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Thoughts on improving the SmPC

London
September 19, 2017
EMA – Payer Community Meeting

Payers' critique on SmPC

Draft for collaborative actions EMA–Payers, MEDEV, June 2017

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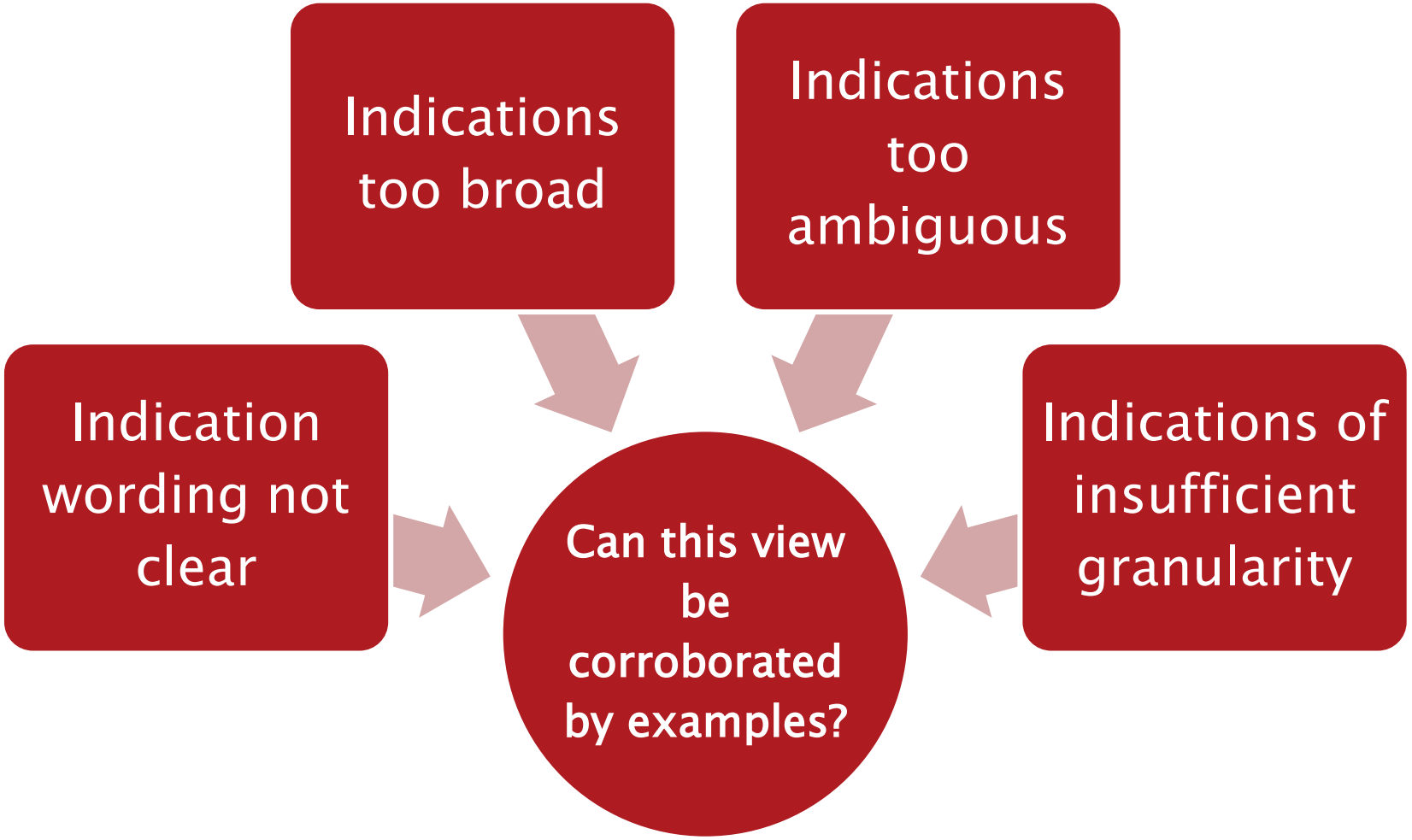

Clarity of Indications

Post-Exposure Prophylaxis of HIV

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Recommendations

TDF + 3TC (or FTC) is recommended as the preferred backbone regimen for HIV post-exposure prophylaxis for adults and adolescents.
(Strong recommendation, low-quality evidence)

LPV/r or ATV/r is recommended as the preferred third drug for HIV post-exposure prophylaxis for adults and adolescents.
(Conditional recommendation, very-low-quality evidence)

Where available RAL, DRV/r or EFV can be considered as alternative options.

Basierend auf Erfahrungen [110], Überlegungen zu Einnahmemodalitäten, Nebenwirkungen und Wechselwirkungen sowie den verschiedenen internationalen Empfehlungen, wird als Standard-prophylaxe die zweimal täglich einzunehmende Kombination von Isentress® 2 Tabletten plus Truvada® 1 Tablette empfohlen. Isentress® ist ein Integrase-Hemmer *(Raltegravir)* und Truvada ist ein Kombinationspräparat, bestehend aus den beiden Inhibitoren der Reversen Transkriptase (RTI') *Tenofovir* und *Emtricitabin.*

Als primäre Alternative zu Isentress® kann der Protease-Inhibitor Kaletra® (Lopinavir), eingesetzt werden.

Sources: WHO, Dec. 2014 / DAIG & ÖAG 2013

Clarity of Indications

Post-Exposure Prophylaxis of HIV

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ISENTRESS is indicated in combination with other anti-retroviral medicinal products for the ***treatment of human immunodeficiency virus (HIV-1) infection*** in adults, adolescents, children, toddlers and infants from the age of 4 weeks (see sections 4.2, 4.4, 5.1 and 5.2).

Kaletra is indicated in combination with other antiretroviral medicinal products for the ***treatment of human immunodeficiency virus (HIV-1) infected*** adults, adolescents and children above the age of 2 years.
The choice of Kaletra to treat protease inhibitor experienced HIV-1 infected patients should be based on individual viral resistance testing and treatment history of patients (see sections 4.4 and 5.1).

PEP := Off-Label Use or On-Label use?

What about PrEP?

Source: SPC of respective products

Clarity of Indications

Consideration of diagnostic advancement

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Bleomycin (‘Article 29’ referral, March 2009):

- Bleomycin is intended for the treatment of:
  […]
  Non-Hodgkin’s lymphoma of intermediate and [illegible]

More general:
How does EMA deal with changing classifications?

[illegible] grade Non-Hodgkin’s lymphoma?
(regardless of available data)

What about e.g. marginal zone lymphoma?
(not defined as separate entity at the time of approval)

Source: SPC of Bleomycin sulfate

Clarity of Indications

Meaning of Headings?

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MabThera® is indicated in adults for the following indications:

- Non-Hodgkin's lymphoma (NHL):
  - MabThera is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.
  - MabThera maintenance therapy is indicated for the trea… responding to induction therapy.
  - MabThera mon… …tment of patients with stage III-IV follicular l… …esistant or are in their second or subsequent relapse after …apy.
  - MabThera is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

What about other Non-Hodgkin's lymphoma?

Source: SPC of MabThera

Ambiguous indications

e.g. Rufinamide (Inovelon®)

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Inovelon is indicated as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome **in patients 4 years of age and older.**

Paediatric population
The efficacy of rufinamide in children aged 4 years and less has not yet been established. Currently available data are described in section 4.8 and 5.1 but no recommendation on a posology can be made.

Should this population be treated outside of clinical trials?

Source: SPC of Inovelon

Broadness of indication

e.g. Regorafenib (Stivarga®)

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Table 7: Updated Overall survival analysis (cut-off 13 November 2011), 14387 (CORRECT) study, ITT population

		Placebo (N=255)	Regorafenib (N=505)	Total (N=760)
N		255	505	760
Number (%) of subjects with event		197 (77.3%)	369 (73.1%)	566 (74.5%)
Number (%) of subjects censored		58 (22.7%)	136 (26.9%)	194 (25.5%)
Hazard ratio (Reg/Pla) [95% CI]*			0.790 (0.664,0.939)	
One-sided p-value from log rank test	Stratified (CRF data)		0.003791	
Median [95% CI]	Days	152 (134, 178)	194 (177, 214)	179 (167, 197)
Overall Survival rate at	Month 3 [95% CI]	0.727 (0.672,0.782)	0.803 (0.768,0.838)	0.778 (0.748,0.807)
	Month 6 [95% CI]	0.431 (0.369,0.492)	0.522 (0.479,0.566)	0.492 (0.456,0.527)
	Month 9 [95% CI]	0.269 (0.212,0.325)	0.349 (0.307,0.392)	0.323 (0.289,0.357)
	Month 12 [95% CI]	0.170 (0.114,0.226)	0.241 (0.198,0.283)	0.218 (0.184,0.252)

** censored observation.
Median, percentile and other 95% CIs computed using Kaplan-Meier estimates.

Grade 3 adverse events with higher frequency in the regorafenib

hand-foot syndrome	16.6%	0.4%
fatigue	15.0%	8.3%
diarrhoea	8.2%	2.0%
hypertension	7.6%	0.8%
rash/desquamation	5.8%	0.4%
reduced platelet counts	3.4%	0.4%
reduced haemoglobin	5.4%	3.2%
mucositis	3.2%	0%
hyperbilirubinaemia	6.8%	4.3%
AST increase	2.4%	1.2%
(abdominal) pain	9.8%	5.7%

Source: EPAR of Stivarga

Broadness of indications

e.g. Regorafenib (Stivarga®)

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Stivarga is indicated for the treatment of adult patients with

- metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy (see section 5.1).

Main study: Study 14387 (CORRECT)

- According to the inclusion criteria, patients were **required to have an ECOG Performance Status score of 0-1,** age ≥ 18 years, measurable or not measurable disease but evaluable by RECIST (version 1.1) and adequate bone marrow, renal and hepatic functions.

Non-interventional RECORA – study

- approx.: **19.3 % ECOG-PS ≥ 2**

Sources: SPC / EPAR / German HTA dossier of Stivarga

Granularity of indications

Meaning of Cross-References

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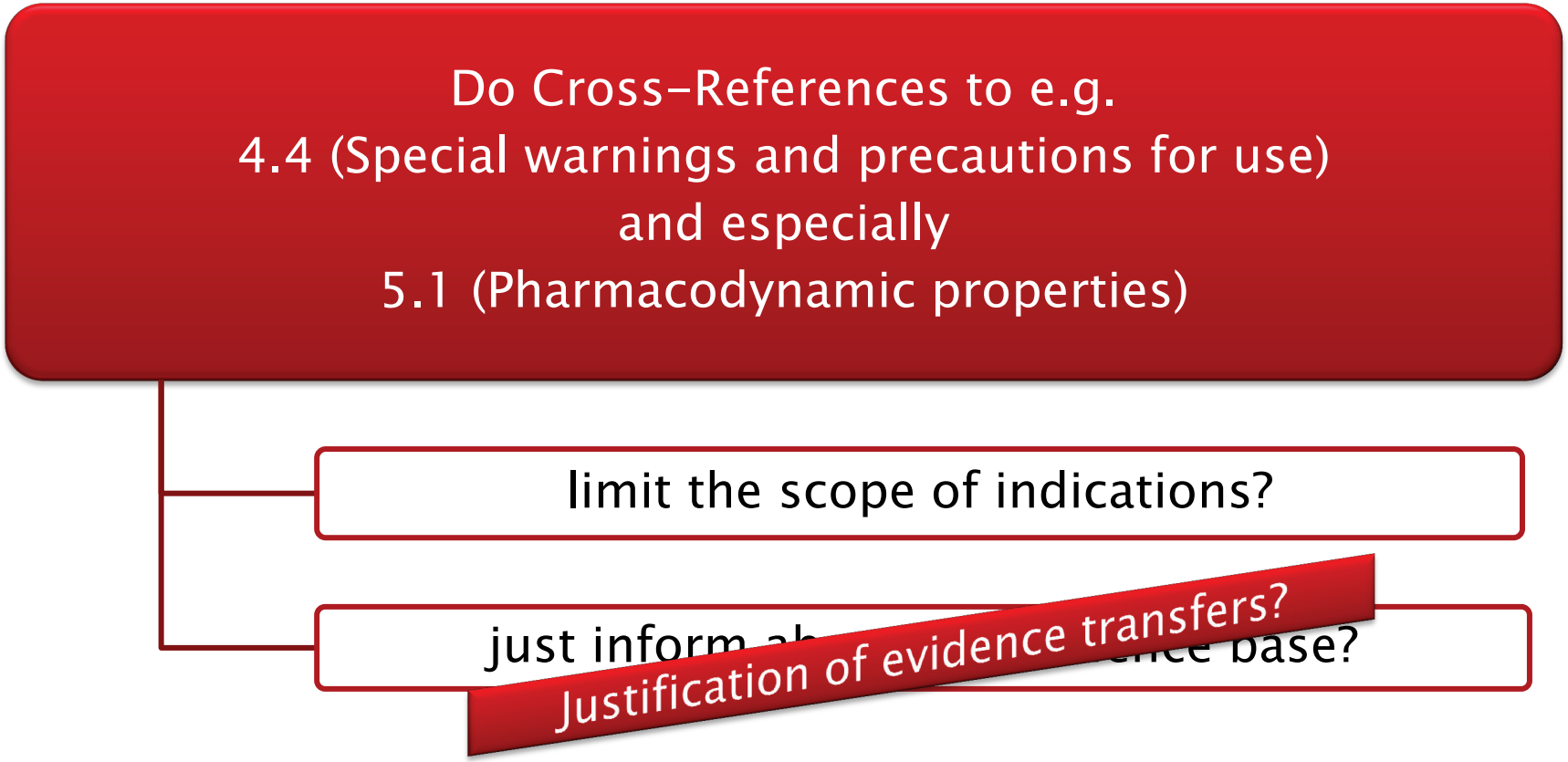

Granularity of indications

e.g. Saxagliptin (Onglyza®)

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Onglyza is indicated in adult patients with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:

- as monotherapy when metformin is inappropriate due to intolerance or contraindications
- in combination with other medicinal products f… tment of diabetes, including insulin … equate glycaem… and 5.1 for available data on differen…).

Just those mentioned positively in 4.5 & 5.1?

Source: SPC of Onglyza

Granularity of indications

Combination Therapies

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Summary: The basic scientific requirements for any fixed combination medicinal product are:

1. Justification of the pharmacological and medical ***rationale*** for the combination.
2. Establishment of the ***evidence base*** for the:
   a. relevant contribution of all active substances to the desired therapeutic effect (efficacy and/or safety);
   b. positive benefit-risk for the combination in the targeted indication.

   Three therapeutic scenarios are foreseen: add-on treatment, substitution therapy and initial combination treatment requiring different types of evidence.
3. ***Demonstration*** that the ***evidence*** presented - if based on combined administration of separate active substances - ***is relevant to the fixed combination medicinal product*** for which the application is made.

Source: EMA/CHMP/158268/2017:
(Guideline on clinical development of fixed combination medicinal products)

Granularity of indications

e.g. Daclatasvir (Daklinza®)

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Daklinza

- in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults (see sections 4.2, 4.4 and 5.1).
- For HCV genotype specific activity, see sectio

4.4 […] C

- Conce ith different HCV genotypes, see section 4.2.
- Conce ype-specific virological and clinical activity, see section 5.1.
- Data to support the treatment of genotype 2 infection with Daklinza and sofosbuvir are limited.

Which genotypes can be treated on label?

Source: SPC of Daklinza

Thank you for the attention!

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