

**Important Safety Information for Repaglinide and clopidogrel  
New Contraindication for Concomitant Use**



2015/07/31

**Audience**

Family physicians, general practitioners, nurses, nurse practitioners, pharmacists, endocrinologists and cardiovascular clinics

**Key messages**

- **Co-administration of repaglinide and clopidogrel (a CYP2C8 inhibitor) may lead to a significant decrease in blood glucose levels due to a drug-drug interaction.**
- **The concomitant use of repaglinide and clopidogrel is now contraindicated.**
- **The prescriber information for GLUCONORM (repaglinide) has been updated. The prescriber information for PLAVIX (clopidogrel) is currently being updated. The prescriber information for the generic products will be updated (see Products affected).**

**What is the issue?**

Co-administration of repaglinide and clopidogrel (a known CYP2C8 inhibitor), may lead to a significant decrease in blood glucose levels due to a drug-drug interaction.

**Background**

Repaglinide is an oral antidiabetic agent used for the treatment of type 2 diabetes mellitus. Clopidogrel is an oral antiplatelet agent used to prevent atherothrombotic events. Please refer to the GLUCONORM (repaglinide) and PLAVIX (clopidogrel) Canadian Product Monographs (CPMs) for full prescribing information.

Health Canada and Novo Nordisk Canada Inc. have reviewed the new safety information regarding repaglinide published in the Clinical Pharmacology and

Therapeutics Journal. This information has now led to new prescribing information in the CPM for GLUCONORM (repaglinide). The CPM for PLAVIX (clopidogrel) is currently being updated. The CPMs for the generic versions will be updated (see **Products affected** listed below).

In a study conducted with healthy volunteers, co-administration of clopidogrel (300 mg on day 1, followed by 75 mg daily for 2 consecutive days), and repaglinide (single dose of 0.25 mg on day 1 and day 3) resulted in an increase in repaglinide systemic exposure ( $AUC_{0-\infty}$ ) by 5.1-fold and 3.9-fold on day 1 and day 3 respectively. Hypoglycemia was noted in healthy volunteers on day 1 (3.3 mmol/L) and on day 3 (3.9 mmol/L).<sup>1</sup>

### **Products affected**

- Repaglinide:  
GLUCONORM and generic products: ACT-REPAGLINIDE, APO-REPAGLINIDE, AURO-REPAGLINIDE, PMS-REPAGLINIDE, REPAGLINIDE, SANDOZ-REPAGLINIDE
- Clopidogrel:  
PLAVIX and generic products: ABBOTT-CLOPIDOGREL, APO-CLOPIDOGREL, AURO-CLOPIDOGREL, CLOPIDOGREL, CO-CLOPIDOGREL, DOM-CLOPIDOGREL, JAMP-CLOPIDOGREL, MAR-CLOPIDOGREL, MINT-CLOPIDOGREL, MYLAN-CLOPIDOGREL, PMS-CLOPIDOGREL, RAN-CLOPIDOGREL, RIVA-CLOPIDOGREL, SANDOZ-CLOPIDOGREL, TEVA-CLOPIDOGREL

### **Information for consumers**

Repaglinide (a medicine used to treat type 2 diabetes) and clopidogrel (a medicine used to prevent blood clots) are not to be used together. Repaglinide when taken by itself is intended to lower blood sugar to a normal level. However, when both medications are taken together, there is a greater risk of the blood sugar becoming too low, also known as hypoglycemia. Severe hypoglycemia can cause loss of consciousness, seizure, brain damage and even death.

If you are taking both medicines together, talk to your doctor or pharmacist before making any changes to your current therapy. Additional information for consumers is also provided in the Part III: Consumer Information section of the product information for GLUCONORM (repaglinide).

### **Information for health care professionals**

The concomitant use of repaglinide and clopidogrel is now contraindicated. Combined use of repaglinide and clopidogrel may lead to hypoglycemia. Please refer to the GLUCONORM (repaglinide) and PLAVIX (clopidogrel) CPMs for full prescribing information.

### **Action taken by Health Canada**

The CPM for GLUCONORM (repaglinide) has been updated to include this new safety information. The CPM for the PLAVIX (clopidogrel) is being updated. The CPMs for

the generic versions will be updated.

### Report health or safety concerns

Managing marketed health product-related side effects depends on health care professionals and consumers reporting them. Any case of serious hypoglycemia or other serious or unexpected side effects in patients receiving repaglinide and clopidogrel should be reported to the respective manufacturer of repaglinide prescribed as indicated below or to Health Canada.

GlucoNorm® (repaglinide)  
Novo Nordisk Canada Inc.  
300-2680 Skymark Avenue  
Mississauga, ON, L4W 5L6  
Telephone: 1-800-465-4334

**Email** [nci-drugsafety@novonordisk.com](mailto:nci-drugsafety@novonordisk.com)

APO-Repaglinide (repaglinide)  
Apotex Inc.  
150 Signet Drive  
Toronto, ON, M9L 1T9  
Telephone: 1-800-667-4708 or 416-401-7780  
Fax: 1-866-429-9133 or 416-401-3819

**Email:** [drugsafety@apotex.com](mailto:drugsafety@apotex.com)

Repaglinide (repaglinide)  
Pro Doc Ltée  
2925 Boulevard Industriel  
Laval, PQ, H7L 3W9  
Telephone: 1 800 361-8559  
Fax : 450-668-0816

**E-mail :** [ideschenes@prodoc.qc.ca](mailto:ideschenes@prodoc.qc.ca)

AURO-Repaglinide (repaglinide)  
Auro Pharma Inc.  
3700 Steeles Avenue West, Suite 402  
Woodbridge ON, L4L 8K8  
Tel: 905-856-8063 ext 223

**Email:** [rana.harb@aurobindo.com](mailto:rana.harb@aurobindo.com)

ACT-Repaglinide (repaglinide)  
Actavis Pharma Company  
6733 Mississauga Road, Suite 400  
Mississauga, ON, L5N 6J5  
Telephone: 866-254-6111

pms-REPAGLINIDE (repaglinide)  
Pharmascience Inc.  
6111, Avenue Royalmount, Suite 100  
Montreal, PQ, H4P 2T4  
Telephone: 1-888-550-6060  
Fax: 1-514-340-0164

**Email:** [medinfo@scientificaffairs.ca](mailto:medinfo@scientificaffairs.ca)

Sandoz Repaglinide (repaglinide)  
Sandoz Canada Inc.  
145 Jules-Léger Street  
Boucherville, PQ, J4B 7K8  
Telephone : 1-800-343-8839 ext : 4636  
Fax : 1-888-243-6221

**Email :** [medinfo@sandoz.com](mailto:medinfo@sandoz.com)

### To correct your mailing address or fax number, contact the manufacturer(s).

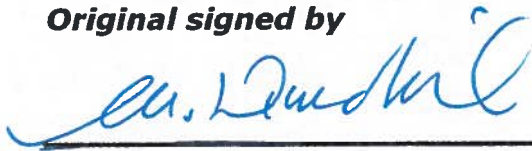
You can report any suspected adverse reactions associated with the use of health products to Health Canada by:

- Calling toll-free at 1-866-234-2345; or
- Visiting MedEffect Canada's Web page on [Adverse Reaction Reporting](http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) (<http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php>) for information on how to report online, by mail or by fax.

For other health product inquiries related to this communication, contact Health Canada at:

Marketed Health Products Directorate  
E-mail: [mhpd\\_dpssc.public@hc-sc.gc.ca](mailto:mhpd_dpssc.public@hc-sc.gc.ca)  
Telephone: 613-954-6522  
Fax: 613-952-7738

**Original signed by**



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Dr. Mohamed Eid  
Vice President, Clinical, Medical and  
Regulatory  
Novo Nordisk Canada Inc.

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Kent Major  
Vice President, Regulatory Affairs  
Actavis Pharma Company

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Dr. Colin D'Cunha  
Director Global Medical Affairs  
Apotex Inc.

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Ms. Rana Harb  
Manager Regulatory Affairs  
Auro Pharma Inc.

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Len Neirinck, Ph.D.  
Vice-president and Chief Scientific  
Officer, Scientific Affairs  
Pharmascience Inc.

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Jovette Deschênes,  
Director, QC/QA and Regulatory Affairs  
Pro Doc Ltée

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Len Arsenault  
Vice President, Scientific Affairs  
Sandoz Canada Inc.

**References**

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1. Tornio A, Filppula AM, Kailari O, et al. Glucuronidation Converts Clopidogrel to a Strong Time-Dependent Inhibitor of CYP2C8: A Phase II Metabolite as a Perpetrator of Drug-Drug Interactions. *Clin Pharmacol Ther* 2014 Oct,96(4):498-507