

**NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC**

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This notification is a referral under Article 31 of Directive 2001/83/EC to the CHMP made by European Commission

<p>Product Name(s), if appropriate, Strength(s) and Pharmaceutical Form(s)</p> <p>Active Substance(s)/Therapeutic class</p>	<p>See Annex</p>
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<Applicant(s)/Marketing Authorisation Holder(s)> <In the referring Member State>

The French Agency on medicinal products, ANSM (Agence Nationale de sécurité du médicament et des produits de santé), conducted an inspection on 19-23 May 2014 (inspection reference GCP-141001-FR) at GVK Biosciences Private Limited (GVK Bio), Swarnajyanthi Commercial Complex, Ammeerpet, Hyderabad 500 038, India.

The findings reported during this inspection raise concerns on the reliability of the clinical part of bioequivalence studies conducted between 2008 and 2014 at the site inspected. Indeed, the following findings were reported:

- falsifications of electrocardiograms were detected in each and every one of the 9 trials inspected by the ANSM;
- these falsifications cast doubts on the authenticity of all other clinical records of these 9 clinical trials. They were therefore considered by the ANSM as not compliant with GCP and their data were considered as not acceptable to support marketing authorisation applications;
- the falsification of these ECGs was performed by at least 10 different individuals. The falsifications took place between at least July 2008 and 2013;
- the systematic nature of the falsifications of electrocardiograms, the extended period of time during which they took place and the number of members of staff involved highlight critical deficiencies in the quality system in place at GVK Bio's clinic in Hyderabad. They also show a lack of GCP training, awareness and understanding of members of GVK Bio staff, a lack of understanding by them of the importance of data integrity and of the possible consequences of their acts, as well as a lack of overview of clinical trial activities by the investigators. The seriousness of the deficiencies identified and the lack of GCP compliance at GVK Bio's clinic in Hyderabad raise questions as to the acceptability of the clinical part of all other bioequivalence trials performed at that site in support of marketing authorisations applications.

These findings are detailed in the ANSM inspection report dated 02 July 2014, to which GVK Bio have responded on 18 July 2014 and in the final inspection report which was issued on 21 July 2014

The CHMP should assess the potential impact of the findings mentioned above on the benefit-risk balance of the medicinal products which have been authorised by the Member States on the basis of relevant trials performed at the inspected site.

Taking into account these critical GCP deficiencies relating to data integrity found on every clinical trial inspected and performed from 2008, the CHMP may consider if the scope of this referral should be extended to studies conducted by GVK Bio in Hyderabad before 2008.

In view of the elements described above and the necessity to take an action at EU level, the European Commission considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it gives its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or withdrawn.



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Head of Unit, Medicinal products – authorisations, EMA

Encl: Annex I  
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National Number (NL)	Product name	Active substance	ATC classification	MAH	Procedure	RMS
37 139	ENTACAPONE TIEFENBACHER 200 mg, comprimé pelliculé - DC - EGE	ENTACAPONE		ALFRED E. TIEFENBACHER- HAMBURG - Allemagne	DE/H/2211/01/DC	DE
37608	DONEPEZIL MYLAN 5 mg, comprimé orodispersible	DONEPEZIL	N06DA02	MYLAN SAS	SE/H/925 - 926	SE
37609	DONEPEZIL MYLAN 10 mg, comprimé orodispersible	DONEPEZIL	N06DA02	MYLAN SAS	SE/H/925 - 926	SE
39 671	RIZATRIPTAN MYLAN 5mg, comprimé orodispersible	RIZATRIPTAN		MYLAN SAS	DE/H/2424/01- 02/DC	DE
39 672	RIZATRIPTAN MYLAN 10 mg, comprimé orodispersible	RIZATRIPTAN		MYLAN SAS	DE/H/2424/01- 02/DC	DE
40 610	REPAGLINIDE CHANELLE MEDICAL 0.5 mg, cp - DC MB	REPAGLINIDE		CHANELLE MEDICAL Loughrea, Co. Galway Ireland	UK/H/2573	UK
40 611	REPAGLINIDE CHANELLE MEDICAL 1 mg, cp - DC MB	REPAGLINIDE		CHANELLE MEDICAL	UK/H/2573	UK
40 612	REPAGLINIDE CHANELLE MEDICAL 2 mg, cp - DC MB	REPAGLINIDE		CHANELLE MEDICAL	UK/H/2573	UK
41 939	ESCITALOPRAM BROWN 5 mg, comprimé pelliculé sécable - EC - DC	ESCITALOPRAM		BROWN & Burk UK Ltd 5 Marryat close, Houslow west, Middlesex TW4 5DQ UK	PT/H/750	PT
41 940	ESCITALOPRAM BROWN 10 mg, comprimé pelliculé sécable - EC - DC	ESCITALOPRAM		BROWN & Burk UK Ltd	PT/H/750	PT
41 941	ESCITALOPRAM BROWN 15 mg, comprimé pelliculé sécable - EC - DC	ESCITALOPRAM		BROWN & Burk UK Ltd	PT/H/750	PT
41 942	ESCITALOPRAM BROWN 20 mg, comprimé pelliculé sécable - EC - DC	ESCITALOPRAM		BROWN & Burk UK Ltd	PT/H/750	PT
41 950	MENTUMIR (escitalopram) 5mg, comprimé pelliculé	ESCITALOPRAM		ABBOTT PRODUCTS SAS42, rue Rouget de Lisle – 92150 SURESNES	FR/H/514/01- 04/DC	FR
41 951	MENTUMIR (escitalopram) 10mg, comprimé pelliculé	ESCITALOPRAM		ABBOTT PRODUCTS SAS	FR/H/514/01- 04/DC	FR

41 952	MENTUMIR (escitalopram) 15mg, comprimé pelliculé	ESCITALOPRAM		ABBOTT PRODUCTS SAS	FR/H/514/01- 04/DC	FR
41 953	MENTUMIR (escitalopram) 20mg, comprimé pelliculé	ESCITALOPRAM		ABBOTT PRODUCTS SAS	FR/H/514/01- 04/DC	FR
43133	ELETRIPTAN MYLAN 40 mg, comprimé pelliculé	ELETRIPTAN		MYLAN SAS	SE/H/1312/01- 02/DC	SE
43134	ELETRIPTAN MYLAN 40 mg, comprimé pelliculé	ELETRIPTAN		MYLAN SAS	SE/H/1312/01- 02/DC	SE
44408	VORICONAZOLE PHARMATHEN 50 mg, comprimé pelliculé	VORICONAZOLE		PHARMATHEN S.A.6 Dervenakion str. 15351, Pallini Attiki Greece	NL/H/ 3162/001- 002/DC	NL
44409	VORICONAZOLE PHARMATHEN 200 mg, comprimé pelliculé	VORICONAZOLE		PHARMATHEN S.A.	NL/H/ 3162/001- 002/DC	NL
44467	OLMESARTAN DISTRQUIMICA 10 mg, comprimé pelliculé	OLMESARTAN		DISTRQUIMICA, S.A.Avda. Mare de Déu de Montserrat, 221 08041 Barcelona Spain	PT/H/1228- 1229/01-03/DC	PT
44468	OLMESARTAN DISTRQUIMICA 10 mg, comprimé pelliculé	OLMESARTAN		DISTRQUIMICA, S.A.	PT/H/1228- 1229/01-03/DC	PT
44469	OLMESARTAN DISTRQUIMICA 10 mg, comprimé pelliculé	OLMESARTAN		DISTRQUIMICA, S.A.	PT/H/1228- 1229/01-03/DC	PT
44470	OLMESARTAN PENSADOSE* 10 mg, comprimé pelliculé	OLMESARTAN		DISTRQUIMICA, S.A.	PT/H/1228- 1229/01-03/DC	PT
44471	OLMESARTAN PENSADOSE* 10 mg, comprimé pelliculé	OLMESARTAN		DISTRQUIMICA, S.A.	PT/H/1228- 1229/01-03/DC	PT
44472	OLMESARTAN PENSADOSE* 10 mg, comprimé pelliculé	OLMESARTAN		DISTRQUIMICA, S.A.	PT/H/1228- 1229/01-03/DC	PT
50 952	ESCITALOPRAM ZYDUS 5 mg, cp pelliculé-CJ	ESCITALOPRAM		ZYDUS France	National	FR
50 953	ESCITALOPRAM ZYDUS 10 mg, cp pelliculé-CJ	ESCITALOPRAM		ZYDUS France	National	FR
50 954	ESCITALOPRAM ZYDUS 15 mg, cp pelliculé-CJ	ESCITALOPRAM		ZYDUS France	National	FR
50 955	ESCITALOPRAM ZYDUS20 mg, cp pelliculé-CJ	ESCITALOPRAM		ZYDUS France	National	FR