

# Misleading score-lines on tablets: facilitated intake or fractional dosing?

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## Summary

*Question under study/principles:* Scored tablets are often split to facilitate swallowing or to fractionate the dose. In the latter case, the fragments of the tablet should comply with the content or mass uniformity requirements of the European Pharmacopoeia. For health professionals the splitting information is expected to be in the Summary of Product Characteristics (SPCs), the package leaflets (PLs) or Hospital Drug Formularies. We investigated the accuracy of splitting statements in these three sources of drug information.

*Methods:* We selected the tablets mentioned as “scored” in the Swiss Compendium Online and in the Drug Formulary of Basel University Hospital, and screened the corresponding SPCs and PLs for information on divisibility and fractional dosing. Missing information was obtained from the drug marketing licence holder.

*Results:* The Swiss Compendium Online contained 698 different scored tablets whose SPCs

mentioned fractional dosing for 43.8% and explicitly forbade it for 2.7%. The Hospital Drug Formulary indexed 188 items as scored tablets. The corresponding SPCs mentioned fractional dosing for 107 (59.4%) and a sentence forbidding it for 5 (2.8%). The manufacturers’ answers permitted fractional dosing for 49 (27.2%) of the remaining tablets and forbade it for 19 (10.5%). Lack of dosage uniformity or presence of “historic decorative” score-lines were the reasons given.

*Conclusions:* For the majority of scored tablets the official sources of drug information contained no explicit indication on fractional dosing. Improvement of splitting information is necessary to avoid potential medication errors.

*Key words:* tablet splitting; tablet fragmenting; score-line; scored tablets; fractional dosing; drug safety

## Introduction

Approximately a quarter of the tablets are split by patients in ambulatory settings [1, 2] and about 12% of the drugs prescribed at hospital discharge are in split form [3]. The pros and cons of splitting tablets are well known: dose flexibility (e.g., for paediatric or geriatric patients, in the case of drug–drug interactions or genetic variants), ease of swallowing, off-label use and cost savings on the one hand [4], difficulty of breaking, unequal parts, loss of mass [5] and hazardous pharmacological effects on the other. The cost saving potential of splitting tablets was emphasised and recommended [6], with the result that tablets with score-lines and higher strengths were prescribed by physicians, recommended by pharmacists [2] and cut by patients. A survey conducted in Germany showed that 67% of patients split their tablets, in 90% of cases because the prescription required it, in 3% of cases to ease swallowing and in 2% of cases to reduce costs [7]. Since 2002, however, fragments of tablets may represent a dosage form only if the

subdivided parts of the tablet comply with the content or mass uniformity requirements of the European Pharmacopoeia [8].

In 2004, the Swiss regulatory authority Swissmedic recognised the threat of splitting tablets and published a bulletin drawing attention to new warnings added to the Summary of Product Characteristics (SPCs) and to the product information leaflets (PLs) [9]. The sentences: “*The tablets must not be split*” («*Die Tabletten sollen nicht geteilt werden*») or “*The tablets are not suitable for the dosing of the half dose through splitting*” («*Die Tabletten sind nicht zur Dosierung der halben Dosis durch Teilen geeignet*»), are intended to irrevocably forbid splitting of the tablets concerned. The function of score-lines, i.e., an aid to cutting, breaking, fragmenting, splitting, or subdividing tablets into smaller segments, should also be either to facilitate intake (i.e., swallow all segments) or fractionate the dose (i.e., swallow one segment). Simultaneously, the European Medicines Agency evaluated splitting of

tablets into segments [10]. In view of the many exceptions rendering subdivision of a tablet impossible (e.g., enteric coated tablets, layered tablets, modified release dosage forms), the conclusion was that, “*The manufacturer may consider providing information that would guide the dispensing pharmacist on the issues surrounding cutting tablets into smaller segments.*”

Health professionals expect SPCs to contain exact information on the possibility of splitting a tablet (i.e., facilitated intake or fractional dosing). These are the legal basis in Switzerland for the physicians who prescribe the medicines and for the pharmacists who dispense them. Since there is at present no reliable and official information

available, various hospital drug formularies contain additional information on fragmenting or powdering of tablets.

In this study we selected the tablets mentioned as “scored” in the Swiss Compendium of Medicines Online and in the Drug Formulary of Basel University Hospital, and screened the corresponding SPCs and PLs for information on divisibility and fractional dosing. We postulated that the phrase: “*The tablet can be split for fractional dosing*”, is marginally mentioned in the Swiss Compendium and that the term “scored tablet” is not sufficiently discriminatory in Hospital Drug Formularies.

## Methods

The Swiss Compendium Online [11] was searched for SPCs and PLs (i.e., monographs) containing the terms “divisible” («teilbar») and/or “score-line” («Bruchrille»). The SPCs containing the negation (“not divisible” [«nicht teilbar»] and/or “without score-line” [«ohne Bruchrille»]) were not included. Each monograph could describe one or more dosage strengths of the same tablet. The listing of the oral solid dosage forms embodied in the Drug Formulary of Basel University Hospital [12] was searched for tablets indexed as “score-line YES” («Bruchrille JA»). Corresponding SPCs were searched for statements about divisibility.

### Assessment of divisibility

The splitting of a tablet was classified as *not allowed* if the SPC contained the sentences “The tablets must not be split” («Die Tabletten sollen nicht geteilt werden») or

“The tablets are not suitable for splitting” («Die Tabletten sind nicht geeignet, geteilt zu werden»), if it was stated that the tablet must not be broken or if there was a recommendation to take the tablet whole or undivided. The fractional dosing of a tablet was classified as *allowed* if a fraction of a single dose was a recommended dosage in the SPCs or PLs (e.g., ¼–½ tablet). When the SPCs of the scored tablets in the Hospital Drug Formulary did not contain precise splitting information, additional information was requested from marketing licence holders. The results are reported as sums or percentages.

## Results

### a) Swiss Compendium of Medicines 2008

Of the 3601 monographs published in the Swiss Compendium Online by 23 October 2008, a total of 395 contained the searched terms covering 698 different tablet strengths. Fractional dosing was mentioned in 256 SPCs and concerned 306 (43.8%) different scored tablets. The crude information “divisible” was primarily found in the section Pharmaceutical Form and Quantitative Contents («Galenische Form und Wirkstoffmenge pro Einheit») at the beginning of the SPCs. Special dosage recommendations involving splitting of a tablet or additional sentences on divisibility were found in the sections Dosage/Method of Administration («Dosierung/Anwendung») or Pharmaceutical Particulars («Sonstige Hinweise») at the end of the monographs. In 77 monographs the SPC detailed several strengths and indicated fractional dosing for only one tablet strength. An explicit word or sentence forbidding fractional dosing was found for 19 different scored tablets (2.7%), which indicates the presence of a decorative score-line on the surface of the tablet (table 1).

### b) Drug Formulary of Basel University Hospital

The listing of the oral solid dosage forms dated 8 February 2008 contained a total of 454 items, i.e., brand names amended with a galenic form (e.g., Akineton® Retarddrag., Akineton® Tabl.) without further breakdown into dosage strengths. A total of 188 oral solid forms were indexed as scored tablets, i.e., with a “YES” («JA») in the column “SCORE-LINE” («BRUCHRILLE»). We excluded a total of eight (4.3%) products, five since they had no SPC published in the Swiss Compendium 2008 (Colchicine, Cynomel, Dapson FatoI®, Isozid®, Pyrazinamid Lederle®), two because they were mentioned twice (Leponex®, Sotalex®) and one that stated “without score-line” («ohne Bruchrille») in the SPC (Zantic®). Fractional dosing was allowed for 107 of the indexed scored tablets (59.4%, fig. 1) according to the presence of fragments of the dosage form as a recommended dosing in the SPCs. Nevertheless, use of “score-line YES” in the Hospital Drug Formulary was misleading for two products. All dosage strengths of Triatec® (1.25 mg, 2.5 mg, 5 mg, 10 mg) and Lopirin® (12.5 mg, 25 mg, 50 mg) are scored, but 1.25 mg Triatec® has a decorative score-

**Table 1**

Tablets with decorative score-lines according to manufacturers' answers (\*) and to the sentences (in German) forbidding a fractional dosing in the SPCs, with wording grouped in categories (A-D).

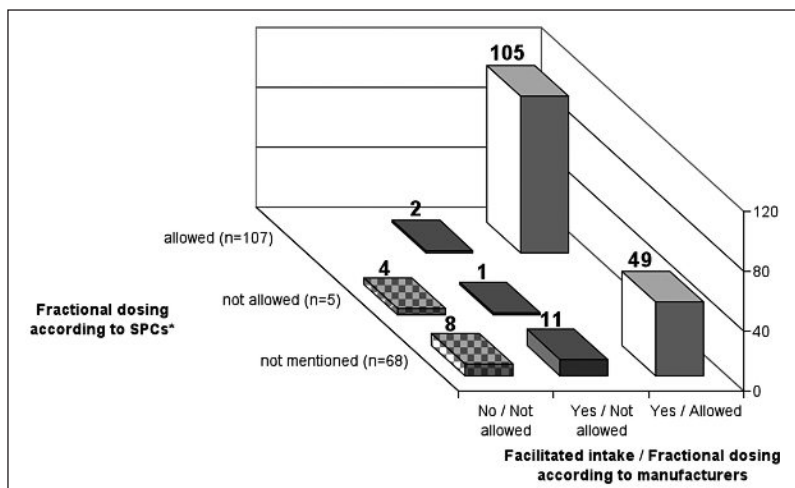
Titel of the SPC [active ingredient]	Cate- gory	Sentence in the SPC
Bexin® [dextromethorphan]	A, B	Die Filmtabletten zu 25 mg sind nicht geeignet zur Dosierung von 12,5 mg durch Teilen der Filmtabletten, obwohl sie eine Bruchrille haben. [The 25 mg film tablets are unsuitable for dosage of 12.5 mg by splitting the film tablets, although they are scored.]
Cafergot® [ergotamine tartrate + caffeine]	*	–
Cibadrex® [benazepril + hydrochlorothiazide]	B	Die Filmtablette zu 5/6,25 mg ist nicht geeignet zur Dosierung der halben Dosis durch Teilen. [The 5/6.25 film tablet is unsuitable for dosing of half dose by splitting.]
Clamoxyl® RC [amoxicillin]	*	–
Co-Acepril® [enalapril maleate + hydrochlorothiazide]	A	Die Tabletten sind nicht zum Teilen geeignet, obwohl sie eine Bruchrille haben. [The tablets are unsuitable for splitting although they are scored.]
Dafalgan® [paracetamol]	B	Falls nötig kann die Tablette in zwei Teile gebrochen werden (Bruchrille), um diese nacheinander zu schlucken. Die Teilung an der Bruchrille ist jedoch nicht zur Halbierung der Dosis (500 mg) geeignet. [If necessary, the tablets may be broken in half (score-line), for successive swallowing of the halves. However, splitting at the score-line is unsuitable for halving of the dose (500 mg).]
Dancor® 10/20 [nicorandil]	A	Tabletten zu 20 mg (mit Bruchrille, nicht teilbar). [20 mg tablets (scored, not splittable).]
Dilzem® [diltiazem]	*	Die Tabletten sollten nicht geteilt werden. [The tablets are not to be split.]
Dilzem RR® [diltiazem]	*	Die Tabletten sollten nicht geteilt werden. [The tablets are not to be split.]
Elpradil® [enalapril maleate]	A, B	Die Tabletten zu 20 mg sind nicht geeignet zur Dosierung von 10 mg durch Teilen der Tabletten, obwohl sie eine Bruchrille haben. [The 20 mg tablets are unsuitable for dosage of 10 mg by splitting, although they are scored.]
Enalapril HCT Actavis® 20/12,5 mg [enalapril maleate + hydrochlorothiazide]	A	Die Tabletten sind nicht zum Teilen geeignet, obwohl sie eine Bruchrille haben. [The tablets are unsuitable for splitting, although they are scored.]
Enalapril HCT Axapharm® [enalapril maleate + hydrochlorothiazide]	A	Die Tabletten sind nicht zum Teilen geeignet, obwohl sie eine Bruchrille haben. [The tablets are unsuitable for splitting, although they are scored.]
Enalapril Helvepharm [enalapril maleate]	A, B	Die Tabletten zu 20 mg sind nicht geeignet zur Dosierung von 10 mg durch Teilen der Tabletten, obwohl sie eine Bruchrille haben. [The 20 mg tablets are unsuitable for dosage of 10 mg by splitting, although they are scored.]
Enalapril-Teva® [enalapril maleate]	A, B	Die Tabletten zu 20 mg sind nicht geeignet zur Dosierung von 10 mg durch Teilen der Tabletten, obwohl sie eine Bruchrille haben. [The 20 mg tablets are unsuitable for dosage of 10 mg by splitting, although they are scored.]
Lanvis® [tioguanine]	*	Die Tabletten sollten nicht geteilt oder zerstoßen werden. [Do not split or powder the tablets.]
Lisinopril HCT Actavis® 10/12,5 mg and 20/12,5 mg [lisinopril + hydrochlorothiazide]	A, B	Die Lisinopril HCT Actavis 20/12,5-Tabletten sind nicht geeignet zur Dosierung von 10/12,5 mg Lisinopril/Hydrochlorothiazid durch Teilen der Tabletten, obwohl sie eine Bruchrille haben. [Lisinopril HCT Actavis 20/12.5 tablets are unsuitable for dosage of 10/12.5 mg lisinopril/hydrochlorothiazide by splitting, although they are scored.]
Lopirin® 25 mg [captopril]	*	(mit Bruchrille) [(with score-line)]
Lopirin® 50 mg [captopril]	*	(mit Bruchrille) [(with score-line)]
Lopresor 50® [metoprolol tartrate]	*	–
Madopar LIQ® [levodopa + benserazide]	*	(wasserlösliche Tabletten, teilbar) [(water soluble tablets, splittable)]
Medrol® [methylprednisolone]	*	Die Tabletten sollen nicht geteilt werden, da sie dafür nicht geeignet sind. [The tablets are not to be split, they are unsuitable for splitting.]

Titel of the SPC [active ingredient]	Cate- gory	Sentence in the SPC
Nocutil® [desmopressin]	C	Die Bruchrille in den Tabletten ermöglicht eine Teilung der Tabletten, um sie leichter schlucken zu können. Die Teilung der Tabletten gewährleistet aber nicht eine exakte Halbierung der Dosis. [The score-line on the tablets allows them to be divided to ease swallowing. However, splitting of the tablets does not ensure two equal halved doses.]
Norvasc® [amlodipine besilate]	*	–
Noveril 240 TR® [dibenzepin]	*	(teilbar) [(splittable)]
Quiril® 5/10/20 [quinapril]	A	Quiril 10: Filmtabletten (mit Bruchrille, aber nicht zum Teilen geeignet) [Quiril 10: film tablets (scored but unsuitable for splitting)]
Quiril® 5/10/20 [quinapril]	A, D	Quiril 20: Filmtabletten (mit Bruchrille, aber nicht zum Teilen geeignet, Zierrille) [Quiril 20: film tablets (scored but unsuitable for splitting, decorative score-line)]
Ramipril Winthrop® [ramipril]	D	Die Tabletten 1,25 mg haben eine Zierbruchrille. Sie sind nicht indiziert, um in zwei Hälften geteilt zu sein. [The 1.25 mg tablets have a decorative score-line. Splitting into two halves is not indicated.]
Ranimed® 75 antacid/150/300 [ranitidine]	D	Bei Ranimed 75 antacid handelt es sich um eine Zierbruchrille, die Filmtabletten sind nicht teilbar. [Ranimed 75 antacid has a decorative score-line; the tablets are not splittable.]
Tegretol® [carbamazepine]	*	–
Torasemid Sandoz® 5/10 [torasemide]	A	Obwohl die Tabletten Torasemid Sandoz 10 eine Bruchrille aufweisen, sollten sie nicht geteilt werden. [Although Torasemid Sandoz 10 tablets are scored, they should not be split.]
Triatec® [ramipril]	D	Die Tabletten Triatec 1,25 mg haben eine Zierbruchrille. Sie sind nicht indiziert, um in zwei Hälften geteilt zu sein. [The 1.25 mg Triatec tablets have a decorative score-line. Splitting into two halves is not indicated.]
Ulcidin® [ranitidine]	A, B	Die Tabletten zu 300 mg sind nicht geeignet zur Dosierung von 150 mg durch Teilen der Tabletten, obwohl sie eine Bruchrille haben. Für diese Dosierung wird die Tablette zu 150 mg angeboten. [The 300 mg tablets are unsuitable for dosage of 150 mg by splitting, although they are scored. For this dose 150 mg tablets are available.]
Viramune® [nevirapine]	*	–
Zyloric® [allopurinol]	*	Die Tabletten sind nicht geeignet, geteilt zu werden. [The tablets are not suitable for splitting.]

Categories of sentences forbidding the splitting: A: “the tablets are not suitable for splitting although they are scored”, B: “the tablets are not suitable for the dosing of the half dose through splitting”, C: “splitting the tablets doesn’t ensure two equal halved doses”, D: “with decorative score-line”.

Figure 1

The 180 indexed scored tablets (i.e., «Bruchrille JA») in the Hospital Drug Formulary were classified according to the divisibility mentioned in the SPCs\*, i.e., if fractional dosing was allowed, not allowed or not mentioned. Missing information was obtained from manufacturers and concerned splitting for facilitated intake (Yes or No) or for fractional dosing (Allowed or Not allowed).



\* SPCs: Summary of Product Characteristics published in the Swiss Compendium of Medicines.

line, and ½ tablet Lopirin® is recommended for the 12.5 mg strength only. The manufacturer confirmed that the splitting of 25 mg and 50 mg Lopirin® to obtain halved doses could not be recommended because of missing data on the content uniformity of fragmented tablets. Thus, general splitting of Triatec® and Lopirin® according to “score-line YES” is forbidden for Triatec® 1.25 mg tablets and Lopirin® 25 mg and 50 mg tablets. For 5/180 (2.8%) indexed scored tablets the SPCs contained a sentence discouraging splitting. The manufacturers were asked how this sentence was to be interpreted. Splitting was forbidden for 4 products (Lanvis®, Dilzem®, Dilzem RR®, Zyloric®), implying the presence of a decorative score-line (table 1). The fifth product (Medrol®) could be split to facilitate intake, but fractional dosing was forbidden (fig. 1).

Information on divisibility of the remaining 68 indexed scored tablets was limited to “divisible” (25 tablets) or was non-existent (43 tablets). We asked the manufacturers about possible fractional dosing. The replies are given in table 2.



**Table 2**

Answers of the manufacturers about the divisibility of the 68 indexed scored tablets of the Hospital Drug Formulary whose SPCs (Summary of Product Characteristics) mentioned "divisible" or no information at all; answers concerned the possibility of splitting for facilitated intake (Yes or No) or for fractional dosing (Yes or No).

Facilitated intake	Fractional dosing	"divisible" in the SPCs (N = 25)	No information in the SPCs (N = 43)
Yes	Yes	21	28
Yes	No	2 (Co-Reniten®, Oспен 1000®)	9 (Ampho-Moronal®, Augmentin®, Cytotec®, Digoxin-Streuli®, Hydrocortone®, Noroxin®, Pethidin®, Riamet®, Valium®)
No	No	because no test on the maintenance of dosage uniformity within the tablet halves had been performed 1 (Noveril 240 TR®)	3 (Cafergot®, Lopresor 50®, Tègretol®)
		because of the presence of a "historic" or "decorative" score-line	2 (Viramune®, Clamoxyl®)
		because the product has no score-line	1 (Norvasc®)
		because of the oxidative sensibility of the active component and the resulting difficulty to store a tablet halve without impairing its efficacy	1 (Madopar LIQ®)

## Discussion

Our study revealed that the SPCs of the Swiss Compendium of Medicines 2008 provided explicit information allowing or forbidding fractional dosing for about 46% of the tablets described with a score-line, leaving the physician and the pharmacist without crucial lack of information. We asked 36 nurses working at Basel University Hospital to give their view on the following statement: "It's allowed to split every tablet with a score-line." Sixty-nine percent answered "Yes". A survey conducted in Germany showed that 67% of the patients currently split their tablets and that almost 40% of them believed that all tablets may be split [7]. If we suppose that the majority of people interpret a score-line as allowing splitting of a tablet and fractionating of its dose, it may be extrapolated that approximately 54% of all scored tablets are fragmented without official published statements. A recent study determined drug content and weight uniformity in half-tablets of 6 drugs commonly split, and showed that the quantity measured was outside the USP specification (90–110%) for 23.9% of the halved tablets [13]. The resulting variation in drug mass may have serious implications for plasma concentrations and therapeutic outcome, ranging from toxic effects (overdose) to loss of efficacy (underdose), especially for drugs that have a narrow therapeutic index or are dose-critical [14, 15].

The Swiss regulatory authorities recognised the potentially confusing interpretation of score-lines on tablets but created a complex situation by adding certain warning statements to the SPCs. Consequently, in the SPC of a scored tablet a health professional can find both mention of score-lines and advice that the forms are not suitable for halving the dose. Since the indications are rarely in the same paragraph of the SPCs (an exception being Bexin®, with exhaustive information in the section Pharmaceutical Form and Quantitative Contents), and the wording of the warnings

differs widely between products, a health professional is in danger of missing the information.

Many hospitals added information to their Drug Formulary, such as the annotation "score-line Yes" behind oral solid forms, but unfortunately without adding further specifications on fractional dosing. Our study revealed that fractional dosing was indeed mentioned in the corresponding SPCs for almost 60% of the indexed scored tablets of the Basel University Hospital listing. For the remaining 40% the SPCs were not conclusive and only the manufacturers were able to provide the ultimate answer. In summary, fractional dosing was forbidden for 14.4% of all scored tablets indexed in the Hospital Drug Formulary, demonstrating that the use of "score-line YES" alone is misleading for 1 tablet out of 7. In fact all possibilities were encountered, (a) both the presence of "divisible" in the SPCs and the instruction not to fractionate the dose (Oспен 1000®), and (b) absence of any mention of score-lines in the SPCs, but the possibility of fractional dosing stated by the manufacturer (Lasilacton®). The fact that no mention of a score-line was found in the SPCs for 43 tablets of the Hospital Drug Formulary indicates that an employee of the hospital pharmacy had probably looked at the medicines to find a score-line. Unfortunately, for 15/43 of these products, the use of "score-line YES" was misleading since their fractional dosing was forbidden.

It is worrying that the official information available to health professionals concerning the fragmenting of scored tablets is incomplete and inhomogeneous. It is equally alarming that Hospital Drug Formularies do not bypass the published information and compile accurate information gathered directly from manufacturers. It is probably a challenge for professional organisations and associations to provide exact and updated databases with exhaustive information, amended with illustrations and measures of the scored tablets.

The warning system built into the electronic prescription system of University Hospital Heidelberg, Germany, was able to nearly halve the proportion of inappropriate splitting prescriptions principally due to the prescription of unscored tablets or capsules [3]. Thus, provision of valid information on divisibility and fractional dosing is urgently needed to avoid medication errors caused by misleading score-lines on tablets, bearing in mind that the crude information “divisible” is not discriminatory enough. The standard statements posted in September 2009 by the European authorities concerning tablets designed with a score-line should improve the currently unpleasant situation and are unequivocal. The sentences “The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses” and “The tablet can be divided into equal halves” will soon be part of the European SPCs in the section Pharmaceutical Form [16]. Finally, we would sug-

gest three relevant categories that are needed to feed a useful database on divisibility of scored tablets: “score line Yes/No”, “division for ease of swallowing Yes/No” and “division for fractional dosing Yes/No”.

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