Bundesamt für Sicherheit im Gesundheitswesen

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February 2014

Public Assessment Report

Scientific discussion

Aspirin + C forte 800 mg/480 mg Brausetabletten

Acetylsalicylic acid, Ascorbic acid

Date: 19.05.2015

This module reflects the scientific discussion for the approval of Aspirin + C forte 800 mg/480 mg Brausetabletten. The procedure was finalised at 22.12.2014. For information on changes after this date please refer to the module 'Update'.

Bundesamt für Sicherheit im Gesundheitswesen
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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Aspirin + C forte 800 mg/480 mg Brausetabletten, from Bayer Austria GmbH.
The product is indicated for*:* the symptomatic relief of mild to moderate pain, e.g. headache, toothache and menstrual pain. In common cold or flu-like symptoms for the symptomatic relief of pain and fever.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

Acetylsalicylic acid belongs to the group of acidic nonsteroidal anti-inflammatory drugs with analgesic, antipyretic and anti-inflammatory properties. Its mechanism of action is based on irreversible inhibition of cyclooxygenase enzymes involved in prostaglandin synthesis. Acetylsalicylic acid also inhibits platelet aggregation by blocking thromboxane A2 synthesis in platelets.
The water-soluble vitamin ascorbic acid is part of a protective system of the organism against oxygen radicals and other oxidants of endogenous and exogenous origin which also play a particular role in the inflammatory process and in leukocyte function.
Both in vitro and ex vivo experiments indicate that ascorbic acid has a positive effect on the leukocytic immune response in humans.
Ascorbic acid is essential for the synthesis of the intracellular basic substance (muco-polysaccharides) which, together with the collagen fibres, is responsible for sealing the capillary walls.

II. QUALITY ASPECTS

II.1 Introduction

Aspirin + C forte 800 mg/480 mg Brausetabletten is a effervescent tablet which is presented in strips of 4 layers (paper/PE/aluminium/ionomere).

II.2 Drug Substance

The active substances in Aspirin + C forte 800 mg/480 mg Brausetabletten are acetylsalicylic acid and ascorbic acid. The specification of the active substances meets the current scientific requirements. The adequate quality of the active substances has been shown by submitting the appropriate control data. The stability of the active substances has been tested under ICH conditions. The results of the stability studies support the established retest-period.

II.3 Medicinal Product

Aspirin + C forte 800 mg/480 mg Brausetabletten contains the following excipients:

- Sodium hydrogen carbonate (modified) - one effervescent tablet contains 473.72 (20.61 mmol) mg sodium
- Citric acid
- Povidone
- Colloidal anhydrous silica
-

The manufacturer responsible for batch release is Bayer Bitterfeld GmbH, Salegaster Chaussee 1, 06803 Bitterfeld-Wolfen, Germany.

The development of the product has been sufficiently made and deemed appropriate. The usage of all the excipients has been described.
The release specification includes the check of all parameters relevant to this pharmaceutical form. Appropriate data concerning the control of the finished product support the compliance with the release specifications.
The packaging of the medicinal product complies with the current legal requirements.
Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SmPC, with a shelf life of 24 months.

The pharmaceutical quality of Aspirin + C forte 800 mg/480 mg Brausetabletten has been adequately shown.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of active substance and medicinal product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of acetylsalicylic acid and ascorbic acid are well known. As acetylsalicylic acid and ascorbic acid are widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Aspirin + C forte 800 mg/480 mg Brausetabletten is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

The pharmacokinetic properties of acetylsalicylic acid and ascorbic acid are well established. To support the application, the applicant has submitted as report one bioequivalence study to compare the bioavailability of the applied effervescent tablet containing 800mg acetylsalicylic acid (ASA) plus 480mg ascorbic acid (AA) with two effervescent tablets containing 400mg ASA plus 240mg AA.

IV.2 Pharmacokinetics

Bioequivalence studies
An Open Label Crossover Pharmacokinetic Trial of Aspirin plus Vitamin C Extra Strength Effervescent Tablet versus Aspirin plus Vitamin C Effervescent Tablet in Healthy Adult Subjects

This was a single centre, randomised, open-label, two-treatment, two period, two-sequence crossover, single dose study, performed under fasting conditions.
The trial consisted of a Screening Period, a Supplementation Period, a Run-In Phase, two treatment periods with a Wash-Out/Run-In Phase in between and a Follow-Up examination.

The subjects were screened for eligibility during the Screening Period and upon satisfying the inclusion/exclusion criteria, eligible subjects were included in the supplementation period of 7 days. Subjects received 400mg ascorbic acid (AA) daily (200mg AA in the morning and evening together with meals, in addition to their normal diet) to ensure that all body pools were at approximately equivalent levels for all subjects prior to the Run-In Phase Period 1.

Subjects were confined to the study centre from the evening of the last day of the supplementation period until the end of PK sampling of the second treatment period.
During the In-house Phase, subjects maintained a diet with low AA content (<5mg AA per day).

During the Run-In Phase of Period 1 and 2, subjects received 200mg AA daily (100mg AA in the morning and evening together with meals).

A commercially available AA product was used for supplementation:

Treatment	AA Supplementation 100 mg	AA Supplementation 200mg
Dose	2 tablets / day	2 tablets / day
Pharmaceutical form	tablet	tablet
Strength	100 mg Ascorbic Acid	200 mg Ascorbic Acid
Batch number	010310	020310
Expiry date	03.2013	03.2013
Marketing authorization holder	medphano Arzneimittel GmbH Rüdersdorf bei Berlin	medphano Arzneimittel GmbH Rüdersdorf bei Berlin

At the end of the Run-In Phase subjects were randomized into one of the two treatment sequences. Each treatment sequence consisted of two treatment periods of 2 days each, with a single dose drug administration of the test product (one effervescent tablet of 800mg ASA plus 480mg AA) or the reference product (two effervescent tablets of 400mg ASA plus 240mg AA) in the morning of the first day of each period, administered with 240ml water (dissolution in 190ml water and rinsed afterwards with another 50ml of water).
Subjects had to be fasted for at least 10 hours prior to administration of the study drug and subsequently fasted for a period of at least 4 hours. Subjects were served controlled meals after 4 hours (lunch), 8 hours (snack) and 12 hours (dinner) postdose, in each period.
Subjects had to abstain from food and drinks which could interact with circulatory, gastrointestinal, hepatic, or renal function (e.g. alcoholic drinks, xanthine containing beverages and/or certain fruit juices such as grapefruit juice) and they had to abstain from any excessive physical activities.
Before and during each treatment phase, subjects were allowed to drink water as desired except for 1 hour before and 1 hour after administration; during this time, only the water accompanying administration was given.

Drug administration was followed by a 48-hours PK plasma sampling period. During the 48-hours PK sampling period the dietary intake of ascorbic acid (AA) was limited to the AA administered with the study drug only.
The two treatment periods were separated by a Wash-Out Period of 2 days which was also the Run-In Phase of the second treatment period.

The Follow-up was performed as an on-site visit within one week after completion of the second treatment period.

Test and reference products
One effervescent tablet of Aspirin plus C forte 800mg/480mg by Bayer Austria GmbH has been compared to two effervescent tablets of Aspirin plus C 400mg/240mg from the German market.

Statistical methods
Determination of Sample Size:
The following assumptions were made: µTest/µReference – 95%, CV = 20%, acceptance range for equivalence: 0.8 to 1.25
The data were log-transformed for analysis. With a significance level of 5% and a power of 90%, a sample size of 26 volunteers was needed for the study. The calculation of the sample size was performed with respect to 2x2 crossover design.

Pharmacokinetic parameters:
For ASA and AA, the assessment of bioequivalence was based upon the 90% confidence intervals for the ratio of the population geometric means (Test/Reference) for AUC0-t and Cmax. BE was to be concluded if the 90% confidence interval for the ratio of the test and reference product were within the acceptance range of 80.00% to 125.00%.
Corrected plasma concentrations of AA were used for the calculation of AA PK parameters.

AUC0-t and Cmax were analysed using ANOVA. The data were transformed prior to analysis using a logarithmic transformation. A confidence interval for the difference between formulations on the log-transformed scale is obtained from the ANOVA model. This confidence interval is then back-transformed to obtain the confidence intervalfor the ratio on the original scale.
The statistical methods were applied according to the "Bayer Global Operational Manual on non-compartmental analysis in pharmacokinetics".
For all PK parameters of interest, in addition summary statistics such as median, minimum and maximum were given.
Tmax was taken directly from plasma concentration time profiles. In case of two identical Cmax values, the first tmax was used.
The following statistics were calculated for each of the sampling time points: number of observations (n), arithmetic mean, standard deviation (SD) and coefficient of variation (CV), geometric mean, geometric SD, geometric CV, minimum, median and maximum.
Descriptive statistics at any point were only calculated if at least 2/3 of the individual data were measured and were quantifiable. For the calculation of descriptive statistics, a data point below the LLOQ was substituted by ½ of this limit.

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for acetylsalicylic acid (ASA)

Treatment	AUC_{0-t} µg/ml/h	$AUC_{0-\infty}$ µg/ml/h	C_{max} µg/ml	t_{max} h
Test (SD)	11.6 (1.22)	12.0 (1.21)	28.2 (1.29)	0.29 (0.21-0.46)
Reference	12.6 (1.20)	12.9 (1.20)	28.1 (1.29)	0.25 (0.12-0.58)
***Ratio (90% CI)**	92.48 (87.57-97.67)		100.15 (90.80-110.47)	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; geometic mean ± SD, t_{max} median, range) for the active metabolite salicylic acid (SA)

Treatment	AUC_{0-t} µg/ml/h	$AUC_{0-\infty}$ µg/ml/h	C_{max} µg/ml	t_{max} h
Test (SD)	276 (1.28)	285 (1.29)	50.8 (1.18)	0.50 (0.33-1.50)
Reference	257 (1.30)	264 (1.30)	50.8 (1.17)	0.58 (0.33-1.00)
***Ratio (90% CI)**	107.85 (105.29-110.47)		100.00 (96.42-103.71)	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed values*

Table 3. Pharmacokinetic parameters (non-transformed values; geometic mean ± SD, t_{max} median, range) for ascorbic acid (AA)

Treatment	AUC_{0-t} µg/ml/h	$AUC_{0-\infty}$ µg/ml/h	C_{max} µg/ml	t_{max} h
Test (SD)	123 (1.49)	138 (1.55)	13.4 (1.41)	2.5 (1.00-5.00)
Reference	123 (1.34)	137 (1.41)	12.2 (1.28)	2.5 (0.00-5.50)
***Ratio (90% CI)**	99.42 (89.02-111.02)		109.42 (99.50-120.34)	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed values*

Acetylsalicylic acid and salicylic acid:
No pre-dose concentrations of acetylsalicylic acid or salicylic acid were detected in period 1 or 2. The values were below the lower limit of quantification (BLLQ) for all subjects.
For ASA and SA, the extrapolated part of $AUC_{0-\infty}$ was smaller than 20% in all cases.

The presence of period, sequence, and treatment effects were evaluated. No significant treatment effect ($p<0.05$) was observed for C_{max} for acetylsalicylic acid or salicylic acid.
For AUC_{0-t}, a significant treatment effect was observed for ASA ($p = 0.0221$). The lower and upper limit of the CI was below 100% but within the lower limit of the acceptance range of 80.00.
For AUC_{0-t}, a significant treatment effect was observed for SA ($p < 0.0001$). The lower and upper limit of the CI was above 100% but within the upper limit of the acceptance range of 125.00.

Significant period or sequence effects were not observed.

Ascorbic acid:
Individual AA plasma levels were corrected by subtraction of the lowest AA plasma value of the concerned subject from all measured AA plasma values (corrected plasma concentration).
The presence of period, sequence, and treatment effects were evaluated. No significant treatment effect ($p<0.05$) was observed for C_{max} and AUC_{0-t}.
Significant period effects were observed for AUC_{0-t} AA.
Significant sequence effects were not observed.

The extrapolated part of $AUC_{0-\infty}$ of AA was larger than 20% for 3 subjects under the test treatment (including Subject No. 03 who was excluded from the pharmacokinetic population) and 5 subjects under the reference treatment.

The submitted pharmacokinetic study to compare the bioavailability of the applied effervescent tablet containing 800mg acetylsalicylic acid (ASA) plus 480mg ascorbic acid

(AA) with two effervescent tablets, each containing 400mg ASA plus 240mg AA, in order to assess bioequivalence is considered sufficient.

Conclusion on bioequivalence studies:
According to the SmPC of the originator product (Aspirin plus C), the drug should not be administered on an empty stomach. As this recommendation is due to safety reasons of gastrointestinal side effects and there is no indication that food influences the absorption of acetylsalicylic acid or ascorbic acid, the administration of the study drug under fasting conditions is considered adequate from a pharmacokinetic point of view.

Based on the submitted bioequivalence study Aspirin + C forte 800 mg/480 mg Brausetabletten is considered bioequivalent with two effervescent tablets of Aspirin plus C 400mg/240mg (reference product).

IV.3 Pharmacodynamics

Pharmacotherapeutic group: Analgesics, Other analgesics and antipyretics, Salicylic acid and derivatives, acetylsalicylic acid, combinations excl. psycholeptics
ATC code: N02BA51

Acetylsalicylic Acid (ASA)

Acetylsalicylic acid belongs to the group of acidic non-steroidal anti-inflammatory drugs with analgesic, antipyretic and anti-inflammatory properties. Its mechanism of action is based on irreversible inhibition of cyclooxygenase enzymes involved in prostaglandin synthesis.
Acetylsalicylic acid also inhibits platelet aggregation by blocking thromboxane A2 synthesis in platelets.

Ascorbic Acid (AA)

The water-soluble vitamin ascorbic acid is part of a protective system of the organism against oxygen radicals and other oxidants of endogenous and exogenous origin which also play a particular role in the inflammatory process and in leukocyte function.
Both in vitro and ex vivo experiments indicate that ascorbic acid has a positive effect on the leukocytic immune response in humans.
Ascorbic acid is essential for the synthesis of the intracellular basic substance (muco-polysaccharides) which, together with the collagen fibres, is responsible for sealing the capillary walls.

Combination of acetylsalicylic acid (ASA) and ascorbic acid (AA)

The addition of ascorbic acid to acetylsalicylic acid improves measures of gastrointestinal damage and oxidative stress. These benefits may result in an improved tolerability profile for the acetylsalicylic acid plus ascorbic acid product compared to acetylsalicylic acid alone.

IV.4 Clinical efficacy

In the bioequivalence study, the 90% confidence intervals for primary pharmacokinetic parameters AUC_0-t and C_{max} for acetylsalicylic acid, salicylic acid (as the main active metabolite) and ascorbic acid are within the acceptance range of 80.00 – 125.00% and the values for t_{max} (median and range) for acetylsalicylic acid and salicylic acid are comparable. Based on the submitted bioequivalence study one effervescent tablet of Aspirin + C forte is considered bioequivalent with two effervescent tablets of Aspirin + C.

IV.5 Clinical safety

Based on the presented data it can be concluded that test and reference product are clinically comparable in their safety profile.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan version 1.4 date of final sign off 25.06.14, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Aspirin + C forte 800 mg/480 mg Brausetabletten (Acetylsalicylic acid, Ascorbic acid)

- Summary table of safety concerns as approved in RMP version 1.4 date of final sign off 25.06.14

Important identified risks	-gastrointestinal toxicitiy/disorders -disturbance in renal function homeostasis in patients with renal, hepatic or cardiac insufficiency -bleeding -sensitivity reactions -hemolysis in patients with Glucose-6-Phosphate dehydrogenase deficiency -interaction with drugs highly bound to plasma proteins and drugs/other products with additive toxicity potential: >methotrexate,anticoagulants/thrombolytics/antiplatelets, digoxin, uricosuric agents, antidiabetic agents, ACE inhibitors, diuretics, selective serotonin re-uptake inhibitors, systemic glucocorticoids, valproic acid, other NSAIDs and alcohol -use in third trimester of pregnancy may expose > the foetus to cardiopulmonary toxicity (with premature

	closure of the ductus arteriosus and pulmonary hypertension) and renal dysfunction > the mother and child to * possible prolongation of bleeding time * an anti-aggregating effect which may occur even after very low doses *inhibition of uterine concentrations resulting in delayed or prolonged labour -risks associated with very high doses: >hyperoxaluria (particularly in patients with renal insufficiency) and hemolysis (in patients with Glucose-6-Phosphate dehydrogenase deficiency) >potential interaction with desferrioxamine

Important potential risks	-Reye's syndrome
Missing information	None

- Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP version 1.4 (date of final sign off 25.06.14)

Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
Important Identified Risks		
Gastrointestinal toxicity /disorders	Proposed text in SPC (for current Aspirin C and proposed for Aspirin plus C Forte) In section 4.2 of the SPC: •Acetylsalicylic acid plus ascorbic acid must notbe taken for more than 3 - 5days without consulting a physician. •A maximum daily dose of 4 grams acetylsalicylic acid must not be exceeded. In section contraindications: •Acute gastrointestinal ulcers In section Warning and precautions: •History of gastro-intestinal ulcers including chronic or recurrent ulcer	none

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	disease or history of gastro-intestinal bleedings In section interactions with other medicinal products: •Alcohol: Increased damage to gastro-intestinal mucosa and prolonged bleeding time due to additive effects of acetylsalicylic acid and alcohol. In section undesirable effects: •Upper and lower gastrointestinal tract disorders such as common signs and symptoms of dyspepsia, gastrointestinal and abdominal pain, rarely gastrointestinal inflammation, gastrointestinal ulcer, potentially but very rarely leading to gastrointestinal ulcer haemorrhage and perforation, with the respective laboratory and clinical signs and symptoms.	
Disturbance in renal function homeostasis in patients with renal, hepatic, or cardiac insufficiency	Proposed text in SPC for current Aspirin C and proposed for Aspirin plus C Forte) In section contraindications: •Severe renal failure •Severe hepatic failure •Severe cardiac failure In section warnings and precautions for use: •Patients patients with impaired renal function or patients with impaired cardiovascular circulation (e.g. renal vascular disease, congestive heart failure, volume depletion, major surgery, sepsis or major hemorrhagic events), since acetylsalicylic acid may further increase the risk of renal impairment and acute renal failure	none

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Bleeding	Proposed text in SPC for current Aspirin C and proposed for aspirin plus C Forte) In section 4.2 of the SPC: •Acetylsalicylic acid plus ascorbic acid must not be taken for more than 3 - 5days without consulting a physician. •A maximum daily dose of 4 grams acetylsalicylic acid must not be exceeded. In section contraindications: •Hemorrhagic diasthesis •Severe hepatic failure In section warning and precautions: •Concomitant treatment with anticoagulants •Due to its inhibitory effect on platelet aggregation which persists for several days after administration, acetylsalicylic acid may lead to an increased bleeding tendency during and after surgical operations (including minor surgeries, e.g. dental extractions). In section undesirable effects: •Due to its inhibitory effect on platelets, acetylsalicylic acid may be associated with an increased risk of bleeding. Bleedings, such as perioperative hemorrhage, hematomas, epistaxis, urogenital bleedings, gingival bleedings, have been observed. Rare to very rare serious bleedings, such as gastrointestinal tract hemorrhage, cerebral haemorrhage (especially in patients with uncontrolled hypertension and/or on concomitant anti hemostatic agents), which in	none

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	single cases may be potentially life-threatening, have been reported. •Hemorrhage may result in acute and chronic posthemorrhagic anemia/irondeficiency anemia (due to e.g. occult microbleeding) with respective laboratory and clinical signs and symptoms, such as asthenia, pallor, hypoperfusion.	
Sensitivity reactions	Proposed text in SPC for current Aspirin C and proposed for aspirin plus C Forte) In section contraindications: •Hypersensitivity to acetylsalicylic acid or other salicylates, ascorbic acid or to any other components of the product •A history of asthma induced by the administration of salicylates or substances with a similar action, notably non-steroidal anti-inflammatory drugs In section warnings and precautions for use: •Hypersensitivity to analgesics or anti-inflammatory agents / anti-rheumatic and in the presence of other allergies •Acetylsalicylic acid may precipitate bronchospasm and induce asthma attacks or other hypersensitivity reactions. Risk factors are pre-existing asthma, hay fever, nasal polyps, or chronic respiratory disease. This also applies to patients exhibiting allergic reactions (e.g. cutaneous reactions, itching, urticaria) to other substances. In section undesirable effects: •Hypersensitivity reactions with	none

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	respective laboratory and clinical manifestations include asthma syndrome, mild to moderate reactions potentially affecting skin, respiratory tract, gastrointestinal tract, and cardiovascular system, including symptoms such as rash, urticaria, edema, pruritus, rhinitis, nasal congestion, cardio-respiratory distress, and very rarely,severe reactions, including anaphylactic shock.	
Hemolysis in patients with Glucose-6-Phosphatase dehydrogenase deficiency	Proposed text in SPC (for current Aspirin C and proposed for aspirin plus C Forte) In section posology: •Acetylsalicylic acid plus ascorbic acid must not be taken for more than 3 – 5 days without consulting a physician. •A maximum daily dose of 4 grams acetylsalicylic acid must not be exceeded. In section warnings and precautions for use: •In patients suffering from severe glucose-6-phosphate dehydrogenase (G6PD) deficiency, acetylsalicylic acid may induce hemolysis or hemolytic anemia. Factors that may increase the risk of hemolysis are e.g. high dosage, fever or acute infections. In section undesirable effects: •Hemolysis and hemolytic anemia in patients with severe forms of glucose-6-phosphate dehydrogenase (G6PD) deficiency have been reported.	
Drug interactions	Proposed text in SPC (for current Aspirin C and proposed for aspirin	none

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	plus C Forte) In section contraindications: •Combination with methotrexate at doses of 15mg/week or more. In section Interactions with other medicinal products: Combinations requiring precautions for use: •Methotrexate, used at doses of less than 15 mg/week: Increased hematological toxicity of methotrexate (decreased renal clearance of methotrexate by anti-inflammatory agents in general and displacement of methotrexate from its plasma protein binding by salicylates). •Anticoagulants,thrombolytics/other inhibitors of platelet aggregation/hemostasis: Increased risk of bleeding. •Other nonsteroidal anti-inflammatory drugs with salicylates at higher doses Increased risk of ulcers and gastrointestinal bleeding due to synergistic effect. •Selective Serotonin Re-uptake Inhibitors (SSRis): Increased risk of upper gastrointestinal bleeding due to possibly synergistic effect • Digoxin: Plasma concentrations of digoxin are increased due to a decrease in renal excretion. •Antidiabetics, e.g. insulin, sulphonylureas: Increased hypoglycemic effect by high doses of acetylsalicylic acid via hypoglycemic action of acetylsalicylic acid and displacement of sulfonylurea from its plasma protein binding.	

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	• Diuretics in combination with acetylsalicylic acid at higher doses: Decreased glomerular filtration via decreased renal prostaglandin synthesis. •Systemic glucocorticoids, except hydrocortisone used as replacement therapy in Addison's disease: Decreased blood salicylate levels during corticosteroid treatment and risk of salicylate overdose after this treatment is stopped, via increased elimination of salicylates by corticosteroids. •Angiotensin converting enzyme inhibitors (ACE) in combination with acetylsalicylic acid at higher doses: Decreased glomerular filtration via inhibition of vasodilatory prostaglandins. Furthermore, decreased antihypertensive effect. •Valproic acid: Increased toxicity of valproic acid due to displacement from protein binding sites. • Alcohol: Increased damage to gastro-intestinal mucosa and prolonged bleeding time due to additive effects of acetylsalicylic acid and alcohol. •Uricosurics such as benzbromarone, probenecid: Decreased uricosuric effect (competition of renal tubular uric acid elimination). •Desferrioxamine: Concurrent use with ascorbic acid may enhance tissue iron toxicity, especially in the heart, causing cardiac decompensation	

The marketing authorization holder has agreed to undertake as a follow up measure (FUM number AT/H/0529/001/FU/001 $1A_{IN}$ variation with due date 22.05.2015) applied to RMP update of the current RMP version 1.4 (date of final sign off 25.06.2014) due to reason of RMPs harmonization within the same drug substance combinations or similar drug substance combinations.

IV.7 Discussion on the clinical aspects

The clinical overview on the clinical pharmacology, efficacy and safety is adequate with respect to the approved indications of the originator product in Austria and the bioequivalence has been shown.

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.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The pharmaceutical quality of Aspirin + C forte 800 mg/480 mg Brausetabletten has been adequately shown and no new non-clinical or clinical concerns have been identified.

Bundesamt für Sicherheit im Gesundheitswesen

Public Assessment Report

Update

Aspirin + C forte 800 mg/480 mg Brausetabletten

Acetylsalicylic acid, Ascorbic acid

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Bundesamt für Sicherheit im Gesundheitswesen
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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)