deNovo Medica

Leader in digital CPD for Southern African healthcare professionals

Earn 3 ETHICS CPD points free

Ethics

Off-label use and prescription of medicines: legal and ethical implications

M E Klinck
B. Iur, LLB, BA(Hons) Applied Psychology

Dr Julien Trokis
Diabetes Care Centre, Capegate Cape Town

Introduction

Prescription and medicines usage, like all aspects of healthcare service provision, could render professionals liable for their actions or failure to take certain steps. The practice of doctors using medications for patient populations, symptoms or diseases for which they have not been officially approved by an appropriate regulatory agency such as the South African Health Products Regulatory Authority (SAHPRA) is known as off-label prescribing. Although practitioners may use medicines off label, legal frameworks in South Africa necessitate extreme caution, particularly in respect of malpractice. Liability could also arise from non-compliance with the Consumer Protection Act (CPA). Informed consent and the issuance of warnings to patients are critical when prescribing medicines off label; these aspects are difficult to implement due to the fact that unregistered uses do not have scientifically proven facts/data, or are not approved by health authorities.

The use of medicines off label is now, in the time of a pandemic, very topical and remains an important area of risk for healthcare professionals. Elsabe Klinck navigates South African law and legislation in this regard. Dr Julien Trokis considers the clinical interpretations of ethical on-label/off-label prescribing in diabetes today, using common clinical situations that require careful thought with regard to the ethical and legal consequences for individual prescribing clinicians.

LEARNING OBJECTIVES

You will learn:

- How South African law relates to off-label usage of medicines and malpractice liability
- The approach of the medical schemes legislative framework to the funding of off-label medicines
- Ethical considerations when justifying off-label prescription.

This report was made possible by an unrestricted educational grant from **Novo Nordisk**. *The content of the report is independent of the sponsor.*

novo nordisk®

ZA20TSM00017

How does South African law and legislation relate to off-label usage of medicines?

The Medicines and Related Substances Act, 1965 (Medicines Act)[1]

Off-label promotion is an offence under the Act in terms of section 29(b), rendering the company and its officials who do so liable to a fine or imprisonment

The Medicines Act requires medicines to be registered, and in terms of section 15 such registration relates to the medicine being proven to be safe, efficacious and of good quality. This registration process includes the evaluation of a package insert (as part of the medicine's labelling requirements) and affirms that everything recorded therein can be proven. This means that those aspects of the medicine have been tested and it can therefore safely be used as documented.

In terms of the Medicines Act, using a medicine off label is therefore 'risky', as it has not been tested for use in, for example, a specific patient population. This use can therefore not be backed up by SAHPRA approval and, in many cases, there are no studies to scientifically support such use.

Companies are also prohibited in section 18 and the General Medicines Regulations[2] from marketing any medicine for treatment that goes beyond its package insert, i.e. the approved indications under the approved circumstances, and for the approved populations or subpopulation groups. Off-label promotion is an offence under the Act in terms of section 29(b), rendering a company and its officials who do so liable to a fine or imprisonment.

Using a medicine off label therefore carries a liability risk, as the healthcare professional would not be able to rely on any regulatory approvals to support or justify its use for certain indications, in certain populations and/or under certain conditions.

The Consumer Protection Act 68 of 2008[3]

In the context of medicines and healthcare, such reasonability would need to be scientifically determined, and cannot merely be based on case studies or personal experience

The CPA applies to all goods, including medicines. Its section 55 states that a consumer (and in the case of healthcare, therefore a patient) is entitled to receive goods that are reasonably suitable for the purposes for which they are intended. The purpose of a medicine is set out in its package insert.

Furthermore, if the patient has expressed an intention to be supplied with certain goods, and the supplier (in this case the prescriber) acts in a manner that suggests they are knowledgeable about the goods, a patient has the right to expect that the goods are indeed reasonably suitable for that purpose. This means that, under consumer legislation, there is a general expectation that prescribers will prescribe medicines that are reasonably suitable for the specific purpose for which the patient intends to use it.

Although it may be possible to make a case that a medicine being used off label is 'reasonably suitable' for a particular purpose, there would need to be some level of proof thereof. Such reasonability would need to be scientifically determined, and cannot merely be based on case studies or personal experience.

Section 55 also obliges the prescriber to warn the consumer (patient) about the goods. Such warnings, in the case of an off-label prescription, cannot be made with any certainty; this uncertainty means there are wide margins for consumers to take action in cases of harm. Providing inadequate warnings creates strict (guiltless) liability under section 61 of the CPA.[3] Where a risk could lead to death or serious consequences (e.g. the loss of an unborn child), the consumer's attention must be drawn to those risks explicitly and specifically.

The law of delict – malpractice

The field of law within which practitioners may be sued is called the law of delict, but is commonly referred to as 'malpractice law'. The elements of the law of delict are as follows:

1. That there was an act or an omission, i.e. something was done or not done
2. There was harm to a patient
3. The specific act or omission caused the harm, and nothing else. This causality is important, as it must be this act or omission that caused the harm
4. *Culpa* (guilt) is a requirement. This could take the form of negligence or intent. Negligence is at the heart of malpractice cases. In some cases, there could be intent, i.e. a clear desire to harm someone. However, negligence is where there has not been an intention to harm, but the harm resulted from a failure to take the care one should have, e.g. by issuing the right warnings or informing the patient, as is expected of a reasonable healthcare practitioner
5. Wrongfulness is also a criterion, and requires that society views what happened as wrong. In Latin, this is called the *boni mores* (good morals) test.

The standard for determining negligence is what the reasonable practitioner would have done in the same circumstances

In respect of the first criterion, the act could be that of off-label prescription or even the failure to inform the patient of the risks that could materialise from that. And, what makes this even more pertinent is that as there is no approved package insert there are limited warnings and indications of such risks for the specific indication, e.g. use in a patient (sub-) population.

Negligence is also about foreseeing potential issues (e.g. harm as a result of off-label use) and taking steps to prevent or mitigate such risks. Treatment guidelines, protocols and standard operating procedures, for example, are therefore all important to establish whether there has been negligence or not. The standard for determining negligence is what the reasonable practitioner would have done in the same circumstances. This includes, for example, the obligation to obtain informed consent. It also includes the duty of the practitioner not to be swayed by, for example, funding issues and in doing so, keeping quiet about medicines duly registered for the specific circumstances of the patient.

The General Medical Schemes Regulations framework

Prescribed minimum benefits (PMBs) must be funded by all schemes on all options 'in full' and without co-payment, according to Regulation 8 of the General Medical Schemes Regulations.[4] In the explanatory notes to the PMBs, the following provision is found:

> *"The following interventions shall however be excluded from the generic medical/surgical management categories unless otherwise specified:*
> …
> *(vii) Treatments, drugs or devices not yet registered by the relevant authority in the Republic of South Africa."*

This means that, unless a treatment has been approved (registered) for a particular indication, schemes should not be funding it. However, this rule related to Regulation 8 is not always consistently adhered to and issues of price often dictate a medication's acceptability, or not, to medical schemes.

Medical schemes have, in terms of section 47(4)(h), to adhere to 'all applicable law'. This means they have to consider the provisions in the Medicines Act on issues such as substitution (therapeutic substitution being prohibited) and the labelling of medicines.

Regulation 15I and medical scheme formularies

Regulation 15I permits medical schemes to set formularies. However, in doing so, they have to abide by the criteria in this regulation, and regulation 15 itself:

- The formulary must be set on evidence-based medicine, which is defined as 'current-based evidence, whereby individual clinical experience is integrated with the best available evidence from external sources'. It would be difficult for a medical scheme to prove that permission for off-label use of a product is indeed evidence based
- The formulary must consider 'cost-effectiveness', and not price *per se*. There is a definite cost associated with the risk of off-label use, in particular in vulnerable patient populations, as well as a risk of adverse events
- Regulation 15I(c) envisages this potential risk of harm, in that it refers to 'cause, or would cause' an adverse reaction in a patient. It therefore recognises that one should not wait for harm to occur but must take steps to avert such harm. Prescribers need to motivate for a non-formulary medicine if a formulary-listed medicine will cause harm, instead of using a formulary-listed medicine off label. In such cases, schemes are obliged to fund a non-formulary-listed medicine without penalty (e.g. co-payment) to the patient.

Practitioners should insist that medical scheme formularies be guided by evidence-based medicine, and that cost-effectiveness and not price be a determining factor

Importantly, off-label prescription prompted by medical schemes on the basis of price would fall foul of medical schemes law. Practitioners should insist that formularies be guided by evidence-based medicine, and that cost-effectiveness and not price be a determining factor. Furthermore, exceptions must be created in the case of potential adverse reactions that could result from off-label use.

How does Regulation 15J relate to off-label use of medicines?

Regulation 15J is also relevant to off-label use, in particular where such use is linked to a formulary where an in-formulary prescription and/or dispensing fee is awarded by the scheme. Subregulation (2) of Regulation 15J states:

> *"Notwithstanding anything to the contrary in these regulations -*
> *(a) a medical scheme and a managed health care organisation may not use any incentive that directly or indirectly compensates or rewards any person for ordering, providing, recommending or approving relevant health services that are medically inappropriate."*

Schemes are therefore prohibited from incentivising or rewarding compliance with an off-label medicine prescription or dispensing where this would not be medically appropriate. It is unlikely that unregistered indications would be deemed medically appropriate, in particular where there is a risk of harm to the medical scheme beneficiary (patient).

Clinical interpretations of ethical on-label/off-label prescribing in diabetes today

Off-label prescribing occurs for a variety of reasons, including advances in medicine that occur faster than the ability of manufacturers or regulatory authorities like the United States' Food and Drug Administration (FDA) to approve or re-label medications. It is suggested that this practice is justified when current scientific evidence supports the efficacy and safety of a medication for which it does not have regulatory approval and, most importantly, the practice is supported by expert consensus or practice guidelines.[5,6]

An example of this is the use of intra-ocular bevacizumab in choroidal neovascularisation, seen in so many South African diabetic patients. An article in the *South African Medical Journal* written in 2009 suggested that the off-label use of bevacizumab in age-related macular degeneration (AMD) was neither careless, imprudent nor unprofessional, due to the fact that it had been used regularly and for a long time for this indication, and its use was endorsed in protocols developed by the Ophthalmological Society of South Africa. Its preferential use was also precipitated by the on-label product being 50 times more expensive at the time. Bevacizumab remains off-label for AMD

to this day, but medical schemes now encourage its use since it costs approximately R500 per month, as compared to R7000-R11 000 for on-label competitors.[7]

Clinical scenarios of off-label prescribing dilemmas

Approximately 20-30% of patients with T2DM have renal impairment

Limited data in certain populations, such as children or pregnant women, may result in clinicians feeling pressured to prescribe off label. In children, the incidence of off-label drug use appears to be greatest in critically ill children and neonates. However, the implications for safety and risk are significant compared to prescribing in accordance with the product licence.[8] In children, adverse drug reactions are more common with off-label prescribing, partly because dosing schedules developed for adult populations have not been assessed in children.[9] In some countries, there is the additional issue that reimbursement of off-label or unlicensed prescriptions may be refused by medical insurance funders.[10]

Off-label prescribing is also common in elderly patients, often due to the poor representation of this group in pre-marketing clinical trials of therapeutic efficacy and safety of novel therapies.[11] This can present challenges in the management of patients with type 2 diabetes (T2DM), many of whom are elderly and have comorbidities.

Approximately 20-30% of patients with T2DM have renal impairment, with an estimated glomerular filtration rate (eGFR) <60ml/min/1.73m^2.[12] Of patients with type 1 diabetes (T1DM), about 20-30% will develop evidence of kidney disease.[13] Kidney dysfunction is diagnosed in more than 50% of patients aged above 75 years.[14] One can appreciate the challenge of diabetes management in elderly patients who often have impaired renal function, as well as co-existing cardiovascular disease. Given the high cardiovascular risk in patients with renal impairment, as well as their greater vulnerability to hypoglycaemia, this is a high-risk group to prescribe off label.

Patients with diabetes also have a high risk of liver disease, encompassing virtually the entire spectrum thereof. This includes abnormal liver enzymes, non-alcoholic fatty liver disease, cirrhosis, hepatocellular carcinoma and acute liver failure.[15] One can therefore appreciate the challenges facing the clinician treating these patients, particularly when deciding whether it would be appropriate to prescribe off label. Furthermore, evidence obtained solely from clinical trials might not be generalisable where off-label prescribing occurs in real-life.[16]

Prescribing dilemmas in the high-risk diabetes patient with renal or hepatic impairment

There are occasions in higher-risk patients when it is difficult to avoid prescribing newer agents that have fewer long-term data, so the product chosen remains critically important.

How to choose a GLP-1 receptor agonist

If one feels compelled to prescribe a glucagon-like peptide 1 (GLP-1) receptor agonist in a patient with known renal impairment, exenatide and liraglutide are the only two choices in South Africa. Exenatide is predominantly renally excreted, with significant reduction in clearance in end-stage renal disease.[12] Liraglutide shows reduction in the development and progression of diabetic kidney disease.[17] No dose adjustment is required for patients with mild or moderate renal impairment (creatinine clearance between 60-90 ml/min and 30-59ml/min respectively). There is no therapeutic experience in patients with severe renal impairment (creatinine clearance below 30ml/min).

How to choose an insulin?

Degludec does not require dose adjustments in renal impairment

The choice of a basal insulin is important in patients with renal or hepatic impairment. A study utilising the insulins glargine and detemir demonstrated that in patients with an eGFR <60ml/min/1.73m^2 as compared to those with eGFR >90ml/min/1.73m^2, glargine doses needed to be reduced by 29.7%, and detemir doses by

27.3%.[19] A study using insulin degludec in patients with different stages of renal failure and terminal chronic kidney disease (CKD) showed no statistically significant differences in absorption or release profiles when compared to patients with normal renal function. Therefore, degludec does not require dose adjustments in renal impairment.[20] While the package insert for glargine merely cautions that dose reductions may be needed in renal or hepatic impairment, therefore not making these conditions strictly off label, it would seem that degludec would be the more on-label choice of the two.[21]

The pharmacodynamic properties of degludec have been shown to be preserved in patients with hepatic impairment, and there were no significant differences in absorption or clearance compared with patients with normal hepatic function.[22] This suggests on-label prescribing when using degludec in patients with hepatic impairment, compared to another basal insulin where some guess at dose adjustment would have to be made.

The FDA has approved its use in patients with both T1DM and T2DM from the age of one year.[23] Comparable pharmacokinetics of degludec in elderly subjects and younger adults with T1DM have meant that its use in elderly patients is not off label, although cautions about dosing are noted in the package insert.[24]

How can SGLT-2 inhibitors be used in CKD patients?

As a clinical trial investigator, Dr Trokis has often used SGLT-2 inhibitors at eGFR levels around 30ml/min/1.73m^2 during trials, with no safety issues arising. "While conceding that the glycaemic-lowering effect would be minimal at this level of eGFR, I feel somewhat comfortable around safety issues, due to my experience in clinical trials," he says.[25,26] Clinicians who have not had the opportunity to use these agents in off-label scenarios may be less comfortable.

Insulin usage in pregnancy

With regard to bolus insulin, insulin aspart does not cross the placental barrier and can be used in pregnancy

As per recommendations by the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) 2017 guidelines,[27] long-acting insulin analogues (detemir or glargine) may be continued in women with diabetes who have established good blood glucose control before pregnancy. It should, however, be noted that only insulin detemir is currently approved by the FDA for use in pregnancy (category B).[28,29] With regard to bolus insulin, insulin aspart does not cross the placental barrier and can be used in pregnancy.

Intensified blood glucose control and monitoring of pregnant women with T1DM, T2DM or gestational diabetes are recommended throughout pregnancy and when contemplating pregnancy. Both hypoglycaemia and hyperglycaemia, which can occur in inadequately controlled diabetes therapy, may increase the risk of malformations and death *in utero*. Insulin requirements usually start in the first trimester and increase during the second and third trimesters. After delivery, insulin requirements rapidly return to pre-pregnancy levels. There are no restrictions on treatment with insulin aspart during breastfeeding as it does not cross into breast milk.[30]

How to find the balance between on-label and off-label prescribing?

As clinicians we may often not offer the patient the best option, even between two different on-label medications, due to cost differences

Many clinicians adopt a pragmatic approach by trying to prescribe on label whenever possible, and only prescribing off label when this is supported by good clinical data that are ethically justifiable and withstand medicolegal scrutiny.

One may find it difficult to justify the use of NPH insulin as the sole basal insulin in children with T1DM, when there are data to show that detemir and degludec are associated with a significantly lower risk of hypoglycaemia in this population.[31,32] Consequently, one may view detemir (2 years and older) and degludec (1 year and older) as the more on-label choice in paediatric patients.

A final point about on-label prescribing is that as clinicians we may often not offer the patient the best option, even between two different on-label medications, due to cost differences. This is particularly topical in view of some of the recent cardiovascular outcomes trials. If the best option offers the patient significantly better outcomes, such as lower hypoglycaemia risk or reduction in cardiovascular risk, and we do not inform the patient of the different options and potential consequences, this may amount to negligence.

Most importantly, when one is not prescribing on label, it is imperative that the patient be fully informed to enable shared decision-making and ensure proper informed consent that meets ethical and medicolegal requirements.

KEY LEARNINGS

- In South Africa, off-label usage of medicines falls under the Medicines Act of 1965, the CPA 68 of 2008 and the law of delict
- The medical schemes legislative framework states that schemes should not fund a treatment unless it is registered for a particular indication; this rule is not always consistently adhered to
- For the management of hepatic, renal, pregnancy, paediatric and elderly populations, the choice of drug is critical; on-label prescribing decisions should be necessary in the management of these populations.

References

Click on reference to access the scientific article

1. Medicines and Related Substances Act 101 of 1965.
2. General Regulations made in terms of the Medicines and Related Substances Act, 1965 (Act No 101 of 1965, as amended). Published in *Government Gazette*, 10 April 2003.
3. Consumer Protection Act 68 of 2008 (CPA).
4. Medical Schemes Act, 131 of 1998 Regulations.
5. Fitzgerald AS, O'Malley PG. Staying on track when prescribing off-label. *Am Fam Physician* 2014; **89**(1): 4-5.
6. Furey K, Wilkens K. Prescribing "off-label": What should a physician disclose? *AMA J Ethics* 2016; **18**(6): 587-593.
7. Jansen R-M, Gouws C. Clinical, legal and ethical implications of the intra-ocular (off-label) use of bevacizumab (Avastin) – A South African perspective. *S Afr Med J* 2009; **99**(6): 446-449.
8. Choonara I. Unlicensed and off-label drug use in children: Implications for safety. *Expert Opin Drug Safety* 2004; **3**(2): 81-83.
9. Hill P. Off licence and off label prescribing in children: litigation fears for physicians. *Arch Dis Child* 2005; **90**(suppl 1): i17-i18.
10. Bucheler R, Schwab M, Morike K, *et al*. Off label prescribing to children in primary care in Germany: retrospective cohort study. *BMJ* 2002; **324**(7349): 1311-1312.
11. Jackson SHD, Jansen PAF, Mangoni AA. Off-label prescribing in older adults. *Drug Aging* 2012; **29**(6): 427-434.
12. Betonico CCR, Titan SMO, Correa-Gianella MLC, *et al*. Management of diabetes mellitus in individuals with chronic kidney disease: therapeutic perspectives and glycaemic control. *Clinics (Sao Paulo)* 2016; **71**(1): 47-53.
13. American Diabetes Association. Nephropathy in diabetes. *Diabetes Care* 2004; **27**(suppl 1): S79-S83.
14. Russo GT, De Cosmo S, Viazzi F, *et al*. Diabetic kidney disease in the elderly: Prevalence and clinical correlates. *BMC Geriatr* 2018; **18**(1): 38-48.
15. Tolman KG, Fonseca V, Dalpiaz A, *et al*. Spectrum of liver disease in type 2 diabetes and management of patients

with diabetes and liver disease. *Diabetes Care* 2007; **30**(3): 734-743.
16. Osborne V, Layton D, Shakir SA. Implications of off-label use: An example from the final results of an observational cohort study on Intrinsa (Testosterone patch). *Post Reprod Health* 2014; **20**(2): 48-54.
17. Mann JF, Orsyed DD, Brown-Frandsen K, *et al*. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med* 2017; **377**(9): 839-848.
18. Victoza package insert. [Accessed on 02/06/2020]
19. Kulozik F, Hasslacher C. Insulin requirements in patients with diabetes and declining kidney function: Differences between insulin analogues and human insulin? *Ther Adv Endocrinol Metab* 2013; **4**(4): 113-121.
20. Kiss I, Arold G, Roepstorff C, *et al*. Insulin degludec: Pharmacokinetics in patients with renal impairment. *Clin Pharmacokinet* 2014; **53**(2): 175-183.
21. accessdata.fda.gov/drugsatfda_docs/label/2009/021081s034lbl.pdf [Accessed on 02/06/2020]
22. Holmes G, Galitz L, Hu P, *et al*. Pharmacokinetics of insulin aspart in obesity, renal impairment, or hepatic impairment. *Br J Clin Pharmacol* 2005; **60**(5): 469-476.
23. AJMC staff. FDA approves pediatric use of Tresiba. *AJMC*, 21 December 2016.
24. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/203314lbl.pdf [Accessed on 03/06/2020]
25. https://docs.boehringer-ingelheim.com/Prescribing%20Information/Pls/Jardiance/jardiance.pdf [Accessed on 03/06/2020]
26. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/202293s012lbl.pdf [Accessed on 03/06/2020]
27. The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA guidelines for the management of type 2 diabetes mellitus. *JEMDSA* 2017; **22**(1) (suppl 1): S1-S196.
28. Mathiesen E, Hod M, Ivanisevic M, *et al*. Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes. *Diabetes Care* 2012; **35**(10): 2012-2017.
29. Pollex EK, Feig DS, Lubetsky A, *et al*. Insulin glargine safety in pregnancy: A transplacental transfer study. *Diabetes Care* 2010; **33**(1): 29-33.
30. NovoRapid R package insert 2016
31. Thalange N, Bereket A, Larsen J, *et al*. Insulin analogues in children with type 1 diabetes: a 52-week randomized clinical trial. *Diabet Med* 2013; **30**: 216-225.
32. Lane W, Bailey TS, Gerety G, *et al*. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 1 diabetes: The SWITCH 1 randomized clinical trial. *JAMA* 2017; **318**(1): 33-44.

Published by

© 2020 deNovo Medica

Reg: 2012/216456/07

70 Arlington Street, Everglen, Cape Town, 7550

Tel: (021) 976 0485 | info@denovomedica.com