A brighter future
for child health

PIP/waiver applications for diabetes in children

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(Slides containing confidential data have been removed)

Specific characteristics of type II diabetes in children / adolescents

- Shorter duration of disease before onset of symptoms
- Greater initial insulin reserve, but more rapid decrease

Interest for β-cell preserving strategies

- However, most patients satisfactorily controlled with diet, esercise and metformin for at least 1-2 years
- Obesity (often marked) is the rule
- Minorities disproportionally affected
- Rare in the EU (not in US)
- Does not occur before 10 years (→waiver below 10 yr)
- Applicant argues that response to medicinal products is lower in children
- Ongoing statural and sexual development (incl. bone maturation)

Authorized products for type II diabetes in children / adolescents in the EU

- Insulin
- Acarbose (France, ≥ 15 year old children)
- Metformin
  - ✓Effect on HbA1c in children: - 1.1% vs. placebo (Jones et al. 2002)
  - ✓Better tolerated than in adults
  - ✓Favourable effect on weight (reduction)
  - ✓Only product demonstrated to improve survival in T2DM (in adults)
  - ✓Known safety profile

Applications for diabetes drugs

Summary of applications received so far by EMEA, for paediatric investigation plans / waiver (to Apr 2009):

- 22 different medicinal products:
  - 14 single active substance
  - 7 fixed dose combinations
- Therapeutic classes:
  - 3 Glitazones (+ 5 combinations including a glitazone)
  - 2 GLP1a (SC)
  - 4 DPP4 inhibitors (+ 2 combinations including them)
  - 1 cannabinoid receptor 1 antagonist
  - 1 dopamine agonist
  - 3 insulins (+ 1 combination)

PPAR modulators – class waiver

EMEA Decision 8/9/08

Class waiver adopted by PDCO on 29/08/08, for all subsets of the paediatric population for the class of:

peroxisome proliferator-activated receptor (PPAR)-gamma modulators, **including dual and multiple PPAR modulators** (e.g., thiazolidinediones, glitazars, triple modulators),

in the treatment of type II diabetes mellitus,

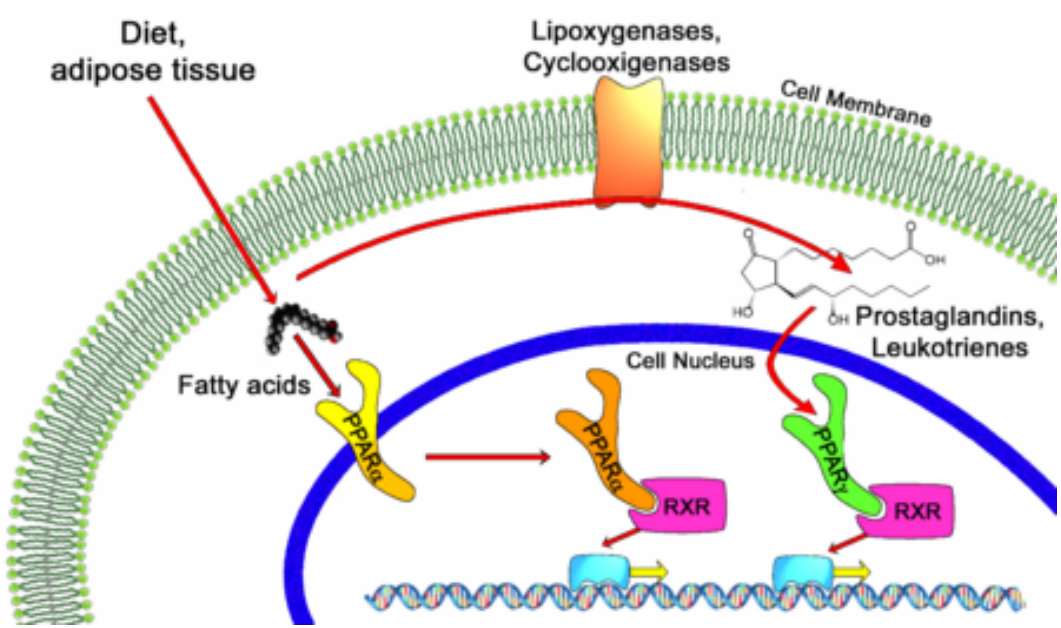
on the grounds that the class of medicinal products in the condition specified is likely to be unsafe in all of the paediatric population.

PPAR modulators – class waiver

The class waiver led to the withdrawal of the applications for pioglitazone-containing products

(with request for either PIP or product-specific waiver),

at various stage of the procedure, including after opinion



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"Standard study" suggested by PDCO at D60 to applicants for DPP4-inhibitors or GLP1 analogues

- Superiority study vs. placebo in naïve patients
- Primary endpoint: HbA_{1c} at 12-16 weeks
- Third arm on metformin for sensitivity and comparison
- Placebo → new compound after 12-16 weeks (metformin arm does not change)
- Beta cell reserve tested baseline and after 52 weeks
- "Total deferral" for art. 7 products

"Standard study" for DPP4-inhibitors or GLP1a: sample size determination

- Required patients per group
  (assuming SD of 1.1% for HbA_{1c}, 0.85 power, 0.05 2-sided sign., drop-out rate 15%):
  - 108 (total 324*) for $\Delta HbA_{1c} \geq 0.4\%$
  - 73 (total 219*) for $\Delta HbA_{1c} \geq 0.6\%$
  - 49 (total 147*) for $\Delta HbA_{1c} \geq 0.7\%$
- PDCO considered 0.6-0.7% the minimum significant HbA_{1c} decrease for new products
- Rosiglitazone in adolescents failed to show non-inferiority to metformin or superiority to baseline (N=197, 2 groups)

**including third arm on metformin*

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"Alternative study" suggested by PDCO at D60 to applicants for DPP4-inhibitors or GLP1 analogues

- Add-on to metformin in patients insufficiently controlled on metformin alone
- Superiority study (metformin + placebo vs. metformin + new compound)
- Advantages:
  - Mimics possible MA/real use utilization
  - Theoretical lower number of required subjects
- Disadvantages:
  - significant recruitment problems (most pts. are controlled on metformin [+ lifestyle modif.] for at least 1-3 years)
  - to test beta-cell reserve, requires treatment with suboptimal therapy for 52 weeks in metformin arm

Problems in the PIPs for type 2 diabetes

- Recruitment difficulties / need to limit n. of children involved
- Development mainly in US / risk of requesting multiple studies (need for cooperation with FDA)
- High drop-out and non-compliance
- Extrapolation of safety not warranted – efficacy possible in specific circumstances (which?)
- Which is a clinically significant HbA_{1c} decrease?
- Is coadministration of non-authorised drugs (in children) acceptable? (e.g. sulphonylureas)
- Are factorial studies appropriate?
  (including naive and metformin-treated patients, both randomised to either placebo or new agent)

Need more information / data?

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