CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209139Orig1s000

NON-CLINICAL REVIEW(S)

NDA 209139 (Prexxartan, Valsartan oral solution)

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Submission date: May 10, 2017

G. Jagadeesh, PhD May 11, 2017
Pharmacologist

Comments on inactive ingredients (excipients) used with valsartan oral solution, 4 mg/ml

The product contains the following excipients:

• Potassium Sorbate, NF
• Methylparaben, NF
• Grape Flavor (b) (4)
• Poloxamer (b) (4) 188), NF
• Sodium Citrate Dihydrate, USP
• Sucralose, NF
• Propylene Glycol, NF

The sponsor has submitted response (dated May 10, 2017) to our 'Information Request' (dated April 11, 2017, review filed in DARRTS on 4/5/2017) on the levels of four excipients (sodium citrate dihydrate, poloxamer, propylene glycol, and methylparaben) that exceed levels found in currently approved products when based on daily doses.

1. Sodium citrate: Acceptable Max Daily Intake as per IIG is 473 mg. Product maximum intake is (b) (4). The sponsor justifies (b) (4) by citing 2 documents (Joint FAO/WHO Expert Committee on Food Additives and 21 CFR 184.1751). Acceptable.

2. Poloxamer: Acceptable Max Daily Intake as per IIG is 200 mg. Product maximum intake is (b) (4) The sponsor justifies (b) (4) by citing a document produced by the manufacturer, (b) (4) that conducted 6 months oral toxicity studies in rats and dogs. In rats and dogs, the NOEL of 2500 and 100 mg/kg/day respectively, was established (Nonionic Surfactants, Ed. Martin J. Schick, Marcel Dekker, Inc. New York, 1967, Chapter 28). Human equivalent dose for the most sensitive species (dog, 100 mg/kg/day) is 54 mg/kg and for 62 kg, it would be 3348 mg/day. However, for a child weighing 10 kg, the dosage

would be (b) (4) day. Thus, the daily dose of poloxamer for children weighing less than 15 kg exceeds the limit (b) (4)

3. Propylene glycol: EMA review on propylene glycol notes that 50 mg/kg/day causes various adverse events and the sponsor suggested threshold of (b) (4) according to EMA review, causes serious adverse events. For a 20 kg child, this would be 1000 mg/day. The sponsor agreed to lower propylene glycol levels to (b) (4) propylene glycol, which is less than the 1000 mg/kg/day level for concern for a 20 kg child.

4. Methylparaben: Sixty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives (series 940, 2006) notes a NOAEL of 1000 mg/kg/day in rodents. Thus, the proposed level in the product is acceptable.

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/s/

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09/27/2017

THOMAS PAPOIAN
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NDA 209139 (Prexxartan, Valsartan oral solution)

(EDR Location: \\CDSESUB1\evsprod\NDA209139\0000)

G. Jagadeesh, PhD
Pharmacologist

April 5, 2017

Comments on inactive ingredients (excipients) used with valsartan oral solution, 4 mg/ml

The product contains the following excipients:

- Potassium Sorbate, NF
- Methylparaben, NF
- Grape Flavor (b) (4)
- Poloxamer (b) (4) 188), NF
- Sodium Citrate Dihydrate, USP
- Sucralose, NF
- Propylene Glycol, NF

The Table below (extracted from the sponsor's submission, Module 3, Section 3.2.P.1: Description and Composition of the Drug Product, pages 5 and 6, Table 4) lists the excipients in relation to: quantity/ml, per 80 ml dosage, maximum limit approved by the FDA (reference to FDA's IIG database), maximum daily intake with Prexxartan at max dose, the acceptable maximum daily intake (calculation based on the approved drug product taken at the maximum dose, see footnote 2 in the Table). From the Table it is clear that the amount of sodium citrate dihydrate, poloxamer, propylene glycol, and methylparaben consumed daily with the maximum dose of Prexxartan (col 7) exceeds the maximum amount in approved drug product by the same route of administration (column 8). This is noted in the last column of the Table against each excipient. We ask the sponsor to re-examine their proposed levels based on our analysis, or provide a safety assessment (e.g., from human and/or animal data) to support their proposed levels, as follows:

To the sponsor:

We have examined levels of excipients being proposed for your drug product and have found levels of four of them (i.e., sodium citrate dihydrate, poloxamer, propylene glycol, and methylparaben) to be above levels found in currently approved products when based on daily doses. Please provide information showing that daily doses of these four excipients are higher in approved products than what will be administered in your product, or provide a safety assessment from human and/or animal studies showing that your proposed levels are safe as a function of daily dose.

Sponsor's Table 4: IIG Comparison of quantity of inactive ingredients/ maximum daily dose to the maximum limit specified in the IID

Ingredient	**% w/v**	**Quantity /ml (mg/ml)**	**Quantity per 80 ml Dose (mg)**	**Maximum Potency; FDA IIG Database**	**Route; Dosage Form**	**Prexxartan Max. Daily Intake[1]**	**Acceptable Max Daily Intake as per IIG[2]**	Remarks
Potassium Sorbate, NF[3]	(b) (4)						1550 mg	
Sodium Citrate, Dihydrate, USP							473 mg	Above the IIG limit. Needs safety assessment
Grape Flavor F-9711							NA	
Poloxamer, NF (Kolliphor P 188)							200 mg	Above the IIG limit. Needs safety assessment
Propylene Glycol, USP							1 to 500 mg/kg based on age[4]	Above the limit. Needs safety assessment
Sucralose, NF							800 mg	
Methylparaben, NF							36 mg[5]	Above the IIG limit. Needs safety assessment
Purified Water							NA	
Gum Arabic & Potassium Sorbate							*Gum Arabic[6]* *Potassium Sorbate 1550.00 mg*	
Flavor							*N/A*	
Water							*N/A*	

1: Maximum Daily Intake of inactive ingredient based on dosing 320 mg of valsartan via 80 ml of Valsartan Oral Solution (4 mg/ml). Maximum Daily Intake = (Max Daily dose/amount of drug per Dosage Unit) x Potency as per IIG database

2: Based on IIG database corresponding to the approved drug product dosage (maximum dose and the concentration of IIG)

3: Potassium sorbate is also present in Grape Flavor (b) (4). The combined amount ((b) (4) (max)) does not exceed the acceptable daily intake of the inactive ingredient.

4: Dosage of PG varies with the age. Maximum daily intake is 1 mg/kg for neonates (up to 28 days); 50 mg/kg for children (1 month to 4 years); 500 mg/kg from 5 yr to adults. Ref: Background review for the excipient propylene glycol. EMA/CHMP/334655/2013. Committee for Human Medicinal Products (CHMP)

5: Sponsor justification: The MSD sheet lists the LD50 (Oral) Rat as 9,380 mg/kg. A 62 kg adult would need to consume (b) (4) grams to approach lethal limits. The (b) (4) mg prexxartan maximum daily dose represents approximately (b) (4) of a lethal dose.

6: Sponsor justification (b) (4)

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/s/

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04/05/2017

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