the performance of the modified release formulation	**Food** • Single dose, design 2-way or 4-way cross over depending on reported food effect of RP) **Gastro-intestinal function** • Coadministration with active substances affecting gastrointestinal physiology • Studies in patients with markedly altered GI function **Unexpected drug release characteristics (dose-dumping)** • Rapid drug release of the entire amount or a significant fraction of active substance, i.e. due to delayed gastric entry **Effect of alcohol**
Other points to consider	• **Special populations** • **Influence** of **site administration** on **plasma levels** • **Prolonged residence time** in the **stomach**

Therapeutic studies

- **Comparative clinical efficacy** and **safety** data are **needed** in addition to PK data
- Demonstration that the **new modified release formulation** is **as safe and effective** as the **existing formulation**

  a. Non-inferiority study if it is **not expected** that formulations have **different safety**

  b. Equivalence study in case **efficacy and safety** are **closely related**

  - **Superiority claims** in terms of **clinical efficacy or safety** need to be **supported** by data from well-designed **clincial trials**
- **Type of studies** depend on whether **appropiate, pharmacodynamic endpoints** can be **defined**, **relation** between **pharmacodynamic markers** and **efficacy** is **known**, and if a **non-inferiority** or **equivalence margin** can be defined
- In **exceptional circumstances, waiving** of **therapeutic studies** may be possible, if **same or better** level of **efficacy and safety** can be concluded based on **PK/PD studies**

Safety considerations

- **Safety profile** of the modified release formulation **needs to be similar** to the approved treatment options → **no increase in risk** due to the **prolonged exposure**, the **different route of administration** and/or **different formulation** or potential **medication errors**
- **Non-adherenc**e to the visits schedule, as well as **missed visits** and **discontinuation** pose a serious safety risk for the patients
  - Depending on the PK-profile, **slow decrease of drug exposure** after discontinuation
  - **Prolonged exposure** at **subtherapeutic levels**
  - Increased **risk** of **virologic failure**,
  - Substantial **risk of resistance development** when patients are **not adequately treated** with an **appropriate regimen**

IMPORTANCE:

→ **PK characterisation** of the MR formulation and **switch-data** are **essential** to allow for the **adequate management** of missed visits and discontinuation

→ **Identification** of **risk-factors** associated with virologic failure

Conclusion on long-acting HBV treatments

- Long-acting HBV treatments are likely **not addressing an unmet medical need** but could **increase patient convenience** by a daily oral administration and **potentially increased patient adherence**
- **Safety** of patients is **paramount → no increase in risk** due to the prolonged exposure, the different route of administration and/or different formulation and potential medication errors
- **Detail pharmacokinetic characterisation** of the modified release formulation and also **clinical studies** are generally required to **ensure the safety and efficacy** of MR formulations
- Recommendations for the management of **non-adherence** to the visits schedule, as well as **missed visits** and **discontinuation** need to be in place, i.e. switching recommendations and clear instruction on use and posology
- The **benefit** of the **new formulation must outweigh** its **potential risks** and the **benefit/risk** must be **similar** to the **approved treatment options**
- **Contact EMA early** in your development programm

Any questions?

Further information

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