What the product label does not tell you about drug–drug interaction management: time for a re-appraisal

Burger, D.M.; Le Comte, M.; Smolders, E.J.; Jacobs, T.G.; Heine, R. Ter; Knibbe, C.A.J.; Pirmohamed, M.

ACCP
American College of Clinical Pharmacology
Advancing Clinical Care through Pharmacology®

What the Product Label Does Not Tell You About Drug–Drug Interaction Management

Time for a Re-Appraisal

The Journal of Clinical Pharmacology
2023, 0(0) 1–5

DOI: 10.1002/jcph.2316

David M. Burger, PharmD, PhD[1,2], Marianne le Comte, PharmD[3], Elise J. Smolders, PharmD, PhD[1,4], Tom G. Jacobs, PharmD[1], Rob ter Heine, PharmD, PhD[1], Catherijne A.J. Knibbe, PharmD, PhD FCP[5,6], and Munir Pirmohamed, FRCP, PhD[7]

Keywords

CYP3A, drug–drug interactions, product information, regulatory approval

The management of drug–drug interactions (DDIs) is a key component of product labels approved by regulatory authorities such as the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA). Based on the product information (PI), both healthcare professionals (HCPs, for individual patients) and content developers responsible for the maintenance of clinical decision support (CDS) systems (on a population level) assess the DDI potential when a new drug is prescribed in patients that use other medications. When there is no recommendation for DDI management for a specific co-medication in the PI, extrapolation based on information from general clinical pharmacology principles can be needed for the drugs of interest, to prevent toxicity or a lack of efficacy.

Unfortunately, there are large gaps between the actual information in the PI and potentially relevant DDIs. Typically, only a small minority of potential co-medications is listed in the PI, which results in HCPs either ignoring potential DDIs or undertaking individual DDI assessments for the non-listed co-medications. This leads to variability in how extrapolations are applied, both for individual patients and in the DDI databases that are compiled in CDS systems. Moreover, although some HCPs will undertake these assessments correctly, for example, by consulting online DDI resources, many will not or will rely entirely on the PI, which may lead to patient harm. It can be argued that providing a vast list of potential DDIs in a label may be unrealistic, but as the PI is a legal document that then serves as a source of information provided in other resources, including CDS systems, we feel that it is important to highlight some of these issues, and through multi-stakeholder discussions, arrive at a consensus that is both consistent with good medical practice and allows the rationalization of prescribing by individual clinicians to maximize benefits and reduce harms.

To illustrate our concerns, we have used the newly published PI of the novel human immunodeficiency virus type 1 (HIV-1) capsid inhibitor lenacapavir (Sunlenca) as an exemplar.[1,2] We have assessed the

[1]Department of Pharmacy, Radboudumc Research Institute for Medical Innovation (RIMI), Radboudumc, The Netherlands
[2]Global DDI Solutions, Utrecht, The Netherlands
[3]Drug Information Center, Royal Dutch Pharmacists Association (KNMP), The Hague, The Netherlands
[4]Department of Clinical Pharmacy, Isala Hospital, Zwolle, The Netherlands
[5]Department of Clinical Pharmacy, St Antonius Hospital, Nieuwegein, The Netherlands
[6]Leiden Amsterdam Center for Drug Research (LACDR), Division of Systems Pharmacology and Pharmacy, LACDR, Leiden University, Leiden, The Netherlands
[7]Wolfson Centre for Personalised Medicine, Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, UK

Submitted for publication 26 April 2023; accepted 19 July 2023.

Corresponding Author:
David M. Burger PharmD, PhD, Department of Pharmacy, Radboudumc Research Institute for Medical Innovation (RIMI), 864 Radboudumc, Geert Grooteplein 10, 6525 GA Nijmegen, The Netherlands
E-mail: david.burger@radboudumc.nl

(in)completeness of the PI, and how we should perform our extrapolations to define potential DDIs. Although we have focused on DDI management in the care of people living with HIV, we feel that the principles we highlight apply to many other therapeutic areas.

Lenacapavir

Similar to other antiretrovirals, lenacapavir has an extensive DDI profile, and instructions for DDI management can be found in the PI published by the EMA and the FDA.[1,2] Lenacapavir is a substrate for cytochrome P450, family 3, subfamily A (CYP3A), P-glycoprotein 1 (P-gp), and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), and hence can be a *victim* of a DDI with inducers or inhibitors of these pathways. In addition, lenacapavir is a moderate CYP3A inhibitor and can thus also be a *perpetrator* of a DDI when combined with CYP3A substrates.

We evaluated the extent to which the DDI management information included in the PI would help us when we are consulted for a potential DDI in a patient about to start treatment with lenacapavir. Despite the potential impact on patient outcomes, to our knowledge, no coordinated efforts have yet been made to optimize DDI management information to guide HCPs.

Lenacapavir as a Potential Victim of a DDI: Inducers

As lenacapavir is a substrate for CYP3A, P-gp, and UGT1A1, the PI states that administration in combination with strong inducers is contraindicated, and its use is not recommended with moderate inducers (Table 1). The agents in this category studied in formal DDI studies were rifampicin and efavirenz as representatives of a strong and a moderate inducer, respectively. Coadministration with rifampicin led to an 84% and 55% reduction in the area under the plot of plasma concentration versus time after dosage (AUC) and maximum serum concentration (C_{max}) of lenacapavir, respectively, and to a 56% and 36% reduction in lenacapavir AUC and C_{max} with the coadministration of efavirenz. Such reductions in lenacapavir exposure would be clinically important, with the potential to lead to virological failure.

However, surprisingly, a number of agents listed on the FDA website as being strong CYP3A inducers are not listed in the lenacapavir PI as contraindicated medications (see Table 1),[3] including apalutamide, enzalutamide, ivosidenib, lumacaftor, and mitotane. Similarly, there is no mention of the moderate CYP3A inducers bosentan, cenobamate, dabrafenib, etravirine, lorlatinib, pexidartinib, primidone, and sotorasib. The current EMA guidelines on the investigation of drug interactions does not provide a table with relevant CYP3A inducers,[4] so no comparison could be made.

Table 1. Classification of Strong Inducers (Contraindicated) and Moderate Inducers (Not Recommended) of CYP3A in the Lenacapavir Product Information

Enzyme inducers mentioned in lenacapavir product information		
Co-medication	Strong inducer (contraindicated)	Moderate inducer (not recommended)
Carbamazepine	×	
Efavirenz		×
Etravirine[a]		×
Nevirapine		×
Oxcarbazepine		×
Phenobarbital		×
Phenytoin	×	
Rifabutin		×
Rifampicin	×	
Rifapentine[b]		×
St John's Wort	×	
Tipranavir/ritonavir		×
Enzyme inducers not mentioned in either FDA or EMA product label for lenacapavir		
Apalutamide, enzalutamide, ivosidenib, lumacaftor, mitotane	×	
Bosentan, cenobamate, dabrafenib, lorlatinib, pexidartinib, primidone, sotorasib		×

[a] EMA PI only.
[b] FDA PI only.

There is a risk that the incomplete list of compounds that potentially perpetrate DDIs with lenacapavir in the PI, and the discrepancies between the PI from different regulators, may lead to confusion for HCPs. The incorrect and/or inconsistent management of DDIs may have potentially significant consequences for the efficacy of lenacapavir in individual patients. We recommend the development of a consensus list of inducers, including a mechanism to update that system; product labels could refer to this consensus list.

Lenacapavir as a Potential Victim of a DDI: Inhibitors

In the PI, the coadministration of combined P-gp, UGT1A1, and strong CYP3A inhibitors with lenacapavir is not recommended. This is based on a formal DDI study with atazanavir/cobicistat, a combination that indeed inhibits all 3 pathways, leading to a substantial increase in lenacapavir AUC and C_{max} (with a geometric mean ratio 6.60 and 4.21, respectively). The potential safety issues of such overexposure to lenacapavir are unknown.

Although we acknowledge that we are not aware of any drug other than atazanavir/cobicistat that has

Table 2. CYP3A Substrates Described in Product Information for Lenacapavir

Therapeutic class	Drug name	FDA: "sensitive substrates primary metabolized by CYP3A"	EMA: "sensitive CYP3A substrate with a narrow therapeutic index"
Ergot alkaloids	Dihydroergotamine	×	×
	Ergotamine		
	Methylergonovine[a]		
Phosphodieasterase-5 inhibitors	Sildenafil	×	×
	Tadalafil		
	Vardenafil		
Corticosteroids	Dexamethasone	×	×
	Hydrocortisone/cortisone		
HMG-CoA-reductase inhibitors	Lovastatin	×	×
	Simvastatin		
Sedatives/Hypnotics	Midazolam		×
	Triazolam		
Anticoagulants	Rivaroxaban	×	×
	Dabigatran		
	Edoxaban		
Opioids	Fentanyl	×	
	Oxycodone		
	Tramadol		
	Buprenorphine		
	Methadone		
Opioid Antagonists	Naloxegol	×	

[a] FDA PI only.

a combined inhibitory activity on CYP3A, P-gp, and UGT1A1 pathways, it is likely that some patients living with HIV are treated with a combination of drugs that *together* will result in the inhibition of all 3 pathways, for instance combined treatment with darunavir/cobicistat (inhibitors of CYP3A and P-gp) and tyrosine kinase inhibitors such as sorafenib and regorafenib (inhibitors of UGT1A1). A warning that addresses this possibility is currently missing in the product labels. This also highlights the fact that with the increasing prevalence of polypharmacy, we need to consider not only the 2-way drug interactions but also those involving 3, 4, or more drugs.

Lenacapavir as a Potential Perpetrator of a DDI: CYP3A/P-gp Substrates with a Narrow Therapeutic Range

The FDA product label warns of the potential risk of adverse reactions when lenacapavir, a moderate CYP3A inhibitor, is combined with drugs primarily metabolized by CYP3A. There is a reference to "sensitive CYP3A substrates" in the FDA PI of lenacapavir. The EMA PI uses slightly different language and cautions the use of "sensitive CYP3A substrates with a narrow therapeutic index". Clearly, the question that follows from this is which agents fall into this category? The CYP3A substrates described in the drug interaction tables in the PI for lenacapavir are listed in Table 2.

Although Table 2 shows an inconsistency between the PI documents from the 2 regulatory agencies in the listing of CYP3A substrates that cannot be combined with lenacapavir, we feel that there are 2 other more fundamental issues that need to be considered:

- What is the procedure for selecting these agents amongst the large number of known CYP3A substrates? The FDA website hosts a table listing sensitive substrates,[3] and for CYP3A there are 2 lists: one of CYP3A substrates with $\geq$10-fold increase in AUC with the coadministration of strong inhibitors, and another where a 5- to 10-fold increase in AUC is expected. Lenacapavir is not a strong but a moderate CYP3A inhibitor. Only a subset of these CYP3A substrates with a narrow therapeutic range are specified in the lenacapavir product label, with relevant agents, such as colchicine, ibrutinib, tacrolimus, vincristine, etc., missing.
- For DDI management when lenacapavir is coprescribed with direct oral anticoagulants (DOACs), there is a reference in the PI for DOACs on how to dose them with moderate CYP3A/P-gp inhibitors. However, we do not understand why there is no specific recommendation in the lenacapavir PI regarding DOACs? Such inconsistencies in the DDI management for some drugs in the respective PI documents may lead to errors and requires additional efforts by HCPs to adequately deal with DDIs.

Suboptimal DDI Information in Product Labels: Is There a Problem?

The PI labels published when a drug is licensed are legal documents agreed between the manufacturing authorization holder and the regulatory agency, and are written to assist HCPs in prescribing medicine rationally to maximize the benefit–harm ratio. HCPs should thus be able to use the information from the PI, combine it with the characteristics of the individual patient, and make a benefit/risk assessment. Developers of DDI databases included in CDS systems use the information in the PI to populate their system when a new drug comes to the market.

As illustrated with lenacapavir, we are concerned that the interpretation of DDI information from the PI, both on an individual and a software system level, may result in substantial variability in the handling of DDIs across the world. Not surprisingly, when comparing the guidance on DDI management from 3 major online drug information resources, Kontsioti et al found the level of consistency to be 10.65%-18.32%, with significant variability in categorizing the severity of DDIs and the clinical advice given.[5] They conclude: "Such variability in information could have deleterious consequences for patient safety." This is supported by many reports of the increased risk of adverse reactions where DDI management failed in preventing adverse clinical outcomes,[6–11] and by many case reports. So yes, in short, there is a problem.

Optimized DDI Management in the Future: We Need a Solution

Although we are not the first group to raise this issue,[12] to the best our knowledge there are no coordinated actions with all stakeholders (pharma companies, regulatory authorities, clinical societies, and academia) to improve the information provided for the management of DDIs. We call for the development of a consortium to optimize DDI management and welcome your suggestions. A tentative agenda for such a consortium is presented in Box 1.

Box 1. Agenda for Optimized DDI Management

- Consensus documents for the assessment of DDI potential (substrates, inhibitors, and inducers) and for the extrapolation of the DDI potential to other drugs
- What is the use of physiologically based pharmacokinetic (PBPK) modeling to fill the DDI knowledge gap?
- Construction of complete DDI datasets for all available medications based on clinical data and PBPK simulations in the absence of other studies
- Consideration of more complex DDI scenarios going beyond the 2-way interactions to include interactions involving more than 2 drugs
- Consideration of drug–drug–gene interactions
- Consideration of comorbidities
- Guidance document for manufacturers on how to construct drug interaction tables
- Harmonization of drug interaction tables
- Guidance for uptake in CDS systems
- Identify research gaps
- Acknowledgement of therapeutic ranges in the label to facilitate pharmacokinetically guided dosing
- Development of educational materials to improve DDI management among prescribers

We do not underestimate the challenges and pitfalls in implementing this framework. But if all stakeholders acknowledge the problem, and are motivated to support this endeavor, we should be able to make a start. We need to think of novel ways of providing up-to-date PI to prescribers, for example by using electronic methods, which can then be used as the ultimate source of truth that can be used by secondary sources such as CDS systems. Hopefully, this commentary is a start. It is incumbent upon all of us to maximize the benefits of medications for our patients and to minimize the harms.

Conflicts of Interest

The views expressed in this article are those of the authors, and not of any organizations they may represent. D.B. is a co-founder of Global DDI solutions, and his employer, RadboudUMC, has received grants from ViiV Health Care, Gilead Sciences, Merck, and Pfizer. M.P. has received partnership funding for the following: MRC Clinical Pharmacology Training Scheme (co-funded by MRC and Roche, UCB, Eli Lilly, and Novartis), and a PhD studentship jointly funded by the Engineering and Physical Sciences Research Council (EPSRC) and Astra Zeneca. He has developed an HLA genotyping panel with MC Diagnostics, but does not benefit financially from this. He is part of the IMI Consortium ARDAT (Accelerating R&D for Advanced Therapies, www.ardat.org). R.t.H. has received funding from AMGEN. All other co-authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Funding

None of the funding that the authors have received is related to this article.

References

1. EMA. Sunlenca. Summary of Product Characteristics 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/sunlenca-epar-product-information_en.pdf
2. FDA. Sunlenca. Prescribing Information. 2022 Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215973s000lbl.pdf
3. FDA. Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducer 2022 Available from: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-3
4. EMA. Guideline on the investigation of drug interactions 2012. Available from. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1_en.pdf
5. Kontsioti E, Maskell S, Bensalem A, Dutta B, Pirmohamed M. Similarity and consistency assessment of three major online drug-drug interaction resources. *Br J Clin Pharmacol*. 2022;88(9):4067-4079.
6. Gronich N, Stein N, Muszkat M. Association between use of pharmacokinetic-interacting drugs and effectiveness and safety of direct acting oral anticoagulants: nested case-control study. *Clin Pharmacol Ther*. 2021;110(6):1526-1536.
7. Cid A, Smetana ME, Hebert C, Coe K, Smith JM. Impact of concomitant fluconazole on direct oral anticoagulant bleeding risk. *Pharmacotherapy*. 2022;42(12):880-9.
8. Wei N, Zheng B, Que W, Zhang J, Liu M. The association between proton pump inhibitor use and systemic anti-tumour therapy on survival outcomes in patients with advanced non-small cell lung cancer: A systematic review and meta-analysis. *Br J Clin Pharmacol*. 2022;88(7):3052-3063.
9. Honda T, Abe K, Oda M, et al. Gastrointestinal bleeding during direct oral anticoagulant therapy in patients with nonvalvular atrial fibrillation and risk of polypharmacy. *J Clin Pharmacol*. 2022;62(12):1548-1556.
10. Turner RM, de Koning EM, Fontana V, Thompson A, Pirmohamed M. Multimorbidity, polypharmacy, and drug-drug-gene interactions following a non-ST elevation acute coronary syndrome: analysis of a multicentre observational study. *BMC Med*. 2020;18(1):367.
11. Grymonprez M, Vanspranghe K, Capiau A, Boussery K, Steurbaut S, Lahousse L. Impact of P-glycoprotein and/or CYP3A4-interacting drugs on effectiveness and safety of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: a meta-analysis. *Br J Clin Pharmacol*. 2022;88(7):3039-3051.
12. Scheife RT, Hines LE, Boyce RD, et al. Consensus recommendations for systematic evaluation of drug-drug interaction evidence for clinical decision support. *Drug Saf*. 2015;38(2):197-206.