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Regulatory Approach in Germany and in the EU to Fixed Dose Combination Medicinal Products Using HIV/AIDS Treatment as an Example

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Overview

- **Regulatory Background / Requirements**
  - **General**
  - **Specific**
- **From Monotherapy of AIDS to HAART**
- **Examples**
  - **Combivir**
  - **Trizivir**
  - **Kaletra**

Regulatory Background (1)

General Requirements (1): (according to the Directive 2001/83/EC*, Article 10, 1(b)):

"In the case of new medicinal products containing known constituents not hitherto used in combination for therapeutic purposes, the results of toxicological and pharmacological tests and of clinical trials relating to that combination must be provided, but it shall not be necessary to provide references relating to each individual constituent."

* of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use

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Regulatory Background (2)

General Requirements (2): (according to the Commission Directive 2003/63/EC*):

"5. Fixed Combination Medicinal Products:

Applications based upon Article 10 (1) (b) shall relate to new medicinal products made of at least two active substances not previously authorised as a fixed combination medicinal product.

For those applications a full dossier (Modules 1-5) shall be provided for the fixed combination medicinal product. …"

* of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use (Annex I, Part II).

Regulatory Background (3)

Specific Requirements (1): (according to the CPMP NfG*):

- **Justify the particular combination of active substances**
- **Should be based on valid therapeutic principles**
- **Assess the potential advantages**
  - **improvement of the benefit/risk and/or**
  - **simplification of therapy**
- **against possible disadvantages**
  - **addition of different ADRs specific to each substance**

* Note for Guidance on Fixed Combination Medicinal Products CPMP/EWP/240/95

Regulatory Background (4)

Specific Requirements (2):

- Each substance of the fixed combination (FC) must have documented contribution within the combination ... to the claimed effect.
- Dose and proportion of each substance should be appropriate for the intended use.
- State if the claimed indication is
  - first-line (for patients receiving previously neither of the substances)
  - second-line (when monotherapy has not demonstrated a satisfactory benefit/risk ratio
- Clinical development ⇒ accordingly

Regulatory Background (5)

Specific Requirements (3): Efficacy and Safety

- For essentially new FC the data needed are similar to a new chemical entity in the situation where the FC is to be proposed (first or sec.-line).
- The proposed dose regimen must be justified.
- Confirmatory clinical trials are necessary to prove efficacy of the FC
  - preferably by parallel group design vs. its individual substances (and placebo when feasible)
  - comparative clinical studies of FC vs. reference might be necessary
- FC for long term use ⇒ safety data on 300-600 patients for 6 months or longer will be required.

From Monotherapy of AIDS to HAART (1)

HAART

=

Highly **A**ctive **A**nti-**R**etroviral **T**herapy

Definition (according to the CPMP NfG on treatment of HIV Infection):

"Antiretroviral Therapy (ART) currently consisting of at least 3 different compounds (typically from 2 different substance classes)"

From Monotherapy of AIDS to HAART (2)

Pre-HAART Era (1)

- **1979/1980: atypical Kaposi's Sarkoma in gay men as the hallmark of the AIDS epidemics**
- **1984/1985: HTLV III = HIV = causative agent of AIDS**
- **1987: first MA (in Germany) for zidovudine/Retrovir as monotherapy for AIDS and AIDS related complex (schedule: 6x (!!) 250 mg per day) based on survival benefit compared to placebo**

From Monotherapy of AIDS to HAART (3)

Pre-HAART Era (2)

- **1992/1993: MAs for 2 further substances/NRTIs:**
  ddI/Videx
  ddC/Zalcitabine
- **1994/1995: Combination Therapy (ddI/ZDV or ddC/ZDV) prolongs survival compared to ZDV monotherapy (Delta and ACTG 175 trials)**

From Monotherapy of AIDS to HAART (4)

HAART Era starting in 1995 characterised by (1):

- **Monotherapy obsolete**
- **new substances (3TC, d4T etc.) and new substance classes (PIs [Indinavir, Norvir, Saquinavir licensed in 1995], NNRTIs [Nevirapine, Efavirenz] and fusion inhibitors [T20])**
- **antiretroviral therapy is (typically/at least) triple combination therapy**

From Monotherapy of AIDS to HAART (5)

HAART Era starting in 1995 characterised by (2):

- **(semi-) quantitative PCRs allowing to determine “viral load”**
- **“hit it hard and early”**
- **replacement of clinical endpoints (survival, AIDS defining events) by the surrogate endpoint viral load**

From Monotherapy of AIDS to HAART (6)

HAART Era (3) starting in 1995 resulted in:

- **a change of the face of the AIDS epidemics to that of the chronicle disease >HIV-infection< with currently unknown/undetermined prognosis in the Northern hemisphere**
- **a focus on long term consequences of HAART (lipodystrophy, cardiac events)**
- **the "PILL BURDEN": complex and difficult to handle combination treatment schedules**

Fix what Fits together: COMBIVIR (1)

COMBIVIR = **150 mg lamivudine (LAM, 3TC)**
300 mg zidovudine (ZDV, AZT)

schedule: **a single tablet bid**

MA granted in: **1998**

MA zidovudine: **1987 (Retrovir; Glaxo Group)**

MA lamivudine: **1996 (Epivir; Glaxo Group)**

Fix what Fits together: COMBIVIR (2)

Basis of approval of COMBIVIR (1)

PK: no interaction

PD: monotherapy both with ZDV and LAM results in rapid evolution of either ZDV or LAM resistant strains; however, ZDV resistant strains become ZDV sensitive when they acquire LAM resistance mutation (M184V) explaining the clinical benefit observed with the combination.

Fix what Fits together: COMBIVIR (3)

Basis of approval of COMBIVIR (2)

Clinical Data: The MA of Epivir (LAM) 2 years before (in 1996) was based on

- **4 large randomised controlled clinical trials (NUCA3001, 3002, NUCB3001, 3002) comparing 3x200 mg ZDV vs 2x150 mg LAM vs 3x200 mg ZDV + 2x150 mg LAM in terms of viral load + meta-analysis of the 4 trials as regards to clinical endpoints**
- **the clinical endpoint trial CESAR (all confirming a contribution of LAM to ZDV in all endpoints investigated, or the findings of the Delta trials [i.e. combination therapy is better than monotherapy])**

Fix what Fits together: COMBIVIR (4)

Basis of approval of COMBIVIR (3)

Clinical Data: Combivir Dossier of 1998

- (single dose) bio-equivalence trial demonstrating bio-equivalent behaviour/comparable exposure of COMBIVIR and single tablets of 150 mg Epivir and 300 mg Retrovir co-administered
- trial NUCB 3027 demonstrating clinical equivalence of COMBIVIR bid (= 300 mg LAM + 600 mg ZDV) vs. 150 mg Epivir bid and 200 mg Retrovir tid (= 600 mg ZDV) in terms of viral load suppression after 12 weeks on treatment.

Fix what Fits together: COMBIVIR (5)

Conclusions on COMBIVIR

Approval of Combivir has

– allowed to fix together what rationally fits together

– reduced pill burden/number from 5 tablets to 2 tablets per day

– stimulated investigations allowing to prolong dosing interval of ZDV from originally 4 hours (including a wake-up call in the night), to 8, and ultimately 12 hours as LAM was for bid use

– demonstrated that fixed dose combination can be "constructed" with new substances only if they are in the property of one company, and for adults only

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HAART in a single tablet: TRIZIVIR (1)

TRIZIVIR =	**150 mg lamivudine**	**(LAM, 3TC)**
	300 mg zidovudine	**(ZDV, AZT)**
(COMBIVIR +)	**300 mg abacavir**	**(ABC)**
schedule:	**1 single tablet bid**	
MA granted in:	**2000**	

MA zidovudine:	**1987 (Retrovir;**	**Glaxo Group)**
MA lamivudine:	**1996 (Epivir;**	**Glaxo Group)**
MA abacavir:	**1999 (Ziagen;**	**Glaxo Group)**

HAART in a single tablet: TRIZIVIR (2)

Basis of approval of TRIZIVIR (1)

PK: no interactions

PD: For ZDV+LAM cf. to Combivir. A specific PD rationale for adding ABC to ZDV+LAM per se not available. Rather, ABC+ZDV+LAM is/was the only triple NRTI combination therapy having clinical properties similar to HAART (see also CPMP definition: *"at least 3 different compounds (typically from 2 different substance classes))"*

HAART in a single tablet: TRIZIVIR (3)

Basis of approval of TRIZIVIR (2)

Clinical Data: The MA of Ziagen (ABC) 1 year before (in 1999) was based on

- trial CNAAB 3003 (in naive patients): ABC+LAM+ZDV therapeutically superior to placebo+LAM+ZDV in terms of viral load at 16 weeks

– trial CNAAB 3005 (in naive patients): ABC+LAM+ZDV therapeutically equivalent to indinavir+LAM+ZDV in terms of proportion of patients with viral load BLoQ (400 copies/ml) at 24 weeks

HAART in a single tablet: TRIZIVIR (4)

Basis of approval of TRIZIVIR (3)

Clinical Data: The MA of Ziagen (ABC) 1 year before (in 1999) was based on

- **CNAAB 3002 (in ART experienced patients): ABC+stable background (SBG) therapeutically superior to placebo+SBG in terms of proportion of patients with viral load BLoQ (< 400 copies/ml) at week 16**
- **USR (urgent safety restriction) as regards the Abacavir hypersensitivity reaction (re-exposure to Abacavir can be fatal !!)**

HAART in a single tablet: TRIZIVIR (5)

Basis of approval of TRIZIVIR (4)

Clinical Data: TRIZIVIR Dossier of 1999/2000

- package of bio-equivalence trials demonstrating bio-equivalent behaviour/comparable exposure of ABC, LAM and ZDV under different conditions (fixed dose tablets vs. co-administered single tablets, single dose vs. steady state etc.)
- no additional (virological or) clinical (endpoint) data (in addition to the COMBIVIR and ZIAGEN dossiers just submitted by the Glaxo Group in 1998 and 1999)

HAART in a single tablet: TRIZIVIR (6)

Conclusions on TRIZIVIR (1)

Approval of Trizivir inside the EU/for the northern hemisphere is in effect an example for a "bad" development of fixed dose combinations as

- **ABC+LAM+ZDV is a PI/NNRTI free HAART, however, the fixing of the doses in a single product offers no relevant additional benefit to the patients else than the slightly reduced pill burden (2 vs. 4 tablets)**
- **it fixes an abacavir problem (potential fatal ABC-hypersensitivity) into a fixed dose combination product**
- **fixing the dose in one "pill" excludes specific populations such as children and patients with renal impairment from the product**

HAART in a single tablet: TRIZIVIR (7)

Conclusions on TRIZIVIR (2)

Approval of Trizivir inside the EU/for the Northern hemisphere may offer to patients of the Southern hemisphere access to a bid single tablet PI free HAART with the following limitations:

- **For otherwise healthy adults only**
- **How to handle the problem of fatal re-exposition to ABC in the context of the Southern hemisphere?**
- **Current data indicate that ABC+LAM+ZDV is/remains a PI-free, or "PI-sparing/first line" HAART. However, boosted PI (such as Kaletra), or NNRTI, containing HAART appears to be clinically superior to ABC+LAM+ZDV.**

Fix the Booster: KALETRA (1)

KALETRA =	**133.3 mg lopinavir (LPV)**
(soft capsules)	**33.3 mg ritonavir (RTV)**
KALETRA =	**40 mg lopinavir/ml (LPV)**
(oral solution)	**10 mg ritonavir/ml (RTV)**

schedule:

3 soft capsules bid

or

a sqm based bid dose of the oral solution in children > 2 years and < 1.3 m^2

Fix the Booster: KALETRA (2)

MA granted in: **2001**

MA ritonavir: **1996 (Norvir; Abbott)**

MA lopinavir: **none (as single agent, as lopinavir in Kaletra granted to Abbott in 2001)**

Fix the Booster: KALETRA (3)

Basis of approval of KALETRA (1)

PK: Lopinavir, as almost all PIs, is metabolised by the p450 isoform CYP3A (and therefore is also a CYP3A inducer as well as an inhibitor)

Currently there is no single agent LPV oral form available which allows to reach reasonable systemic exposure to LPV.

Fix the Booster: KALETRA (4)

Basis of approval of KALETRA (2)

PK: Ritonavir is, among the PIs on the market, the strongest CYP3A inhibitor. Therefore, low dose RTV ("baby dose", < 300 mg RTV) is used to "pharmacokinetically enhance" ("to boost") exposure to a second PI metabolised via CYP3A

PD: None, as by definition a "PK booster / enhancer" (RTV) should not have any systemic PD effect (such as selection for RTV mutations).

Fix the Booster: KALETRA (5)

Basis of approval of KALETRA (3)

Clinical Data: The MA of Norvir (RTV) 5 years before (in 1996) was nearly irrelevant as:

- it is not expected / it has to be shown that low dose (here 3x33.3 mg = 100 mg bid) RTV has, in contrast to the in Norvir licensed dose of 600 mg RTV bid, no antiretroviral effects
- low dose RTV as a PK enhancer was not licensed in 2001and such a use is currently only indirectly reflected in the SPC of Norvir (or other PIs such as saquinavir or indinavir).

Fix the Booster: KALETRA (6)

Basis of approval of KALETRA (4)

Clinical Data: KALETRA Dossier of 2000/2001

- overall 23 PK trials (including interaction and dose-relation-optimisation trials) confirmed the poor bio-availability of single agent LPV (just observed in animals) which can be circumvented by low dose RTV. PK trials were pointing on a 400 mg LPV to 100 mg RTV dose relationship to be optimal
- complex interactions, e.g. co-administration of efavirenz (a NNRTI) requires dose increase of Kaletra etc.

Fix the Booster: KALETRA (7)

Basis of approval of KALETRA (5)

Clinical Data: KALETRA Dossier of 2000/2001

- PK (or "phase I/II") trials submitted included as special population children (trial M98-940)
- Confirmatory phase III trials M98-863 (in ART naive patients) and M98-888 (in ART/PI experienced patients) confirmed that lopinavir, provided that it can reach systemic circulation, is currently the most potent PI available as it was compared to nelvinavir (M98-863) or "ISPI" (investigator selected [single or dual] PI; M98-888)

Fix the Booster: KALETRA (8)

Conclusions on KALETRA (1)

Approval of Kaletra has set new scientific and regulatory standards as:

- **the confirmatory phase III trials M98-863 (in ART naive patients) was designed to demonstrate clinical non-inferiority of boosted lopinavir as compared to nelfinavir, however, the result was superior clinical efficacy of boosted lopinavir.**
- **At least in ART naive patients Kaletra combinations (+ 1-2 NRTIs +/- efavirenz) are currently the most potent, or "highest" active ART of HIV infection, thus, the comparator which should be used in future MAA-trials.**

Fix the Booster: KALETRA (9)

Conclusions on KALETRA (2)

However, from a pure scientific point of view it has to be stated that:

- **the scientific and medical progress conferred by Kaletra was not due to the fixing of two substances in a single fixed dose combination product**

Fix the Booster: KALETRA (10)

Conclusions on KALETRA (3)

Rather, progress was due to

- **the new substance lopinavir (LPV)**
- **the observation that oral LPV can be made bio-available by low dose ritonavir (RTV).**

In theory, lopinavir could be made bio-available by parenteral administration or (free) co-administration of low dose RTV.

In practice, however, this is not possible as parenteral administration is not feasible in ART naive patients, single agent LPV is not on the market, and both substances/products are in the property of a single Company (Abbott).

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Thank you very much for your Attention