







FOR PERSONAL USE ONLY. NOT TO BE REPRODUCED WITHOUT PERMISSION OF THE EDITOR

WHAT IS THE SUMMARY OF PRODUCT CHARACTERISTICS?

-  **The Summary of Product Characteristics (SmPC) forms the basis of prescribing information for healthcare professionals**
-  **The SmPC is an intrinsic part of the approval (licensing) process of a medicine**
-  **The SmPC content is continuously updated to reflect up-to-date knowledge of the medicine**
-  **The promotion of a medicine must be done within the terms of the current SmPC**

INTRODUCTION

The issuing of a prescription is acknowledged to be the commonest healthcare intervention.¹ However, studies have shown that prescribers vary in the sources of information they use when making prescribing decisions.^{2,3,4} Within the EU, the Summary of Product Characteristics (abbreviated to SmPC and formerly known as the datasheet) forms part of the licence (marketing authorisation or MA) that a company must acquire for any medicine it wishes to bring to market.^{5,6} The content of the SmPC is based on the scientific information presented by the company relating to the medicine and has been described as the definitive document in terms of prescribing information.⁷ However, many clinicians may not be aware of the value of the SmPC as a source of prescribing guidance and advice (in terms of dosing, precautions etc) for use at individual patient level.⁷

This bulletin will outline the background to the marketing authorisation approval process and the generation of the SmPC for a medicine, and demonstrate how this information can guide the prescriber to the optimal use of that medicine in the individual patient in clinical practice.

HOW IS A MEDICINE AUTHORISED?

Within the EU, all medicines must fulfil specific scientific requirements before they can be authorised for sale.^{5,6} As part of the MA application process, the company must provide evidence that the medicine adheres to clear and predefined standards of quality, safety and efficacy, relevant to its proposed therapeutic use.⁸ MA approval is given on the basis of a positive benefit / risk ratio for a specific therapeutic indication(s). The process of evaluation of these data is undertaken by the local regulatory authority (Irish Medicines Board in Ireland) or the European Medicines Agency (see below).

For certain new medicines (see Table 1), the company must use **a centralised authorisation procedure**, via the European Medicines Agency, for approval.

Table 1: Medicines that must use the centralised route for MA approval in the EU⁶

1. Medicines developed by means of specified biotechnological processes: (e.g. recombinant DNA technology, controlled expression of genes, hybridoma and monoclonal antibody methods)
2. Any new active substance for the treatment of
 - acquired immune deficiency syndrome
 - cancer
 - neurodegenerative disorder
 - diabetes
 - auto-immune diseases and other immune dysfunctions
 - viral diseases
3. Medicines designated as orphan medicinal products (used to treat rare diseases)

These medicines include highly innovative therapies and medicines for life-threatening diseases and this procedure ensures that these are granted an identical MA (and identical trade name) that is valid throughout the EU; this potentially enables simultaneous availability in all member states.^{6,8} Other medicines may also use this route, with permission from the Agency's scientific committee - Committee for Medicinal Products for Human Use (CHMP) - in order to gain a pan-EU authorisation. In each case, the scientific review is undertaken by the CHMP, whose membership comprises scientific experts from each member state. Once a recommendation for approval is given by the CHMP, the MA is issued by the European Commission, who acts as the licensing authority for centrally authorised medicines.⁸

Medicines that have been authorised via this centralised process are recognisable by the EU number on their packaging and documentation (in the form of EU/xxx/xxx/xxx).

For the remainder of new medicine applications, MA approval can be achieved via one of the "non-centralised" routes.^{5,8} For those medicines which will only be marketed in one member state, it is possible to seek **national MA approval** from the national regulatory authority (IMB in Ireland).⁹ However, as is usually the case, if the aim is to market in more than one member state then the company must use one of the following routes:^{5,8}

- **the decentralised procedure** where the same application is submitted simultaneously to the local regulatory authorities in the desired (concerned) member states, with one state known as the reference member state (RMS) taking the lead in assessment or
- **the mutual recognition procedure** where the company already has an active MA in one member state which acts as the sponsor (RMS) of the procedure in order to get “mutual recognition” of its existing MA in the other (concerned) member states.

In each of these cases, the MA approved will be identical in all the concerned member states, although it is possible to have different trade names in the different member states.⁸ In addition, the MA documentation will be issued at member state level by the national licensing authority (IMB in Ireland).

Medicines that have been authorised via any one of these routes in Ireland are recognisable by the PA number on their packaging and documentation (in the form of PA xx/xx/xx).

HOW DOES THE SmPC FIT INTO THE MARKETING AUTHORISATION PROCESS?

The SmPC is a legal document, which forms part of the MA documentation issued to the company and which sets out the agreed position of the medicine, as determined during the course of the assessment process.¹⁰ When a company submits an application for MA approval, it is obliged to include a proposed SmPC, which will outline the proposed prescribing information (therapeutic use(s), dosage, safety in use etc), based on its own review of the data package submitted.⁸ This is evaluated during the assessment process, along with the scientific information, and final MA approval will be on the basis of a legally binding SmPC which has been agreed between the company and the relevant authority.⁷ **Therefore the SmPC forms an intrinsic and integral part of the MA process.**¹⁰

Once a medicine has been awarded a MA, any changes (e.g. pharmaceutical changes, new therapeutic uses, updated safety information) should be notified by the company to the relevant licensing authorities and the MA amended as appropriate (by way of a process known as “variation” to the existing MA).^{11,12} This usually involves a change to the content of the SmPC. In practice, SmPCs are changed on a regular basis – the date of the most recent revision is included at the end of the text. The SmPC is the document that pharmaceutical company representatives are legally obliged to provide to prescribers (or alternatively direct them to an internet site where the SmPC may be accessed) and any **promotion of a medicine must be within the terms of the most up-to-date SmPC.**¹³

The SmPC is the document on which the package leaflet / patient information leaflet (PIL) is based. This is also agreed at the time of MA approval^{5,6} with the aim of providing reader-friendly information for the end-user of the medicine. Both the SmPC and PIL are publicly accessible from many sources online. [See “Online Sources” at the end of the bulletin]

WHAT INFORMATION IS CONTAINED IN THE SmPC?

The SmPC of a medicine provides specific product information for prescribers and healthcare professionals on how to use that medicine safely and effectively.¹⁰ **The content provides specific details of the use of the medicine in its treatment of a specific disease(s);**^{7,10} its content does not include general advice on the treatment of particular medical conditions.

The SmPC has an agreed standard template (Figure 1), which ensures a consistent presentation of data across all SmPC documents; the same format of SmPC is applicable in all EU member states. Consistency of presentation should allow the reader easy retrieval of the data on a day-to-day basis.¹⁰ In addition, the SmPC is designed to use a standard medical terminology, which also ensures consistency of the information being provided for the prescribers and other healthcare professionals. Full details on the information that is required in an SmPC can be found at: <http://www.ema.europa.eu/htms/human/grd/grdreference.htm>

Figure 1: Content of the Summary of Product Characteristics^{7,10}

- | | |
|--|---|
| 1. Name of the medicinal product (the brand name) with the strength and pharmaceutical form | 5. Pharmacological properties |
| 2. Qualitative and quantitative composition (i.e. the INN [approved name[s]] of the active ingredient[s] and declaration of the quantity in terms of active substance) | 5.1 Pharmacodynamic properties |
| 3. Pharmaceutical form (e.g. tablets, capsules) and the visual description of the medicinal product | 5.2 Pharmacokinetic properties |
| 4. Clinical particulars | 5.3 Preclinical safety data |
| 4.1 Therapeutic indications (i.e. the licensed indication[s]) | 6. Pharmaceutical particulars |
| 4.2 Posology (i.e. dosage) and method of administration | 6.1 List of excipients (a full list of the product's ingredients, apart from the active drugs[s]) |
| 4.3 Contraindications | 6.2 Incompatibilities (information on physical and chemical incompatibilities with other products likely to be administered simultaneously) |
| 4.4 Special warnings and precautions for use | 6.3 Shelf life |
| 4.5 Interaction with other medicinal products and other forms of interaction | 6.4 Special precautions for storage |
| 4.6 Pregnancy and lactation (i.e. including information about use in women with child-bearing potential when appropriate) | 6.5 Nature and contents of container |
| 4.7 Effects on ability to drive and use machines | 6.6 Special precautions for disposal and other handling |
| 4.8 Undesirable effects | 7. Marketing authorisation holder (name and address) |
| 4.9 Overdose | 8. Marketing authorisation number |
| | 9. Date of first authorisation/renewal of the authorisation |
| | 10. Date of the revision of the text |

Pharmaceutical data are contained in sections 1 to 3 and 6.1 to 6.6. These are useful in the identification of the specific medicine. The trade name is given along with the international non-proprietary name (INN - see NMIC bulletin on Generic Prescribing)¹⁴ to enable identification of the active substance, while details such as visual appearance of the product (colour, markings, actual size of solid oral formulations) may facilitate identification of a specific tablet if the patient is not aware of the name of his/her medicine. **Sections 2 and 6.1** provide important information on the qualitative and quantitative composition of the medicine; this has particular relevance if a patient has a known allergy to some of the constituents such as a specific active ingredient or more commonly, an excipient. **An excipient is defined as any constituent of a medicine, apart from the active substance**¹⁵ and includes fillers, lubricants, colouring matters, antioxidants, preservatives, adjuvants and stabilisers (see Table 2). In certain instances, additional safety warnings are placed in the SmPC (in section 4.4) and / or PIL for some excipients (Table 2).

Table 2: Examples of excipients used in medicines^{15,16}

Listed in Section 6.1 of the SmPC	Section 6.1 plus specific SmPC (section 4.4) and/or PIL warnings
Gelatin	Arachis oil (peanut oil) – risk of allergic reaction
Microcrystalline cellulose	Sucrose/fructose/lactose – intolerance to sugars
Magnesium stearate	Lanolin (topical) – contact dermatitis
Ascorbic acid	Benzalkonium chloride (ocular) – eye irritation

Section 6.6 provides important instructions on handling and disposal of specific medicines such as cytotoxic agents and some biological products. This information outlines the necessary protective measures for healthcare professionals, patients or their carers who might be involved in the handling of such medicines.¹⁰ In addition, where required, advice on the disposal of unused medicines or of items that come into contact with the medicine (e.g. nappies – live vaccines - or spoons used to administer oral live vaccines) will be included in this section.

Sections 7 to 10 contain administrative information (see Figure 1) regarding the holder of the MA, the date of MA approval and the date of the most recent update (which informs the prescriber whether the SmPC he/she consults contains the most up-to-date information on the specific medicine).

WHAT TYPE OF CLINICAL DATA CAN THE PRESCRIBER EXPECT IN THE SmPC?

The main bulk of the information contained in the SmPC relates to the clinical usage of the medicine (**Section 4**) and the relevant pharmacological details (**Section 5**). The content is based on clinical information, presented to the regulators by the company, relevant to its use in the approved therapeutic indication(s). Each section follows a standard format (Figure 1). Cross-referencing between subsections is used to explain the background to a specific statement; for example if section 4.3 states that use of a medicine is contraindicated in pregnancy, there will usually be a cross-reference to sections 4.6 and/or 5.3 where the scientific basis for the contraindication is described.

Section 4.1: Therapeutic Indication outlines the approved therapeutic use(s) of the medicine.¹⁰ Any use outside of the approved therapeutic use is often referred to as “off-label / unlicensed” as it is outside the terms of the MA of that medicine. Particularly in the case of the newer medicines, **Section 5.1** contains additional information on the clinical efficacy data, supporting the approved indication, which may be helpful for the prescriber.

Section 4.2: Posology and Method of Administration gives detailed information on the approved dosage regimen(s) for the therapeutic use(s) in the target population.¹⁰ It supplies information on any modifications that may need to be made to dosing (including a recommendation against use) when prescribing the medicine for vulnerable patients (e.g. children, the elderly, patients with renal or hepatic dysfunction) or with concomitant medicines / food (See Table 3).¹⁷⁻²⁰ The data contained in this section facilitate individualisation of the dosing regimen. In addition, any specific recommendations relating to the method of administration (e.g. speed of infusion for an intravenous solution or warning not to crush a prolonged release tablet) or requirements regarding location of administration (e.g. need to have resuscitation facilities available when administering vaccines) are also contained in this section.

Table 3: Dosing Information provided in Section 4.2: Examples¹⁷⁻²⁰

Medicine	SmPC content	Value to prescriber
Alendronate [Once weekly]	Detailed information on how drug should be taken by patient: 30 minutes before first food, with >200ml water only; tablet should be swallowed whole and patient should stay upright for at least 30 minutes. Also not recommended for use in children (lack of data) or severe renal dysfunction	Clear guidance ensures optimal absorption and protects patient against GI toxicity
Simvastatin	Dose to be given in the evening; higher doses not to be used in severe renal dysfunction or with concomitant use of certain medicines; not recommended for use in children (lack of data)	Enables individualisation of dosage regimen

Section 4.3: Contraindications outlines situations where the medicine must not be given for safety reasons.¹⁰ These situations should be comprehensively and clearly outlined in the text. Examples include the presence of a particular condition / diagnosis or concomitant disease or hypersensitivity to any ingredient (active or excipient) in the medicine (See Table 4).^{21,22}

The content of **Section 4.4: Special warnings and precautions for use** varies according to the medicine. Information includes: conditions in which the use of the medicine is acceptable, provided that special precautions with use are fulfilled and/or particular situations (e.g. patient group at increased risk of adverse drug reaction; potential first dose or rebound effects; need for specific clinical or laboratory monitoring).¹⁰ **The order of the warnings and precautions is determined in principle by the importance of the safety information being provided** (See Table 4).²³ The aim of this section is to enable the prescriber to prescribe a specific medicine safely for his/her individual patient.

Table 4: Information on the safety of use of a medicine in the SmPC: Examples from sections 4.3 and 4.4²¹⁻²³

Section	Medicine	SmPC Content	Value to Prescriber
4.3	enalapril	Contraindicated in: history of angioedema with previous ACEIs or hereditary or idiopathic angioedema; 2nd and 3rd trimesters pregnancy (cross ref. to 4.4 and 4.6 for explanation)	Clear information on which patients should not receive ACEIs
4.4	methotrexate tablets	Detailed warnings including risk of bone marrow suppression, hepatic, renal, GI + pulmonary toxicity, effects on fertility and foetus; caution that the prescriber should be experienced with drug profile; outlines monitoring that is required during treatment with methotrexate	Provides guidance on how to manage patients with these conditions prior to therapy, how to monitor users and what to do if toxicity occurs with therapy

Section 4.5: Drug interactions provides information on the **potential for clinically relevant interactions** based on the known pharmacology of the medicine and *in vivo* pharmacokinetic studies undertaken with standard “marker” medicines (e.g. ciclosporin, warfarin, protease inhibitors, erythromycin), as appropriate, depending on the known pharmacokinetic profile of the medicine (see Table 5).^{24,25} Contemporary management of many diseases requires the prescription of several drugs concomitantly;²⁸ therefore the possibility of a drug-drug interaction must always be borne in mind. This section of the SmPC should follow a strict order. Interactions affecting the use of the specific medicine should be given first, followed by any clinically relevant interaction(s) affecting the concomitant medicine(s). **The order of presentation relates to the seriousness of the potential interaction:** contraindicated combinations are listed first, followed by those where concomitant use is not recommended, followed by others (which might require dose adjustment, or laboratory monitoring). Typically, this section is cross-referenced to other parts of the SmPC in order to provide the prescriber with the scientific basis for each safety warning.

Table 5: Information on the safety of use of a medicine in the SmPC: Examples from sections 4.5 and 4.6²⁴⁻²⁷

Section	Medicine	SmPC Content	Value to Prescriber
4.5	clarithromycin	Detailed information on potential for drug-drug interactions with drugs metabolised by CYP 3A resulting usually in increased levels of other drug + potential adverse outcome (e.g. ↑ QT interval; ↑ risk myopathy if a statin; ↑ effect of warfarin)	SmPC outlines clinically relevant interaction risk(s) with other drug classes. Useful as this medicine is frequently co-prescribed with other medicines in practice
4.6	fluoxetine	Information based on a large number of exposed pregnancies do not indicate a teratogenic effect. Caution to be exercised especially during late pregnancy (effects in newborn) and during breastfeeding (long half life)	Data based on real life usage Specific advice regarding potential outcome of usage in late pregnancy Specific advice if use considered during breastfeeding (options given)

Clinical trials are not undertaken in pregnant or breastfeeding women, therefore **Section 4.6: Pregnancy and Lactation**, takes all available sources of usage (such as post-marketing surveillance, observational studies, non-clinical studies, experience from compounds within the same class) to provide a basis for the recommendations contained therein relating to use during pregnancy or breast-feeding (see Table 5).^{26,27} This section will also normally contain recommendations on the need for contraceptive measures, if appropriate for that medicine. These data may be an important source of information for the prescriber when discussing the potential use of the medicine with a female patient. Greater emphasis is now being placed on information relating to the potential impact of a medicine on male and/or female fertility and these data will be systemically included in this section of the SmPC in the future.¹⁰ Frequently there is a cross-reference to **Section 5.3 (Preclinical Safety Data)** to provide background data from animal studies.

The information contained in **Section 4.7: Effects on ability to drive and use machines** is composed of the pharmacodynamic and pharmacokinetic profile of the medicine, together with the safety data collected from clinical trials, and any specific studies undertaken in the target population relating to driving and road safety / using machines.¹⁰ These data are used to state whether the medicine has a) no or negligible influence, b) minor influence, c) moderate influence or d) major influence on these abilities. As appropriate, information on the duration of the impairment, if any, or the development of tolerance will also be mentioned. There may be a cross-reference to section 4.4 in case of serious concern.

Section 4.8: Undesirable effects. The aim of this section is to provide clear, comprehensive and readily accessible information on the safety profile of the medicine. It includes the most frequently reported adverse reactions and their severity (reported from all sources including clinical trials, use in practice, literature reports etc) that have a reasonable suspicion of causality. **The format consists of a summary of the most serious and/or most frequently occurring adverse reactions, followed by a tabulated summary of adverse reactions and descriptions of selected safety concerns.**¹⁰ Frequency is classified using the following convention: very common ($\geq 1/10$ uses), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) or *unknown*. Details on specific safety concerns relating to certain patient groups (e.g. paediatric or elderly patients) will also be supplied under separate headings. These data should provide sufficient information for the prescriber to put the benefit/ risk of a medicine into context for his/her individual patient.

Section 4.9: Overdose provides all available information on the expected symptoms and signs and potential sequelae of different dose levels of the medicine. This information comes from accidental intake, mistakes in doses and deliberate overdose and is updated as such information becomes available.^{7,10} Advice on monitoring, possible antidotes or methods to increase elimination of the medicine is supplied.

SUMMARY

The SmPC is the basis for prescribing information on authorised medicines for healthcare professionals within the EU. Its role is to provide specific advice on how to use a medicine safely and effectively. Its content is based on information provided from the development of that medicine and experience of its use in clinical practice. SmPCs are freely available online from many sources (see below). The content is updated as new information on safety, efficacy and use in specific patient groups (e.g. children) becomes available, thereby providing the prescriber with the most up-to-date information on the benefits and risks of use of a medicine in clinical practice.

ONLINE SOURCES OF SUMMARIES OF PRODUCT CHARACTERISTICS*

- **Irish Medicines Board - SmPCs of all medicines authorised for use in Ireland**
(<http://www.imb.ie/EN/Medicines/HumanMedicines/HumanMedicinesListing.aspx>)
- **European Medicines Agency - SmPCs of centrally authorised medicines****
(<http://www.ema.europa.eu/htms/human/epar/>)
- **Medicines Information Online - IPHA website of branded authorised medicines**
(<http://www.medicines.ie/>)

*addresses accessed 25th February 2010

** this page on the website also contains the Scientific Discussion / Public Assessment Report which give more complete background information on the medicines authorised via the centralised procedure

List of references available on request. Date of preparation: March 2010

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the individual Summary of Product Characteristics (SmPC) for specific information on a medicine

References for bulletin “What is the Summary of Product Characteristics?”
NMIC Bulletin Volume 16; 1: 2010

1. Freemantle N, Does the UK National Health Service need a fourth hurdle for pharmaceutical reimbursement to encourage the more efficient prescribing of pharmaceuticals? *Health Policy* 1999; 46: 255-65
2. McGettigan P et al, Prescribers prefer people: The sources of information used by doctors for prescribing suggest that the medium is more important than the message. *Br J Clin Pharmacol* 2001; 51: 184-9
3. Mason A, New medicines in primary care: a review of influences on general practitioner prescribing. *J Clin Pharm Therap* 2008; 33: 1-10
4. Fischer M et al, Prescribers and Pharmaceutical Representatives: Why are we still meeting? *J Gen Intern Med* 2009; 24: 795-801
5. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Available online at:
http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-1/index_en.htm (accessed 5th March 2010)
6. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Available online at:
http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-1/index_en.htm (accessed 5th March 2010)
7. Why look at an SPC? *DTB* 2009; 47: 45-8
8. EudraLex - Volume 2 - Pharmaceutical Legislation Notice to applicants and regulatory guidelines medicinal products for human use. Available online at:
http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-2/index_en.htm (accessed 5th March 2010)
9. Human Medicines (Irish Medicines Board). Available online at:
<http://www.imb.ie/EN/Medicines/Human-Medicines.aspx> (accessed 5th March 2010)
10. Guideline on Summary of Product Characteristics. Available online at:
http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf (accessed 5th March 2010)
11. Commission Regulation 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products. Available online at:
http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-1/index_en.htm (accessed 8th March 2010)
12. EC Directive 2009/53/ EC as regards variations to the terms of marketing authorisations for medicinal products. Available online at:
http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-1/index_en.htm (accessed 8th March 2010)
13. Code of Marketing Practice for the Pharmaceutical Industry, 7th Edition. Available online at: <http://www.ipha.ie/alist/pub-codes-of-practice.aspx> (accessed 5th March 2010)
14. Generic Prescribing, *NMIC* 2009;15: 1. Available online at www.nmic.ie (accessed 26th February 2010)

15. CHMP guideline on excipients in the dossier for application for marketing authorisation of a medicinal product. Doc Ref: EMEA/CHMP/QWP/396951/2006
16. Volume 3b guidelines: Excipients in the label and package leaflet of medicinal products for human use. Doc Ref ENTR/F2/BL D (2003)
17. SmPC for Fosamax once weekly®. Available online at www.medicines.ie (accessed 26th February 2010)
18. SmPC for Fostepor once weekly®. Available online at www.medicines.ie (accessed 26th February 2010)
19. SmPC for Zocor®. Available online at www.medicines.ie (accessed 26th February 2010)
20. SmPC for Simzor®. Available online at www.medicines.ie (accessed 8th March 2010)
21. SmPC for Innovace®. Available online at www.medicines.ie (accessed 26th February 2010)
22. SmPC for Enapril Stada®. Available online at www.imb.ie (accessed 1st March 2010)
23. SmPC for Methotrexate 2.5mg tablets. Available online at www.imb.ie (accessed 2nd March 2010)
24. SmPC for Klariger®. Available online at www.medicines.ie (accessed 1st March 2010)
25. SmPC for Klacid®. Available online at www.medicines.ie (accessed 1st March 2010)
26. SmPC for Gerozac®. Available online at www.medicines.ie (accessed 2nd March 2010)
27. SmPC for Prozac®. Available online at www.medicines.ie (accessed 2nd March 2010)
28. Drug Interactions I: How they occur. NMIC 2008; 14:4 Available online at www.nmic.ie (accessed 26th February 2010).