Misleading comparative advertising of drugs

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On 20 February 2018 the Supreme Court ruled on an interesting case relating to comparative advertising.

Use of vitamin K antagonists and NOAKs

The anticoagulant drug group comprises two sub-groups:

- vitamin K antagonists; and
- non-vitamin K-based oral anticoagulants (NOAKs).

The case at hand involved two NOAKs:

- Pradaxa, which was authorised in 2008 and contains the active ingredient dabigatran; and
- Lixiana, which was authorised in 2015 and contains the active ingredient edoxaban.

Uses

The vitamin K antagonist warfarin has traditionally been used as the standard treatment for strokes and systemic embolisms, venous thrombosis and pulmonary embolisms. Due to several disadvantages because of the mechanism of action associated with vitamin K antagonists (eg, repeated clotting, the need for individual dose calculations, close monitoring and long-lasting effects which could lead to complications during surgery), NOAKs were developed as a therapeutic alternative. NOAKs do not require regular coagulation control or ongoing dose adjustments; they also reduce the risk of surgery. Notably, Pradaxa must be taken twice daily, while Lixiana must be taken only once daily.

For prophylaxis of stroke and systemic embolism, Pradaxa and Lixiana are recommended in specific dosages or for long-term use. This is true of other NOAKs. Further, the initiation phase and guidelines for use are the same for all NOAKs. However, other NOAKs may recommend a dosage increase after a certain period.

Risk factors

If certain risk factors are present (eg, moderate or severely impaired renal function or lower body weight in the case of Lixiana) a dose reduction is recommended. The patient's age also has significant influence, as does their body weight (specifically, anyone under 50kg will require close clinical monitoring).

Further, patients with severe renal impairment should not take Pradaxa, whereas patients with terminal renal impairment should not take Lixiana. Before prescribing either drug, the patient's kidney function must be tested. The same is true for liver function, as severe restrictions are a contraindication. If elderly patients are taking Pradaxa, their renal function must be assessed annually. Any elderly patient taking Lixiana that has a change in renal function must stop taking the

drug.

Compared with stable warfarin patients, patients on Lixiana often experience decreased efficacy and an increase in creatinine clearance. However, this was not considered a contraindication at authorisation.

The switch from vitamin K antagonists to NOAKs is comparable. However, switching from Lixiana to a vitamin K antagonist is harder than switching from Pradaxa. The risk of (potentially fatal) bleeding increases in both cases. When switching between medicines, the anticoagulant effect cannot be reliably controlled in either case, although tests on the use of Pradaxa have provided additional information in this regard. Unlike Pradaxa, Lixiana has no antidote that mitigates clotting inhibition following life-threatening bleeding, which affects a small percentage of patients. If the bleeding cannot be stopped by delayed ingestion of Lixiana, a traditional prothrombin complex concentrate must be administered 30 minutes after the end of the infusion. In relation to Pradaxa, a specific antidote is available, which immediately mitigates the anticoagulant effect. No studies directly compare Lixiana and other NOAKs. In clinical trials, Lixiana and other NOAKS have been compared only with warfarin.

Facts

The claimant marketed the medicinal product Pradaxa, while the defendant marketed the medicinal product Lixiana.

The defendant published a full-page ad in a medical journal with the headline "New choices in NOAKs" and the tagline "Once daily LIXIANA. Simple. Unequivocal. Safer." The ad also contained the following (hard-to-read) fine print:

> **Once a day for all approved indications (see ref 1). Standard dosage edoxaban 60 mg once daily for all approved indications (for VTE [venous thromboembolism] after initial administration of a parenteral anticoagulant for at least 5 days) with dose reduction to 30 mg (reduced renal function [CrCl 15-20 ml/min], low body weight < 60 kg, P-gp-inhibitors [Dronedaron, Erythromycin, Ketoconazol, Cyclosporin])*
>
> ***in the VTE- and nvVHF admission studies*
>
> **compared to warfarin in the primary safety end point.*
>
> *VTE: clinically relevant bleeding (severe bleeding or clinically relevant non-severe bleeding)*
>
> *nvVHF: severe bleeding (see ref. 2-5)*
>
> *1. SmPC LIXIANA, as of August 2016*
>
> *2. Giugliano ARP et al NEJM 2013, 369 (22), 2093-2104*
>
> *3. The Hokusai-VTE Investigations MEJM 2013, 369 (15), 1406-1415*
>
> *4. Ruff CT et al, Lancet 2014, 383(9921); 955-962*
>
> *5. BlackSA et al, Thromb haemost 2015, 114(3).*

In support of its claim for injunctive relief, the claimant requested that the defendant cease and desist from providing misleading or, alternatively, insufficiently substantiated statements in its ads for Lixiana. The claimant contended that the defendant's ad suggested that Lixiana had significant advantages over other NOAKs; however, this was misleading and potentially untrue.

First-instance and appeal decisions

First-instance ruling

The first-instance court(1) issued the requested injunction, ruling as follows:

- The eye-catching comparison within the ad obviously referred to other NOAKs.
- There was no indication that the ad was referring to vitamin K antagonists.
- The doctors addressed by the ad will not understand the terms 'simple' and 'unequivocal' in relation to the administration of the drug, but rather as a claim to highlight the additional benefits that Lixiana offered (eg, easy-to-read dosage information and clearer application specifications).
- The certification procedure did not show that Lixiana had better compliance rates compared with other NOAKs.
- The fine print did not clearly refute the impression made by the eye-catching ad.
- Contrary to the Association of the Austrian Pharmaceutical Industry's code of conduct, the term 'safer' was not clearly defined.(2) In particular, the ad contained no information as to which primary and secondary safety endpoints were the subject of the cited studies and which results were produced by said studies.

Based on the above, the first-instance court found that the defendant had failed to prove its claims and that the ad was misleading. Thus, the court ruled that the ad violated the principles of drug advertising law.

Court of appeal ruling

The court of appeal(3) dismissed the claim, stating that the subject of the decision exceeded €30,000 in value and that an ordinary appeal was inadmissible.

According to the court, the relevant public understood the term 'simple' in this context to mean that the drug had a particularly simple application (ie, that it need be taken only once daily). This understanding could easily be parsed from the ad and was further indicated by an asterisk, which also pointed to the fact that intake was required only once daily.

Further, one of the footnotes mentioned that a single daily dose was, in principle, required for all approved indications of Lixiana, but that in the case of venous thromboembolism, the initial use of a parenteral anticoagulant would be required. The court found that an average doctor (the intended audience) would understand this reference. Further, not all distinctions must be placed in an ad. According to the court, the ad could be limited to normal cases in which only one daily dose was required and that this could be considered simple (compared with the twice daily dose required with Pradaxa or the elaborate fine-tuning required with vitamin K antagonists).

The court maintained that the use of the term 'simple' neither represented a unique selling point, nor compared the drug with competing products (in particular, the plaintiff's product). The fact that the footnotes were provided in a smaller font was not detrimental because they provided only supplementary information. The overall context of the ad was apparent from the eye-catching text: "Once daily LIXIANA". The court of appeal thus found that the term 'simple' was neither untrue nor misleading due to the easily recognisable overall context and supplementary information provided.

On consideration, the court of appeal also found that the term 'unequivocal' referred only to the method of application. In short, as with the term 'simple', an average doctor would understand that 'unequivocal' referred only to the application method of the advertised drug. The court found that since the term 'unequivocal' in connection with the application of a medicinal product was even more vague than the term 'simple', it required further explanation. This explanation was provided (ie, that the drug should be taken only once daily). Thus, there was no misdirection.

In conclusion, the court of appeal ruled that the average doctor would understand that the term 'safer' was comparing Lixiana with other medicines. The product with which Lixiana's safety was compared was apparent due to the asterisk, which clearly stated that it was being compared with warfarin. Thus, the applicant's allegations that Lixiana was not safer than other NOAKs (in particular, Pradaxa) need not be further discussed. The only matter for the court to consider was whether Lixiana was safer than warfarin with respect to the referenced parameters. The court found that the defendant had shown this to be true and thus the ad was not misleading.

Supreme Court decision

The Supreme Court permitted the plaintiff's extraordinary appeal and restored the first-instance court's decision.(4)

Legal background

The EU Directive on the Community Code relating to Medicinal Products for Human Use (2001/83/EC) harmonised the field of advertising for medicinal products. The directive was implemented in Austria by the Medicines Act.

Article 87(3) of the EU directive both requires objectivity and bans the misleading advertising of medicinal products. Drug ads must therefore:

- promote the appropriate use of a medicinal product by presenting its characteristics objectively and without exaggeration; and
- not be misleading.

Both the objectivity requirement and the ban on misleading advertising are implemented by Sections 6 and 50a(3) of the Medicines Act. The ban on misleading advertising in this regard has a specific character of fairness – as a manifestation of the general ban on misleading advertising – since this standard serves similar regulatory purposes as the Unfair Competition Act.

The Medicines Act and the Unfair Competition Act are applied in conjunction. Section 6(3) of the Medicines Act lists the cases in which misleading advertising may exist, but does not provide a general ban on providing misleading information. This is instead set out in Section 2 of the Unfair Competition Act. Section 6 of the Medicines Act does not provide for injunctive relief. As long as appropriate information about business conditions – in particular, the nature of goods – is provided for purposes of competition, an injunction may be filed under Section 2 of the Unfair Competition Act.

Section 6(2) of the Medicines Act prohibits parties from providing information about medicinal products or active substances which is untrue or misleading. Further, Section 6(3) provides that a party will be guilty of providing misleading information if:

- it claims that a medicinal product is effective or contains properties which have not been substantiated by sufficient scientific testing or practical experience;
- it guarantees that the product will provide the desired results or that no adverse effects will occur after intended or prolonged use; or
- the product's name or presentation may create confusion.

Section 50a(3) of the Medicines Act provides that ads for medicinal products must objectively represent the product's properties and must not exaggerate or contain statements or pictorial representations which:

- attribute an effect that exceeds the product's actual effect;
- falsely imply that success can be guaranteed; or
- are incompatible with the product's labelling, listed characteristics or package leaflet.

Under Section 55 of the Medicines Act, any medicinal product ads which are directed at professionals must:

- contain accurate, up-to-date and verifiable information; and
- provide enough information to ensure that the recipient understands the therapeutic value of the medicine.

Further, medicinal product ads must be sufficiently substantiated based on the current state of scientific knowledge. In general, this means that statements of effectiveness must be evidence-based and therefore measurable.(5)

Final ruling

The court ultimately found that the challenged announcement was 'comparative advertising' within

the meaning set out in Section 2a(1) of the Unfair Competition Act, as it directly and indirectly identified a competitor and a competitor's goods and services. According to the court, comparisons of this nature are permissible only if they do not violate Section 2 of the Unfair Competition Act. A business practice is considered misleading if, among other things, it contains inaccurate information or otherwise deceives a market player as to the essential characteristics of the relevant product or the essential characteristics of tests or exams to which the product has been subjected.

In the case of misleading evidence, it is settled case law that the following must be assessed:

- how an informed and reasonable customer, paying due attention to the acquisition of the advertised product, understands the statement;
- whether their understanding is correct; and
- whether this understanding is likely to induce the consumer into making a business decision which they would otherwise not have made.

The decisive issue is whether those addressed in the ad understand its context. In essence, in the case of health-related advertising, it is paramount that the advertiser ensure that the information provided is correct and unambiguous, as misleading health claims can result in considerable danger to individuals and the population at large. According to the court, a strict standard must be applied when assessing medicinal product ads, even if the ads are aimed at professionals.

The court went on to state that the meaning behind ads depends on their overall context and the impression that they convey. Notably, the overall impression of an ad is not synonymous with the overall context, as particularly eye-catching parts (ie, individually highlighted details) of an ad may decisively shape the viewers' overall impression. These individual parts must not be misleading.

The overall impression of an ad must be assessed according to objective standards – in particular, how average viewers (who have paid appropriate attention) perceive the ad.

If there is any ambiguity, the advertiser must also provide information regarding unfavourable aspects (eg, side effects) of the medicinal product in a way which ensures that the public understands them.

Further, intimating to certain information can prevent a deception in an ambiguous ad only if the hint is obvious to the targeted public. As a rule, all information on the ad must be equally conspicuous. However, conspicuousness is not solely based on comparable font sizes. Rather, an average and sensible viewer must understand the message.

Based on these principles, the Supreme Court ruled that the comparison between the drugs in question was prohibited.

The target group of physicians (ie, those prescribing anticoagulants to their patients) understood the striking headline "New choices in NOAKs" to mean that a new NOAK had come into the market. Therefore, the average viewer believed, at first glance, that the ad was comparing drugs within the NOAK group. Only once they read the explanatory footnote did they understand that this assumption was incorrect. However, the court ruled that this note was insufficient to elucidate the error, as the footnote text was considerably smaller – to the point of being almost illegible.

The court of appeal had originally found that the terms 'simple' and 'unequivocal' which were listed below the dosage (ie, "Once daily LIXIANA") provided sufficient detail. However, the Supreme Court held that this view was unconvincing. According to the Supreme Court, the average viewer would not automatically associate the vague term 'simple' with the dosage of a drug, but rather as a further promotion of the additional benefits provided by the drug. This latter interpretation was more obvious because the asterisks next to these descriptive words pointed to information that would be superfluous if only dosing were concerned. As such, the Supreme Court held that the terms 'simple' and 'unique' were misleading in the given context.

Finally, as previously stated, the average reader understood the term 'safer' to apply only to drugs within the NOAK group. Therefore, in order to promote Lixiana as safer, the defendant would have had to certify that the drug was actually safer than other NOAKs. This was not proven as, according

to the underlying facts, unlike the plaintiff's product, Lixiana had no antidote in the case of life-threatening bleeding. The Supreme Court thus held that the term 'safer' was misleading.

Comment

The Supreme Court's decision follows the letter of the law and perfectly summarises the legal structure regarding comparative and drug advertising in Austria. It is settled case law that a strict standard must be applied in respect of medicinal product ads which address professionals. In this regard, the defendant was probably surprised by the court of appeal's decision.

For further information on this topic please contact Rainer Herzig at Preslmayr Attorneys at Law by telephone (+43 1 533 16 95) or email (herzig@preslmayr.at). The Preslmayr Attorneys at Law website can be accessed at www.preslmayr.at.

Endnotes

(1) Commercial Court Vienna 19 Cg 7/17a.

(2) The Association of the Austrian Pharmaceutical Industry's code can be found at pharmig.at/uploads/vhc_2015_englisch_web_14705_DE.pdf (English version).

(3) Higher Regional Court Vienna 2 R 57/17t.

(4) 4 Ob 136/17d.

(5) *Ciresa*, Arzneimittelwerberecht 2014, margin note 116.