Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Aspirin 75 mg tablets

(Acetylsalicylic acid)

UK Licence Number: PL 22389/0003

Callisto Regulatory Consulting Limited.

LAY SUMMARY

Aspirin 75 mg tablets
(Acetylsalicylic acid)

This is a summary of the Public Assessment Report (PAR) for Aspirin 75 mg tablets (PL 22389/0003). It explains how Aspirin 75 mg tablets were assessed and their authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Aspirin 75 mg tablets..

This product will be referred to as Aspirin tablets throughout this public assessment report.

For practical information about using Aspirin tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Aspirin Tablets and what are they used for?
Aspirin tablets are a medicine with 'well established use'. This means that the medicinal use of the active substance of Aspirin tablets is well-established in the European Union (EU) for at least ten years, with recognised efficacy and an acceptable level of safety.

Aspirin tablets are taken to reduce the risk of blood clots forming and thereby prevent further:

- Heart attacks
- Strokes
- Cardiovascular problems inpatients who suffer from stable or unstable angina (a type of chest pain)

Aspirin tablets are also used to prevent the formation of blood clots after certain types of heart surgery in order to widen or to unblock the blood vessels.

Aspirin tablets are also used in the treatment of acute myocardial infarction.

How do Aspirin tablets work?
Aspirin tablets contain the active ingredient acetylsalicylic acid, which in low doses belongs to a group of medicines called anti-platelet agents. Platelets are tiny cells in the blood that cause the blood to clot and are involved in thrombosis. When a blood clot occurs in an artery it stops the blood flowing and cuts off the oxygen supply. When this happens in the heart it can cause a heart attack or angina, in the brain it can cause a stroke.

How are Aspirin tablets used?
The pharmaceutical form of Aspirin tablets is a tablet and the route of administration is by mouth (oral). Aspirin tablets should be swallowed with sufficient fluid (half a glass of water).

The patient should always take this medicine exactly as the patient's doctor has told them. The patient should check with their doctor or pharmacist if the patient is not sure.

The recommended dose in adults for
Prevention of heart attacks:

- 75-160 mg once daily

Prevention of strokes:

- 75-300 mg once daily.

Prevention of cardiovascular problems in patients who suffer from stable or unstable angina (a type of chest pain):

- 75-160 mg once daily

Prevention formation of blood clots after certain types of heart surgery:

- 75-160 mg once daily

Treatment of acute myocardial infarction:

- The recommended initial dose is 150-500 mg followed by a lower dose of 75-160 mg thereafter

This medicine should not be used at higher doses unless advised by the patient's doctor, and then the dose should not exceed 300 mg a day.

The recommended dose in older people
As for adults. In general, acetylsalicylic acids should be used with caution in elderly patients who are more prone to adverse events. Treatment should be reviewed at regular intervals.

The recommended dose in children and adolescents:
Acetylsalicylic acids should not be administered to children and adolescents younger than 16 years of age, unless prescribed by a doctor as acetylsalicylic acid may cause Reye's syndrome when given to children, Reye's syndrome is a very rare disease which affects the brain and liver and can be life threatening.

This medicine can only be obtained with a prescription.

What benefits of Aspirin tablets have been shown in studies?
As acetylsalicylic acid is a well-known substance, and its use in the treatment to reduce the risk of blood clots forming thereby preventing further heart attacks, strokes, cardiovascular problems in patients who suffer from stable or unstable angina, formation of blood clots after certain types of heart surgery in order to widen or to unblock the blood vessels and in the treatment of acute myocardial infarction is well established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of acetylsalicylic acid in the treatment of treatment to reduce the risk of blood clots, cardiovascular problems in patients who suffer from stable or unstable angina, formation of blood clots after certain types of heart surgery in order to widen or to unblock the blood vessels and in the treatment of acute myocardial infarction.

What are the possible side effects of Aspirin tablets?
For the full list of all side effects reported with Aspirin tablets, see section 4 of the package leaflet available on the MHRA website.

For the full list of restrictions, see the package leaflet.

Why are Aspirin tablets approved?
The MHRA decided that Aspirin tablets benefits are greater than its risks and recommended that they were approved for use.

What measures are being taken to ensure the safe and effective use of Aspirin tablets?
A risk management plan (RMP) has been developed to ensure that Aspirin tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Aspirin tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Aspirin tablets

The Marketing Authorisation for Aspirin tablets was granted on 29 March 2018.

The full PAR for Aspirin tablets follows this summary.

For more information about treatment with Aspirin tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2018.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted the Marketing Authorisation Holder (MAH), Callisto Regulatory Consulting Limited, a marketing authorisation for the medicinal product Aspirin tablets (PL 22389/0003). This product is a prescription only medicine (POM) and is indicated for:

- Secondary prevention of myocardial infarction.
- Prevention of cardiovascular morbidity in patients suffering from stable angina pectoris.
- History of unstable angina pectoris, except during the acute phase.
- Prevention of graft occlusion after Coronary Artery Bypass Grafting (CABG).
- Coronary angioplasty, except during the acute phase.
- Secondary prevention of transient ischaemic attacks (TIA) and ischaemic cerebrovascular accidents (CVA), provided intracerebral haemorrhages have been ruled out.
- Acute myocardial infarction.

This application was submitted as an abridged national application according to Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use.

Acetylsalicylic acid inhibits the platelet activation: blocking the platelet cyclooxygenase by acetylation, it inhibits thromboxane A2 synthesis, a physiological activating substance released by the platelets and which would play a role in the complications of the atheromatous lesions. Inhibition of TXA2-synthesis is irreversible, because thrombocytes, which have no nucleus, are not capable (due to lack of protein synthesis capability) to synthesise new cyclooxygenase, which had been acetylated by acetylsalicylic acid. The repeated doses from 20 to 325 mg involve an inhibition of the enzymatic activity from 30 to 95%. Due to the irreversible nature of the binding, the effect persists for the lifespan of a thrombocyte (7-10 days). The inhibiting effect does not exhaust during prolonged treatments and the enzymatic activity gradually begins again upon renewal of the platelets 24 to 48 hours after treatment interruption. Acetylsalicylic acid extends bleeding time on average by approximately 50 to 100%, but individual variations can be observed.

No new non-clinical studies were submitted, which is acceptable given that this is a bibliographic application for a product containing an active substance of well-established use.

No new clinical data have been submitted and none are required for an application of this type, since the scientific evidence found in the published literature was sufficient to discuss all pharmacological, pharmacokinetic and toxicological profiles of the proposed medication and similar medicinal products containing the same active ingredients have been on the market in the EEA for several decades.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the MHRA has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA

has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

No new or unexpected safety concerns arose during the review of information provided by the MAH and it was, therefore, judged that the benefits of taking Aspirin tablets outweigh the risks and a Marketing Authorisation was granted on 29 March 2018.

II QUALITY ASPECTS

II.1 Introduction

Each tablet contains 75 mg of acetylsalicylic acid.

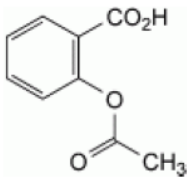
Other ingredients consist of the pharmaceutical excipients lactose monohydrate, microcrystalline cellulose, colloidal anhydrous silica and potato starch.

The finished product is available in polyvinylchloride (PVC)/aluminium blister packs containing 10, 20, 28, 30, 50, 56, 60, 90 or 100 tablets. Not all pack sizes may be marketed

Satisfactory specifications and Certificates of Analysis have been provided for the packaging components.

II.2 Drug Substance

INN:	Acetylsalicylic acid
Chemical name:	2-(Acetyloxy)benzoic acid
Structure:	



Molecular formula:	$C_9H_8O_4$
Molecular weight:	180.2 g/mol
Description:	White or almost white, crystalline powder or colourless crystals
Solubility:	It is slightly soluble in water, freely soluble in ethanol (96%).

Acetylsalicylic acid is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, acetylsalicylic acid, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, tablets containing 75 mg of acetylsalicylic acid per tablet.

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for each excipient. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the product, together with an appropriate account of the manufacturing process. Process validation data on the pilot-scale batches have been provided. The results are satisfactory.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data complying with the release specification have been provided. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 3 years with the storage conditions 'Keep the blister in the outer carton in order to protect from moisture'.

Suitable post approval stability commitments to continue stability testing on batches of finished product have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS
III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of acetylsalicylic acid are well-known, no new non-clinical studies are required, and none have been provided. An overview bases on the literature review is, thus, appropriate.

The MAH's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Aspirin tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary**.**

III.6 Discussion on the non-clinical aspects

There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction

Acetylsalicylic acid is a well-established active substance, with recognised efficacy and acceptable safety, and has been licenced in the European Union for many years. The details of its pharmacology are documented in various publicly accessible sources and a comprehensive review of the published literature has been provided by the MAH, citing the well-established clinical pharmacology, efficacy and safety of acetylsalicylic acid.

The clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

The pharmacokinetic properties of acetylsalicylic acid are discussed in detail in the MAH's clinical overview. The summaries of these findings are presented below.

Aspirin exhibits zero order kinetics. Consequently, plasma steady state concentrations of salicylate increase disproportionately with dose. The antiplatelet effect of aspirin shows saturability at low doses and clinical studies evaluating the antithrombotic effects show a lack of dose response relationship.

Absorption

After oral administration, acetylsalicylic acid is rapidly and completely absorbed from the gastrointestinal tract. The principal site of absorption is the proximal small intestine. However, a significant portion of the dosage is already hydrolysed to salicylic acid in the intestinal wall during the absorption process. The degree of hydrolysis is dependent on the rate of absorption. After intake of Aspirin tablets the maximum plasma levels of acetylsalicylic acid and salicylic acid are reached after about 20 minutes and 1 hour, respectively, following administration in the fasted state.

Distribution

Acetylsalicylic acid as well as the main metabolite salicylic acid are extensively bound to plasma proteins, primarily albumin, and distributed rapidly into all parts of the body. The degree of protein binding of salicylic acid is strongly dependant of both the salicylic acid and albumin concentration. The volume of distribution of acetylsalicylic acid is ca. 0.16 l/kg of body weight. Salicylic acid slowly diffuses into the synovial fluid, crosses the placental barrier and passes into breast milk.

Metabolism

Acetylsalicylic acid is rapidly metabolised to salicylic acid, with a half-life of 15-30 minutes. Salicylic acid is subsequently predominantly converted into glycine and glucuronic acid conjugates, and traces of gentisic acid. Elimination kinetics of salicylic acid is dose-dependent, because the metabolism is limited by liver enzyme capacity. Thus, elimination half-time varies and is 2-3 hours after low doses, 12 hours after usual analgesic doses and 15-30 hours after high therapeutic doses or intoxication.

Excretion

Salicylic acid and its metabolites are predominantly excreted via the kidneys.

Special populations

Older people

- The usual adult dose is recommended in the absence of severe renal or hepatic insufficiency. Treatment should be reviewed at regular intervals.

Paediatric population

- Acetylsalicylic acid should not be administered to children and adolescents younger than 16 years, except on medical advice where the benefit outweighs the risk.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for this bibliographic application. The pharmacodynamic properties of acetylsalicylic acid are discussed in detail in the MAH's clinical overview.

IV.4 Clinical efficacy & IV.5 Clinical Safety

The bibliography contains extensive evidence on the well-established clinical pharmacology and pharmacokinetics of aspirin, derived from the critical reviews and clinical guidelines on efficacy and safety of the low-dose formulation. The summaries of these findings are presented below

One such review summarised that aspirin resistance as the inability of aspirin to produce a measurable response on ex vivo tests of platelet function, to inhibit TXA2 biosynthesis in vivo, or to protect individual patients from thrombotic complications.

Also, among patients with occlusive vascular disease, both individual studies and a meta-analysis of trials of antiplatelet therapy indicate that aspirin and other antiplatelet drugs reduce the risk of a serious vascular event (nonfatal myocardial infarction, nonfatal stroke, or death from vascular causes) by approximately 25%. Thus, among a wide range of patients with vascular disease, in whom the annual risk of a serious vascular event ranges from 4-8%, aspirin typically prevents at least 10-20 fatal and nonfatal vascular events for a number of patients treated for one year.

The mechanism of action, pharmacokinetics, and pharmacodynamics of aspirin, reversible cyclooxygenase inhibitors, thienopyridines, and integrin IIb receptor antagonists has been described in another literature-based review. The relationships among dose, efficacy, and safety are thoroughly discussed, with a mechanistic overview of randomized clinical trials. The article does not provide specific management recommendations; however, it does highlight important practical aspects related to antiplatelet therapy, including the optimal dose of aspirin, the variable balance of benefits and hazards in different clinical settings, and the issue of interindividual variability in response to antiplatelet drugs.

Randomised trials of an antiplatelet regimen versus control, or of one antiplatelet regimen versus another, in high risk patients (with acute or previous vascular disease or some other predisposing condition) from which results, were reviewed. Studies involved a large number of patients in comparisons of antiplatelet therapy versus control and in comparisons of different antiplatelet regimens. Trials had to use a method of randomisation that precluded prior knowledge of the next treatment to be allocated and comparisons had to be unconfounded—that is, have study groups that differed only in terms of anti-platelet regimen. The main outcome measure was "Serious vascular event", i.e. non-fatal myocardial infarction, non-fatal stroke, or vascular death.
Conclusion: Aspirin (or another oral antiplatelet drug) is protective in most types of patient at increased risk of occlusive vascular events, including those with an acute myocardial infarction or ischaemic stroke, unstable or stable angina, previous myocardial infarction, stroke or cerebral ischaemia, peripheral arterial disease, or atrial fibrillation. Low dose aspirin (75-150 mg daily) is an effective antiplatelet regimen for long term use, but in acute settings an initial loading dose of at least 150 mg aspirin may be

required. Adding a second antiplatelet drug to aspirin may produce additional benefits in some clinical circumstances, but more research into this strategy is needed.

The pharmacokinetic properties of acetylsalicylic acid have been reviewed adequately in the MAH's clinical overview.

Clinical conclusion
The bibliography has provided adequate evidence of sufficient quality to support this application

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC, as amended.

There are no differences from the reference product in terms of proposed uses, maximum pack size / strength or pharmaceutical form / formulation that would have any implications for safety. Only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the patient information leaflet (PIL)) will be performed.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the Competent Authority
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a Periodic Safety Update Report and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended for this application from a clinical viewpoint.

V User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with Aspirin tablets is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

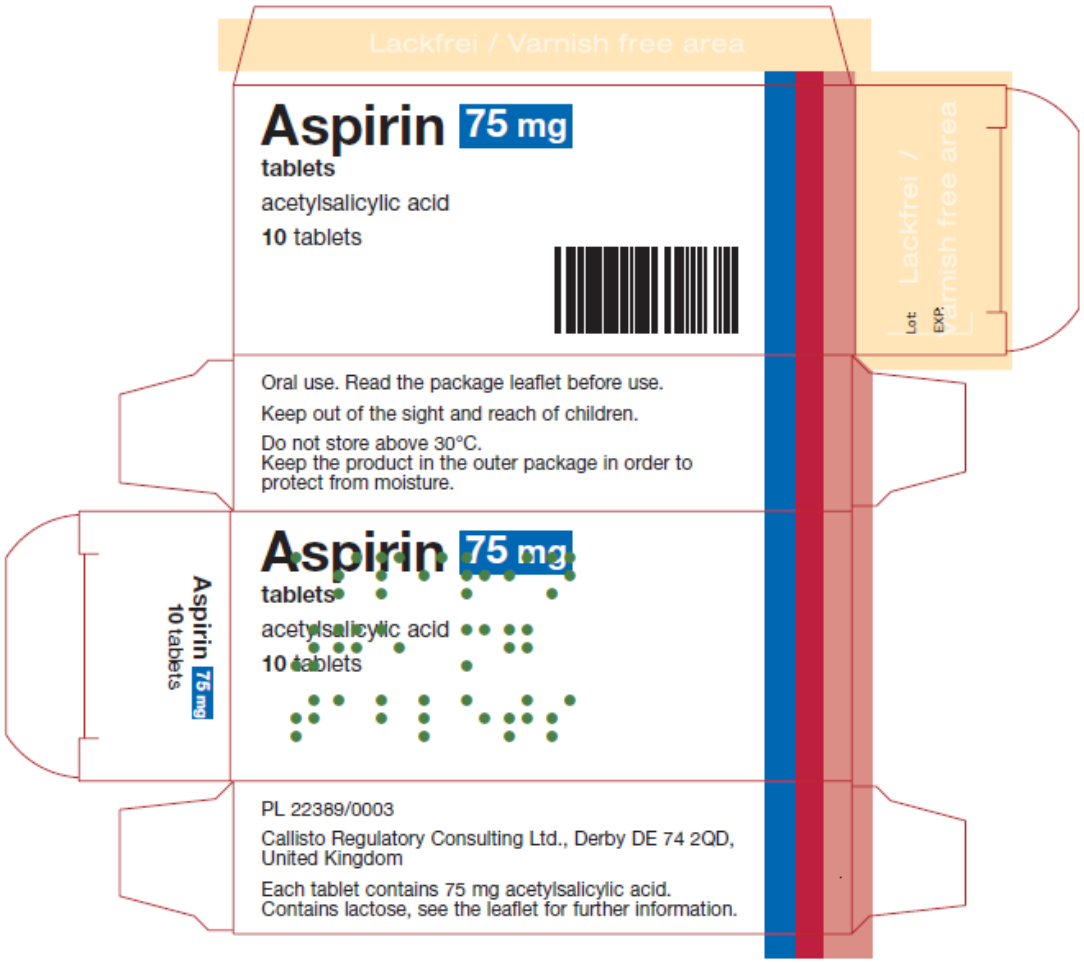
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Aspirin tablets is presented below.

Präparatenamen/Stärke: Aspirin 75 mg
Darreichungsform: Tabletten
Abpackungsart: Blister

Land: Großbritannien / uk
Format des Einzelblisters: 83 x 35 mm Datum/Version: 19. 6. 2017 – 1
Packmittelart: Blisterfolie ◆ Produktion: intern
Schrift: Helvetica 7,5 – 10,0 Punkt, var. Daten 5,0 Punkt
Druckfarbe: ◆ Schwarz



Präparatenamen/Stärke: Aspirin 75 mg
Darreichungsform: Tabletten
Abpackungsart: Blister

Braille-Text:

Land: Großbritannien / uk ◆ Format: 38 x 22 x 87 mm ◆ Datum/Version: 19. 6. 2017 –1
Packmittelart: Faltschachtel ◆ Produktion: intern
Schrift: Helvetica 7,7 – 22,0 Punkt, var. Daten 5 Punkt
Druckfarben: Pantone 293 c ◆ Pantone 200 c ◆ Schwarz
Drucktechnisches: Stanze / die cut ◆ Braille ◆ lackfreie Fläche / varnish-free area
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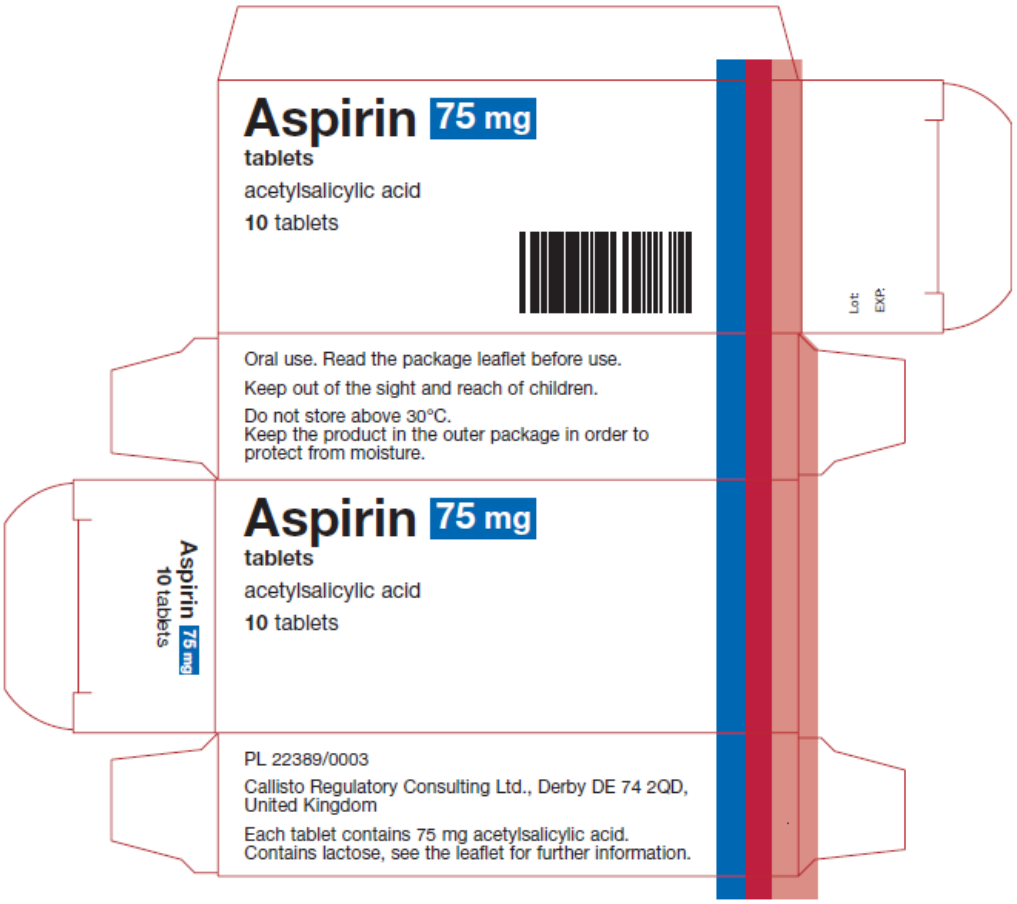

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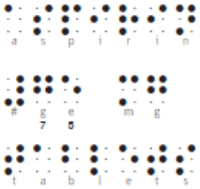

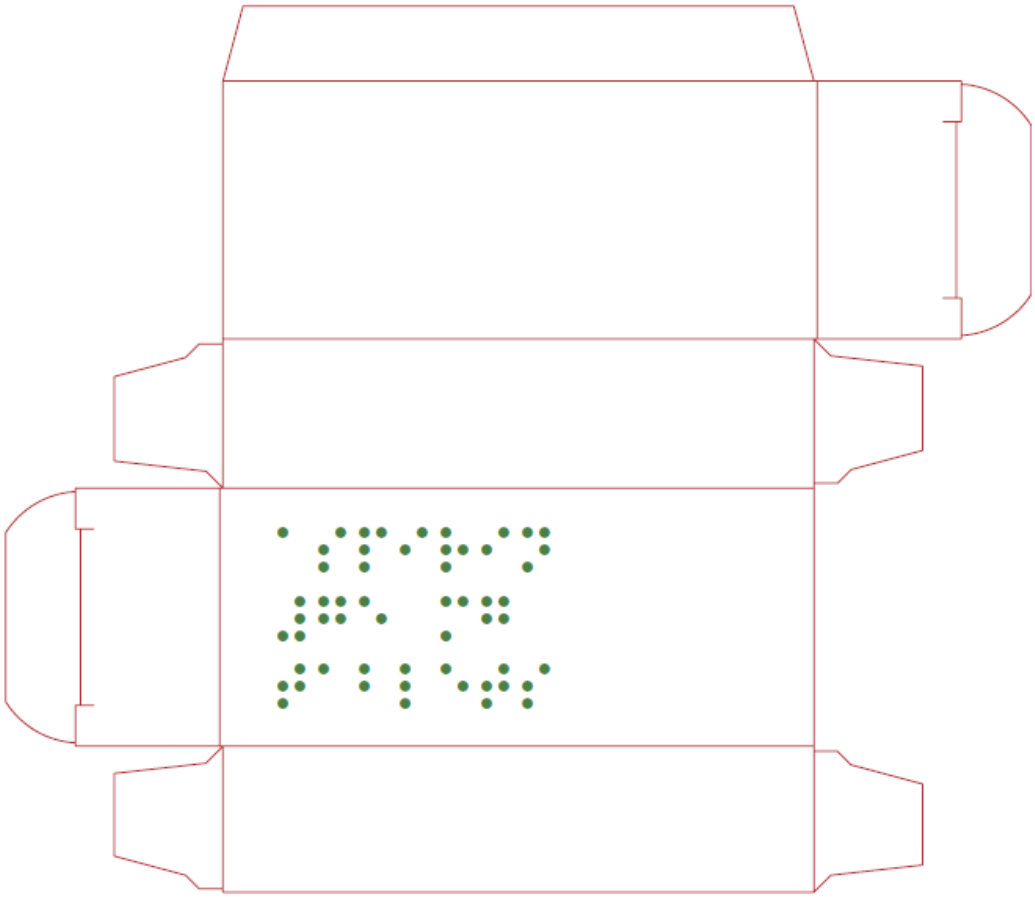

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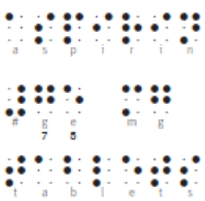

Annex 1

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)