European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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EUROPEAN MEDICINES AGENCY DECISION

of 8 September 2008

on a class waiver on a class of medicinal products in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council as amended

(ONLY THE ENGLISH TEXT IS AUTHENTIC)

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THE EUROPEAN MEDICINES AGENCY,

Having regard to the Treaty establishing the European Community,

Having regard to Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use as amended and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004[1],

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency[2],

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued of its own motion on 29 August 2008 in accordance with Article 12 of Regulation (EC) No 1901/2006 as amended,

Having regard to Article 25 of Regulation (EC) No 1901/2006 as amended,

WHEREAS:

(1) The Paediatric Committee of the European Medicines Agency has given a positive opinion of its own motion on a class waiver on a class of medicinal products in a specified condition,

(2) It is therefore appropriate to adopt a Decision on a class waiver on a class of medicinal products in a specified condition.

[1] OJ L 378, 27.12.2006, p.1
[2] OJ L 136, 30.4.2004, p. 1

HAS ADOPTED THIS DECISION:

Article 1

A class waiver on a class of medicinal products in a specified condition, the details of which are set out in the Opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, is hereby agreed.

Article 2

This decision is applicable to all natural and legal persons intending to market a product falling within the scope of Article 1 of this Decision.

Done at London, 8 September 2008

For the European Medicines Agency
Thomas Lönngren
Executive Director

(Signature on file)

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

EMEA/PDCO/363663/2008

OPINION OF THE PAEDIATRIC COMMITTEE ON A CLASS WAIVER ON CLASSES OF MEDICINAL PRODUCTS

Scope of the waiver

Class of medicinal products: see Annex I

Condition(s): See Annex I

Opinion

1. The Paediatric Committee, having considered the class of medicinal products mentioned below in the condition specified pursuant to Article 12 of Regulation (EC) No 1901/2006 as amended, recommends granting a waiver in 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, in accordance with Article 11(1)(a) of Regulation (EC) No 1901/2006 as amended.

The Norwegian and Icelandic Paediatric Committee members agree with the above-mentioned recommendation of the Paediatric Committee.

2. The grounds for the granting of a waiver are included in the Annex II.

This opinion is forwarded to the Executive Director of the Agency.

London, 29 August 2008

On behalf of the Paediatric Committee
Dr Daniel Brasseur, Chairman

(Signature on file)

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ANNEX I
LIST OF CLASSES OF MEDICINAL PRODUCTS WAIVED

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- 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

ANNEX II
GROUNDS FOR THE GRANTING OF A WAIVER

GROUNDS FOR THE GRANTING OF A WAIVER

Scope

Whereas the class of medicinal products listed below are likely to be unsafe, the Paediatric Committee (PDCO) recommends that for a medicinal product belonging to the mentioned class and which is intended to treat the condition(s) specified, the production of the data in all subsets of the paediatric population in compliance with an agreed paediatric investigation plan shall be waived.
However, development of these classes of medicinal products in other conditions is still subject of the requirements of Regulation (EC) No 1901/2006, as amended.

The PDCO may adopt further opinions recommending the granting of waivers in other conditions or other classes of medicinal products.

In addition the PDCO may adopt an opinion advocating the review of granted waivers as per Article 14 of Regulation (EC) No 1901/2006, as amended.

Voluntary submission of a paediatric investigation plan for a waived condition is still possible.

Grounds for granting a waiver

The references provided were identified through systematic search and may not be exhaustive nor necessarily available for the EU population.

- **PPAR γ modulators in Type II diabetes in children**

a) Thiazolidinediones ("glitazones")

Thiazolidinediones form a class of specific PPARγ agonists influencing insulin sensitivity and thus being widely applied as hypoglycaemic drugs in type 2 diabetes in adults.

Peroxisome proliferator-activated receptor molecules (PPARs) are nuclear lipid-activated transcription factors. Three subsets encoded by distinct genes α, δ/β, γ have been identified. They act primarily by binding to sequence specific target elements as bound heterodimer with the retinoid –X- receptor in the promoter region of target genes and regulate the expression of genes involved in lipid metabolism and peroxisome proliferation. They act as lipid sensors, which locally adapt gene expression and coordinate inter organ communication

One major cellular output of PPAR action is the regulation of the balance between cell proliferation, survival and differentiation. PPARγ is expressed in adipose tissue and in lower concentration in spleen, gut, liver, heart and skeletal muscle, promoting adipogenesis and increasing lipid storage. Activation improves insulin sensitivity and glucose disposal.

Although thiazolidinediones as specific PPAR γ agonists are effective in the treatment of type II diabetes (T2DM), the global safety profile of this class of products remains unconvincing, especially for prolonged use. The relatively non-specific mechanism of action and the number of intracellular targets of the drug justify the pleiotropic nature of the adverse events observed, and increase the probability of new, possibly unexpected findings when use spans over many years or decades.

Increasingly class and specific side effects are reported.

The main class specific side effects include body weight gain, mainly due to increase in adipose tissue and body fluid retention, haemodilution, peripheral oedema, anaemia and increased risk for congestive heart failure. Weight gain is also of concern as adolescents with T2DM are often severely obese. Decreased bone mineral density, with an increased risk of fractures, and liver failure have been reported.

Tumour induction potency in PPARγ agonists depends on PPAR γ agonist potency and concerns already exist on carcinogenicity (bladder tumour, liposarcoma, fat tumours, haemangiosarcoma, liver tumour).

Children and adolescents with T2DM may have an increased probability of incurring adverse events than adults, because: a) they have a longer life expectancy than most adult patients with T2DM, and b) effects on growth, including bone growth, and reproduction may be more pronounced than in adults, when the balance between cell proliferation, survival and differentiation is changed due to potent PPAR agonists.

b) PPARγ-α double agonists ("glitazars") in Type II diabetes in children

Several molecules with combined PPARγ and PPARα modulation activity have been developed recently and studied in type II diabetes in adults (ragaglitazar, muraglitazar, tesaglitazar, aleglitazar and farglitazar). The development in diabetes has been stopped for all except one of them, during or after phase III or phase II studies; the reasons apparently involved safety issues pertaining to increased incidence of urothelial tumours, cardiovascular or renal adverse events, and oedema). Considering that this class of products is claimed to have the same mechanism of action of thiazolidinediones (PPARγ modulation) associated to an additional activity (PPARα modulation), the safety concerns expressed for thiazolidinediones do apply, and seem to be consistent with the arrested development of many products in this class.

Conclusion

A class waiver for PPARγ modulators, including thiazolidinediones ("glitazones"), PPARγ-α dual modulators ("glitazars") and multiple PPAR modulators which have activity on PPARγ (e.g. triple modulators), in the treatment of Type 2 diabetes mellitus in children is adopted. More data in adults, particularly in long term use, are considered necessary to review this waiver.

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