COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Acetylsalicylzuur Ratiopharm 500 mg, tablets (acetylsalicylic acid)

NL/H/5055/001/DC

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This module reflects the scientific discussion for the approval of Acetylsalicylzuur Ratiopharm 500 mg, tablets. The procedure was finalised on 17 November 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AE	Adverse event
ASA	Acetylsalicylic acid
ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CrCl	Creatinine clearance
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
NNTs	Numbers needed to treat
NSAID	Non-steroid anti-inflammatory drug
OR	Odds ratio
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Acetylsalicylzuur Ratiopharm 500 mg, tablets, from Ratiopharm GmbH.

Acetylsalicylzuur Ratiopharm 500 mg, tablets is indicated for symptomatic treatment for fever and/or mild to moderate pain. The product is indicated in adults and adolescents from 12 years of age.

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

Rationale

Clinical studies of acetylsalicylic acid in oral doses of in general 0.3 to 1.0 g have shown efficacy for the relief of pain, such as tension-type headache, migraine headache, dental pain, sore throat, primary dysmenorrhoea, muscular and joint pain, and in febrile conditions, such as colds or influenza, for the reduction of temperature. It is also used in acute and chronic inflammatory disorders such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.
Acetylsalicylic acid also inhibits platelet aggregation by blocking thromboxane A2 synthesis in platelets. Thus, it is used for various vascular indications at doses of in general 75 to 300 mg daily.

Legal base

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC, as acetylsalicylic acid in fever and/or mild to moderate pain has well-established clinical use with an acceptable level of safety and efficacy. For this type of application, applicants need to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least ten years in the specific therapeutic use. The results of non-clinical and clinical trials are replaced by detailed references to published scientific literature in which the efficacy and safety is thoroughly assessed. The MAH also submitted data showing that the bioavailability of Acetylsalicylzuur Ratiopharm is similar to the bioavailability of the product most commonly studied in the scientific literature.

II. QUALITY ASPECTS

II.1 Introduction

Acetylsalicylzuur Ratiopharm is a white, round, biconvex tablet with cross break score on one side. The tablet can be divided into equal halves. The cross break score is only to facilitate breaking for ease of swallowing and not to divide into equal quarters.

The tablet contains as active substance 500 mg acetylsalicylic acid (Ph.Eur.).

The tablets are packed in white opaque PVC foil/Aluminium foil blister packs.

The excipients are maize starch and powdered cellulose.

II.2 Drug Substance

The active substance is acetylsalicylic acid, an established active substance described in European Pharmacopoeia. The active substance is a crystalline powder and is slightly soluble in water, and freely soluble in ethanol. The active substance does not appear to exhibit polymorphism.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., and of the CEP. The MAH has discussed additional testing for microbial purity which has been included in the specification. A particle size test has been included in the drug product manufacturer's specification for the drug substance. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for three years when stored at a temperature not exceeding 25°C in low-density polyethylene bags kept in fibre drums or in polypropylene big bags. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. Critical process parameters

have been determined and are justified based on development and validation data. The MAH has provided a description of the characteristics of the drug substance and their effect on the drug product. Relevant information on the choice of the excipients and the drug product characteristics required for the intended use in children have been submitted as well.

Additional data has been provided for bridging the drug product at issue with those described in the literature references for this well-established use application. The MAH has shown similarity between acetyl salicylic acid products previously authorised on the European market with a similar composition to the drug product in this application. This is supported by the raw data submitted. The MAH has also submitted data from a bioequivalence study between a 500 mg ASA formulation of the MAH and a similar product already authorised on the European market. This study showed that the 500 mg ASA formulation was bioequivalent regarding the extent of absorption with the 'old' 500 mg acetyl salicylic products.

The MAH has also shown the suitability of the chosen dissolution method to be used for the same comparisons submitted. Based on the batches used for bridging of the test product to the literature reference product, and chosen as recommended in the relevant European guidance documents, the MAH has tightened the dissolution QC limit to Q = NLT 85% in 30 minutes.

Manufacturing process

The manufacturing process consists of mixing, homogenisation, compression, filling and packaging. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three industrial batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for identification, uniformity of dosage units, resistance to crushing, content, related substances, microbiological purity and dissolution. The release and shelf-life specification are identical except for the limit of resistance to crushing. The applicant has discussed the impurity profile for the drug product. This was supported by stress studies performed during validation of the analytical methods. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Elemental impurities have been assessed in a risk management exercise, with maximum values included in the risk assessment based on declarations of the suppliers. A nitrosamine risk evaluation concludes that there is no risk identified for the presence of nitrosamine impurities in the drug product. The MAH has submitted the validation of the specific

microbial tests used for the drug product to verify that the Ph.Eur. test methods (monographs 2.6.12 and 2.6.13) are suitable for use with the drug product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three commercial scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for two batches in accordance with applicable European guidelines demonstrating the stability of the product at 25°C/60% RH (36 months), at 30°C/65% RH (12 months) and at 40°C/75% RH (up to three months). The stability data show compliance with the limits for the drug specification at long-term and intermediate conditions. Significant changes were observed at intermediate conditions (change in 5% of the assay of its initial value) and out-of-specification results were observed for one impurity at accelerated conditions. On basis of the data submitted, a shelf life was granted of two years. The labelled storage conditions are: “Do not store above 25°C”, and “Store in the original package, in order to protect from moisture”.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Acetylsalicylzuur Ratiopharm has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

The non-clinical overview provided by the MAH provides a review on the pharmacology, pharmacokinetics and toxicology of acetylsalicylic acid, based on public literature. These data show that acetylsalicylic acid is a well-known NSAID with analgesic, antipyretic and anti-inflammatory properties. The review is adequate, therefore, additional non-clinical studies are not needed.

III.1 Pharmacology

The main action of acetylsalicylic acid is the inhibition of the prostaglandin synthesis [(PG)E2, PGF2a, PGD2, prostacyclin (PGI2), and thromboxane (TX)A2]. The mechanism of action is based on irreversible inactivation of cyclo-oxygenase 1 (COX-1) and cyclo-oxygenase 2 (COX-2) by acetylation of a specific serine moiety (Ser529 of COX-1 and Ser516 of COX-2) (Dovizio 2013). The analgesic and anti-inflammatory effects are due to COX-2 inhibition in inflamed tissues. Prostaglandins appear to sensitize pain receptors to other noxious substances such as histamine and bradykinin (Collier, 1969; Dovizio, 2013). By preventing the synthesis and release of prostaglandins in inflammation, acetylsalicylic acid may avert the sensitization of pain receptors. The antipyretic activity of ASA is due to its ability to interfere with the production of prostaglandin E2 in the brain by inhibition COX-2 endothelial cells lining the hypothalamic blood vessels (Collier, 1969; Botting 2003).

III.2 Pharmacokinetics

ASA is readily absorbed from the gastro-intestinal tract after oral administration. In dogs, cats and pigs, the half-life of absorption is about 0.6 hours. Absorption is slower in cattle (half-life of absorption about 2.9 hours after oral administration of doses between 20 and 100 mg/kg bodyweight) and in horses (EMA-CVMP 2003). The qualitative metabolism is similar in all animal species studied involving hydrolysis of the parent compound in plasma, liver and some other organs to salicylic acid followed by the formation of salicyluric acid, salicyluric glucuronide, salicyl ester glucuronide, salicyl phenol glucuronide, gentisic acid and gentisuric acid (EMA-CVMP 2003).

Salicylate is the active metabolite of ASA (Smith 1978). This is the mechanism by which ASA, which has only a short half-life *in vivo*, is able to reduce carrageenan-induced paw oedema in animals raised on a diet so that their tissues are markedly deficient in the normal precursors of prostaglandins (Bonta, 1977). It also explains why ASA and salicylate are equipotent in reducing the infiltration of leucocytes into inflammatory exudates since this effect is independent of an interaction with the prostaglandin synthetase system (Smith, 1975). Distribution of salicylate throughout most body fluids and tissues proceeds at a rapid rate after absorption. Tissues containing high concentrations of the drug are the kidney, liver, heart and lungs. Excretion of salicylates occurs principally via the kidney. After intravenous administration of sodium salicylate to goats, the excretion of parent compound and salicyluric acid amounted to 67.9% and 34.6% respectively (EMA-CVMP, 2003). After oral dosing the respective figures were 30.2% and 71.7%. In cattle intravenous treatment with sodium salicylate resulted in a lower excretion of parent compound (54%), but a higher fraction of salicylic acid (49.9%). The same pattern was found after oral administration. In both species almost 90% of the drug excreted as sodium salicylate was found in the urine (EMA-CVMP 2003).

III.3 Toxicology

III.3.1 Single-dose toxicity

Single-dose toxicity studies revealed LD50 values in mice and rats for ASA above 1000 mg/kg and ASA DL-lysine in the range of 2200 to 2600 mg/kg bodyweight by oral route (EMA-CVMP 2003).

The clinical signs of toxicity are non-specific: nausea, restlessness, seizures, coma, stimulation of respiration with respiratory alkalosis. In dogs and cats ASA toxicosis is usually characterized by depression, fever, hyperpnea, seizures, respiratory alkalosis, metabolic acidosis, coma, gastric irritation or ulceration, liver necrosis, or increased bleeding time. Ataxia and seizures may occur as a consequence of ASA intoxication, although the exact aetiology is unknown. Erosive gastritis has been seen after a single 325 mg dose in dogs (Khan, 2012).

III.3.2 Repeated-dose toxicity

Repeated-dose toxicity studies were provided in rats and dogs. In rats, equivalent doses of 0, 50, 150 and 500 mg/kg bodyweight of ASA were given daily as ASA DL-lysine and 500 mg/kg bodyweight as sodium ASA. The highest dose induced severe clinical abnormalities and mortality. No clinical signs were observed at 150 mg/kg bodyweight. Congestion, petechiae, haemorrhages, and punctiform lesions were observed in the stomach at 150 and 500 mg/kg bodyweight (EMA-CVMP 2003). Necropsy examination revealed a dose-related hepatomegaly, with no histological expression. Kidney weights were increased in males at all dose levels. A dose-related decrease in serum globulins was recorded. This effect was still significant at the lowest dose tested (50 mg/kg bodyweight) in females. In dogs, ASA DL-lysine was administered at doses of 0, 50, 150, 250 and 500 mg ASA equivalents/kg bodyweight/day for 3 months and sodium ASA was administered at doses of 0, 250 and 500 mg/kg bodyweight/day. The highest dose induced rapid mortality and all animals died within 2 to 7 days post treatment initiation. Doses of 150 and 250 mg/kg induced vomiting and mortality. Vomiting was still observed at the dose of 50 mg/kg but at a lower frequency. In this group (n=6) one dog presented gastric striae and two dogs presented focal atrophy of the mucosa with dedifferentiation of the epithelial lining and glandular epithelium. A slight decrease in the heart rate in all of the treated animals was recorded. Repeated doses of SA caused mainly gastrointestinal, renal and auditory toxicity (EMA-CVMP 2003).

III.3.3 Reproduction toxicity

Embryotoxicity and foeto-toxicity studies in dogs (days 15 to 21, days 23 to 30), mice (treatment period not stated) and rats (days 6 to 15) with doses of 500 to 1200 mg/kg bodyweight orally resulted in a high incidence of stillborns in dogs and a resorption in mice and rats. In rabbits 7 doses (150 mg/kg bodyweight) of ASA were administered prior to implantation. The animals showed reduced fertility and abnormal blastocysts. Doses of 40 mg/kg bodyweight given to pregnant Rhesus monkeys (days 25 to term) did not induce in an oral teratology study, rats were treated on days 6 to 15 of pregnancy with doses of 30, 90 and 180 mg sodium ASA/kg bodyweight (EMA-CVMP 2003). A significant dose-related reduction in foetal wright and significant increases in delayed ossification of the limbs and vertebrae were observed at 90 and 180 mg/kg bodyweight. In the 90 mg/kg bodyweight

group, one foetus had anophthalmia and another had generalised oedema together with malformed tail. 30% of the foetuses in the 180 mg/kg bodyweight group were malformed; the predominant malformation was craniorachischisis affecting 22.7% of the foetus in this group. The dose of 30 mg/kg bodyweight was without foetotoxicity or teratological effects. In rat *in vitro* studies (embryo mid-brain cells) level lower than 50 mcg/ml plasma did not provoke teratogenic effects (EMA-CVMP 2003).
In dogs no teratogenic nor embryotoxic effects were seen with doses of 100 mg ASA/kg bodyweight; by contrast maternal-toxicity, increase in the number of resorption and malformations (including cleft palate, micrognathia, anasarca, cardiovascular malformations and tail malformations) were observed with doses of 400 mg/kg bodyweight (EMA-CVMP 2003).

III.3.4 Genotoxicity

Negative results were obtained in five independent bacterial gene mutation assays in both the presence and absence of metabolic activation with sodium salicylate. In vitro DNA-repair tests in bacteria and in primary rat hepatocytes also gave negative results. ASA did not induce recessive lethal mutations in Drosophila melanogaster. Inconsistent results were obtained in *in vitro* metaphase analyses: positive results were obtained in fibroblast and lymphocyte cultures, but negative results were obtained in V79 cells both with and without metabolic activation (King, 1979; Kadotani, 1984; Oldham, 1986; Jasiewicz, 1987) Negative results were also obtained in a cell transformation assay in mouse embryo cells. Positive results were reported in an *in vitro* metaphase analysis in rat bone marrow. *In vivo* chromosomal aberration assays in rat embryos and *in vivo* micronucleus tests in bone marrow from rats and mice also gave negative results (EMA-CVMP, 2003).

III.3.5 Carcinogenicity

Animal studies showed no evidence of a carcinogenic effect. Studies have been performed on the potential of ASA to promote tumours initiated by other agents. The results of a study of the promotional activity of chemicals on tumours of the rat glandular stomach showed a lower incidence of hyperplasia and tumours of the glandular stomach and duodenal tumours in animals given ASA (1% in diet for 32 weeks) than in control animals .
Similarly, 0.05 and 1% ASA in the diet for 58 weeks did not increase the incidence of liver tumours in rats pre-treated with a potent initiator of liver cancer. In contrast, 0.5% ASA in the diet for 12 weeks after initiation with a potent inducer of bladder cancer caused an increased incidence of bladder carcinoma (EMA-CVMP, 2003).
An important role for COX-2 in colon tumorigenesis has been shown. Mice with a deletion of the adenomatous polyposis gene develop large numbers of colon polyps starting by 10 weeks of age. When these animals were bred to mice with a knockout of COX-2, the number of polyps was reduced by 90% showing that COX-2 expression is critical for polyp development. The size of the polyps in these mice was also markedly reduced to about 1/5th the size of polyps in control mice. In this study treatment of APC gene deleted mice with a tricyclic inhibiter specific for COX-2 also resulted in markedly reduced numbers of polyps (Oshima 1996).
On the other hand, evidences have shown that some NSAIDs, including ASA, are able to inhibit the proliferation and to induce apoptosis of colon cancer cells *in vitro* independently

from their inhibitory effect on COX-dependent prostanoid biosynthesis. some of the major molecular mechanisms affected by ASA which may play a role in its antiproliferative and pro-apototic effects: 1) the interruption of nuclear factor kappa B (NF-kB) signalling, 2) the interruption of extracellular signal-regulated kinases (ERK), 3) the induction of various apoptotic pathways, 4) the inhibition of Wnt/b-catenin signalling (Dovizio, 2013; Umar, 2016; Goodman, 2014; Wu, 2003).

III.4 Ecotoxicity/environmental risk assessment (ERA)

Acetylsalicylic acid is a well-known drug substance. Several medicinal products are already on the market containing acetylsalicylic acid as the active substance, at the same or similar strengths, and are registered for the same indication. Hence, an increase in use, and therefore in environmental exposure, is unlikely. The provided justification for the absence of an Environmental Risk Assessment is adequate.

III.5 Discussion on the non-clinical aspects

A comprehensive non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. These data show that acetylsalicylic acid is a well-known active substance with analgesic, antipyretic and anti-inflammatory properties. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Acetylsalicylic acid is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The bridge to literature is sufficiently supported and it can be considered that the efficacy and safety of the 500 mg active substance formulation is established based upon the literature data, as:

- Acetylsalicylic acid is a BCS Class I drug and the MAHs formulation does not contain critical excipients, so no concerns are expected regarding absorption of acetylsalicylic acid.
- The literature covered a broad range of type of ASA formulations and doses hampering identification of pivotal formulations for bridging, however, the bridge to literature by a acetylsalicylic acid product referred to in the literature is considered supported by showing comparable dissolution using the Quality Control (QC) method.
- *In vivo* bioequivalence data showed comparable bioavailability with regard to the acetylsalicylic acid product previously authorised on the European market.

Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Acetylsalicylic acid can be considered a BCS Class I drug, as it is highly permeable and highly soluble. Regarding solubility, at higher pH, i.e. especially at pH 6.8, during solubility experiments a pH shift can be expected due to the strong acidity level of ASA. It seems that this effect at lower doses is less pronounced. From a scientific point of view this phenomenon does not affect solubility and therefore ASA is a highly soluble drug.

IV.2.1 Absorption

After oral administration, acetylsalicylic acid is rapidly and completely absorbed from the gastrointestinal tract (Gatti 1989). Following oral administration of an aqueous solution, the absorption kinetics of ASA in man were found to follow a first-order process. In this study, 68% of the ASA dose reached the systemic circulation unhydrolysed, although there was wide variation in the absorption half-life (from 4.5 to 16 minutes). The remainder of the dose was considered to have been metabolised during passage from gastrointestinal fluids to the systemic circulation into its main active metabolite salicylic acid by esterases within the gut wall, plasma or liver (Rowland 1972).
The maximum plasma levels of acetylsalicylic acid and salicylic acid are reached after 10-20 minutes and 0.3-2 hours, respectively. Reference was made to Dressman et al (2012), that ASA products which meet the dissolution criteria of “rapidly dissolving” (≥85% release in 30 min) or “very rapidly dissolving” (≥85% release in 15 min)

IV.2.2 Distribution

Both acetylsalicylic acid and salicylic acid are extensively bound to plasma proteins and are rapidly distributed throughout the body (Needs, 1985). Reported values for the apparent volume of distribution (Vd) of salicylate range from 9.6 to 12.7 liter in adults (Graham, 1977), with similar values (0.12 to 0.14 l/kg) in children (Wilson, 1982).

Both ASA and salicylic acid are partially bound to serum proteins, primarily albumin. It has been suggested that the binding of salicylic acid to albumin occurs mainly at 2 primary, and a number of secondary binding sites. At therapeutic concentrations (1.1-2.2 mmol/l), salicylic acid is in molar excess compared with albumin such that binding is strongly dependent on both the salicylic acid and the albumin concentrations. The normal protein binding value of salicylic acid at therapeutic concentrations is 80 to 90%. As the plasma concentration increases, the non-protein bound (free) fraction increases. ASA has been shown to acetylate the minor group of the 199 lysine residue in the human serum albumin primary sequence and there is some evidence that this site is also shared by salicylic acid leading to a binding interaction between the two compounds. Protein acetylation is considered to be a major mechanism of action of ASA leading to inactivation of enzymes such as prostaglandin synthetase (Needs 1985, Ghahramani, 1998).

In saliva, the concentration of salicylic acid has been found to be proportional to the plasma concentration (Rowland, 1972). However, the concentration may vary with salivary pH at the site of production and it has been suggested that this method is unsuitable for routine salicylate concentration monitoring (Levy, 1980a; Levy, 1980b).
It has been shown that the protein binding of salicylic acid in synovial fluid is considerably lower than in plasma. Although the total salicylic acid concentration in synovial fluid is lower than that in plasma, this is likely to be explained by the lower albumin concentrations found in synovial fluid. ASA concentrations in synovial fluid are also significantly lower, but peak much later, than those concentrations seen in plasma, and ASA remains in the synovial fluid long after it has disappeared from the plasma (Soren, 1979).

Both salicylic acid and ASA have been found to diffuse slowly into the cerebrospinal fluid (CSF) due to the high degree of ionisation of salicylic acid at the pH (7.4) of plasma. The ratio of CSF to plasma salicylic acid is often less than would be predicted on the basis of pH changes alone. Plasma pH is the major factor determining salicylic acid concentrations in the CSF: the lower the plasma pH, the more salicylic acid enters (Needs, 1985).

Salicylic acid readily crosses the placenta, foetal plasma concentrations being higher at birth than concurrent maternal concentrations (Levy, 1975). Salicylate distributes readily into breast milk, and although after a single dose the amount ingested by a nursing infant is small, considerable exposure to salicylate is possible if the mother regularly ingests large doses (Findlay, 1981).

IV.2.3 Metabolism

ASA is rapidly converted to salicylic acid with a half-life of only 15 to 20 minutes. This hydrolysis is due to nonspecific esterases found in many body tissues. The acetyl component of ASA after oral and intravenous dosing is found in gastric mucosal cells or is excreted as carbon dioxide after passing through the Krebs cycle. During absorption, ASA esterase activity in the gastrointestinal mucosal membranes contributes 28 to 35% of the hydrolysis of ASA. This esterase activity is highest in the mucosal cells of the gastric fundus, though considerable age, sex and disease differences may exist in tissue esterase activities; for example, ASA esterase activity is reduced in patients with alcoholic liver disease. ASA is the dominant form of the drug in the plasma during the first 20 minutes after ingestion and can be detected for several minutes before there is any measurable salicylic acid. However, it then disappears from the blood rapidly and hence the ASA concentration is remarkably dependent on the rate of absorption. Diurnal variations in ASA pharmacokinetics have also been demonstrated.

IV.2.4 Excretion and elimination

Salicylic acid is eliminated predominantly by hepatic metabolism. Its metabolites are salicyluric acid, salicylic phenolic glucuronide, salicylacyl glucuronide, gentisic acid, and gentisuric acid (Wilson, 1978).
Salicylic acid is partly excreted unchanged and partly metabolised (see figure PK 2 in section Metabolism). Free salicylic acid diffuses readily across the glomerulus and is also actively secreted by the proximal tubule. The conjugates of salicylic acid are also renally excreted,

being dependent on glomerular filtration and tubular secretion. The hydroxylated metabolite gentisic acid is excreted in the same way as free salicylic acid (Needs, 1985).
The elimination kinetics of salicylic acid is dose-dependent, as metabolism (i.e. the formation of four metabolites) is saturable, limited by liver enzyme capacity (Needs, 1985). The elimination half-life therefore varies from 2 to 3 hours after low doses to up to about 15 hours at high doses.
Salicylic acid and its metabolites are excreted mainly via the kidneys. Renal excretion of salicylic acid occurs by first-order kinetics and is extremely sensitive to urinary pH, urinary organic acids and urinary flow rate. The effect of urinary pH on salicylate clearance is most marked at high salicylate concentrations but is still observable at low dosage. Antacid-induced changes in urinary pH will cause decreases in steady-state plasma salicylate concentration to occur. The renal excretion of salicylic acid is also reduced by probenecid, which competes for secretion in the proximal tubule (Needs, 1985).

IV.2.5 Effect of food

An open, randomised, four-way crossover study using a Williams Squares Design was used to compare the pharmacokinetics of three 900 mg soluble ASA tablets and two solid 1000 mg paracetamol tablets in both fed and fasted volunteers (N=16). The overall bioavailability of soluble ASA was unaffected by food and the bioavailability of salicylic acid was increased in the fed state, whereas that of solid paracetamol was lowered in the fed state. Greater inter-individual variation was seen in paracetamol concentrations compared with ASA or salicylic acid levels. These results showed that the absorption of soluble ASA was largely unaffected by food, whereas, in the same volunteers, the absorption of solid paracetamol tablets is greatly affected (Stillings et al., 2000).

IV.3 Pharmacodynamics

IV.3.1 Mechanism of action

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 cyclo-oxygenase enzymes involved in prostaglandin synthesis.

IV.3.2 Primary pharmacology

The mechanism of action of ASA was discovered by Vane and confirmed by others after about eighty years of medical use of the drug (Vane 1971; Ferreira 1972).

In 1971, there was already evidence suggesting that prostaglandine E1 (PGE1) was an extremely potent pyretic agent in several species and that PGE1 or PGE2 mimicked the inflammatory response when injected intradermally. Prostaglandines (PGs) had also been detected in inflammatory exudates, so there were grounds for speculating that PGs might be responsible, at least in part, for the genesis of fever or inflammation and that the „aspirin-like" drugs might owe their therapeutic activity to their ability to prevent PG biosynthesis. The concentrations of these drugs required to inhibit synthesis were within the plasma levels found during therapy, even when protein binding was taken into account.

Vane proved that ASA and other non-steroid anti-inflammatory drugs (NSAIDs) inhibit the activity of the enzyme later called cyclooxygenase (COX) which leads to the formation of prostaglandins that cause inflammation, swelling, pain and fever. However, by inhibiting this key enzyme in prostaglandin synthesis, the „aspirin-like" drugs also prevented the production of physiologically important prostaglandins which protect the stomach mucosa from damage by hydrochloric acid, maintain kidney function and aggregate platelets when required. This conclusion provided a unifying explanation for the therapeutic actions and shared side effects of the aspirin-like drugs. Twenty years later, with the discovery of a second COX gene, it became clear that there are two isoforms of the COX enzyme. The constitutive isoform, COX-1, supports the beneficial homeostatic functions, whereas the inducible isoform, COX-2, becomes upregulated by inflammatory mediators and its products cause many of the symptoms of inflammatory diseases such as rheumatoid and osteoarthritis (Vane 1971, Vane 2003).

The analgesic effect of ASA in humans has been assessed by experimental procedures, like experimental algesimetry. In a double blind, cross-over study with 12 subjects the effects of ASA (1000 and 1500 mg) vs. placebo on subjective pain induced by alternately applied 12 N (Newton) and 8 N stimuli was tested. During the sessions blood samples were taken in regular intervals to measure ASA and salicylate plasma levels. Both the 12 N and the 8 N ratings discriminated between placebo and ASA, however, only the ratings obtained from the stronger stimuli discriminated between two doses of ASA. Significant (negative) correlations of pain ratings and salicylate plasma levels were found for the high dose of ASA, but there were no significant correlations of ASA levels and ratings (Forster, 1988).

IV.3.3 Pharmacodynamic interactions with other medicinal products or substances

Interactions between acetylsalicylic acid with diclofenac, flurbiprofen, ibuprofen, isoxicam, ketoprofen, naproxen, phenytoin and tolmetin, valproic acid and zomepirac, benzoic acid, salicylamide, m-xylene, zomepirac and possibly cimetidine, oral contraceptive steroids and corticosteroids, acetazolamide and methotrexate, indomethacin and antacids are described.

In addition, substances due to their platelet aggregation inhibitory properties are involved in interactions: abciximab, acetylsalicylic acid, cilostazol, clopidogrel, epoprostenol, eptifibatide, iloprost, iloprost trometamol, prasugrel, ticlopidine, tirofiban, ticagrelor.

In the submitted clinical overview, contraindicated combinations, combinations that are not recommended, and combinations requiring precautions for use and combinations to be taken into account are discussed. These are included in the SmPC.

IV.4 Clinical efficacy

IV.4.1 Headache

Reference is made to nine double blind, randomised, placebo-controlled single-dose studies conducted between 1964 and 2012 (Lipton, 2005; Steiner, 2003; Gatoulis, 2012; Murray, 1964; Ryan, 1977; Graffenried 1980a and 1980b; Diamond, 1983; Peters, 1983; Martinez-

Martin, 2001). The studies had assay sensitivity because the active substances separated from placebo, in a dose dependent way. Efficacy of ASA in reduction of headache was better than placebo and less rescue medication was needed compared to placebo. From the studies by Steiner (2003), Murray (1964) and Graffenried (1980a,b) a dose-response was observed. The minimum effective dose appears to be 250 mg. The efficacy of ASA was comparable to other active treatments; paracetamol (+codeine), ibuprofen or metamizol.

IV.4.2 Acute migraine headaches

The use of ASA in the treatment of migraine is established. The European Federation of Neurological Societies (EFNS) recommends a dose of 1000mg ASA as a treatment of acute migraine attacks (Evers et al., 2009). This dose is also found to be efficacious in a Cochrane review that aimed to determine the efficacy and tolerability of a single oral dose of ASA, alone or in combination with an antiemetic, compared with placebo and other active treatments in the treatment of acute migraine headaches in adults (Kirthi 2013a; Kirthi 2013b).

IV.4.3 Dental pain/oral surgery

Reference is made to six double blind, randomised, placebo-controlled studies conducted between 1986 and 2012 (Gatoulis, 2012; Forbes, 1990; Forbes, 1991; Forbes, 1992; Or, 1988; Gaston, 1986). Some studies also included an active comparator: paracetamol (+codeine), ibuprofen, mefenamic acid or etodolac. The dose of ASA given were single doses of 650 mg and 1000 mg.

The studies had assay sensitivity because the active substances separated from placebo. Efficacy of ASA in treatment of dental pain/after oral surgery was better than placebo. The analgesic efficacy of ASA in dental pain is supported by an early review on ASA in postoperative dental pain (Seymour 1984) and a recent meta-analysis conducted for oral ASA in postoperative pain (Edwards 1999). The efficacy of ASA was comparable to paracetamol (+codeine) and mafenamic acid, a NSAID (not authorised in The Netherlands). In the studies, ibuprofen and etodolac were found to be superior compared to ASA.

IV.4.4 Sore throat/common cold and fever

Reference is made to five double blind, randomised, placebo-controlled studies, conducted between 1986 and 2005 (Eccles, 2003; Schachtel, 1991; Bachert, 2005; Broggini, 1986; Bettini, 1986). The studies by Eccles (2003) and Schachtel (1991) were in patients with sore throat. The treatment arms were placebo or ASA 800 mg, with or without 64 mg caffeine. The studies had assay sensitivity because the active substances separated from placebo. ASA was found to be more efficacious than placebo. The other studies investigated ASA versus active treatments (Broggini, 1986 and Bettini, 1986) + placebo (Bachert, 2005). Assay sensitivity was shown in these studies. Efficacy of ASA in treatment of fever was better than placebo and comparable to paracetamol, flurbiprofen and diclofenac. For ASA and paracetamol dose-response relations were observed (Bachert, 2005).

IV.4.5 Menstruation pain

The efficacy of ASA in menstruation pain is documented in placebo-controlled studies (Klein, 1981; Pendergrass, 1985) and in two meta- analyses (Zhang, 1998; Laska, 1982) involving a total of more than 2000 patients.

The study by Klein (1981) had a double-blind, placebo-controlled crossover design. Of the 47 subjects initially enrolled, 29 completed two or four months of participation in the study. The number of women that completed the four months study is not described. Albeit the results in pain relief were statistical significant greater in ASA compared to placebo, the clinical relevance of 1.5 point difference on the Menstruation Distress Questionnaire, containing 47 items, is questioned.

In the study by Pendergrass (1985), ASA and paracetamol were found to be as effective in reducing pain of cramps. Both drugs were more efficacious than placebo. In addition, it was found that ASA did not exert a fibrinolytic effect promoting bleeding either during the period as a whole or during any of the first three days of menses. Which is reassuring given the inhibiting platelet aggregation properties of ASA. Nevertheless, in the SmPC patients with metrorrhagia or menorrhagia are included in section 4.4. This is supported.

The meta-analyse by Zhang (1998) is not discussed as it provides no relevant efficacy data of ASA in symptomatic treatment of menstrual pain. This analysis concerns mainly postpartum patients and some patients with other gynaecological or obstetrical postoperative pain.

IV.4.6 Backpain

Evans et al. (1980) conducted a crossover trail and one of the treatments was ASA 3600 mg/day (3qds300mg). Compared to 32.5 mg dextro- 2 tablets 260 mg dextropropoxyphene plus 325 mg paracetamol 2q.d.s., ASA was preferred. The number of adverse events was relatively high compared with the other treatments and concerned mainly gastro-intestinal and neurological side effects.

A meta-analysis by Koes (1997) includes four studies including ASA as single treatment or in combination with other medicines. Results for efficacy of ASA in the treatment of low back pain are inconclusive. The main conclusion of this meta-analysis is that there are flaws in the design of most the 26 studies. The results of the 26 randomised trials that have been carried out to date, suggest that NSAIDs might be effective for short- term symptomatic relief in patients with uncomplicated low back pain. ASA is not considered appropriate for long-term treatment considering its risk of gastrointestinal events.

IV.4.7 Muscular and joint pain/minor arthritis pain

Little literature on the treatment of muscular, joint and minor arthritis pain with ASA specific is available.

IV.5 Clinical safety

In this section on Clinical safety, the undesirable effects of ASA are described. This section also includes discussions regarding fertility, pregnancy and lactation, extensive discussion on interactions, contraindications and warnings and overdose. To improve readability this public assessment report will reflect the most important information provided by the MAH.

IV.5.1 Adverse events

Reference is made to the PAIN study, a randomised double-blind trial of paracetamol, ASA or ibuprofen for common pain in general practice. 8633 included patients provided data, of which 2890 used ASA. ASA had the poorest tolerability: respectively 25.9%, 18.7% and 10.6% of the patients had at least one adverse event for respectively all adverse events (AEs), serious AEs and gastrointestinal serious AEs, compared to paracetamol (21.4, 14.5 and 7.3%) and ibuprofen (19.5, 13.7 and 5.8%, respectively). This study showed that the ASA treatment had an odds ratio (OR) of 1.4; (1.2–1.6) for serious AEs compared to paracetamol, whereas ibuprofen treatment had an OR of 0.9; (0.8–1.1). The main risk factors identified for AEs of firstline OTC analgesics for common pain were the number and nature of concomitant medication. It should be noted that this study was designed and powered to study tolerability: it was not designed to study gastrointestinal bleeding, perforations or ulcers, nor serious AE (Moore et al., 2003).

IV.5.2 Undesirable effects of ASA

The following adverse events, as included in the SmPC, are provided with a short discussion and literature references, no frequency can be estimated:

Respiratory, thoracic and mediastinal disorders

- Bleeding and haemorrhagic tendency
- Hypersensitivity reactions, anaphylactic reactions, asthma, angioedema
- Headache, dizziness, sensation of hearing loss, tinnitus (as indication of an overdose)
- Intracranial haemorrhage
- Rhinitis, dyspnoea, bronchospasm
- Dyspepsia, nausea, vomiting abdominal pain
- Occult or patent gastrointestinal haemorrhage (hematemesis, melena, etc.) resulting in iron-deficiency anaemia
- Gastric ulcers and perforations
- Elevation of hepatic enzyme mainly reversible when the treatment is stopped, liver injury, mainly hepatocellular
- Urticaria, skin reactions
- Reye syndrome
- Impaired renal function

IV.5.3 Safety in special populations

No specific discussion on safety in special populations is provided by the MAH. Elderly are discussed in the view of increased risk of gastrointestinal bleeding or ulcers/perforations, concomitant heparin use -which should be avoided- and the risk of overdose. In the SmPC,

the warnings and precautions are sufficiently described. The discussion on fertility, pregnancy and lactation is adequate.

IV.5.4 Immunological events

ASA-exacerbated diseases are important examples of drug hypersensitivities and include ASA-exacerbated respiratory disease (AERD), ASA- or non-steroidal anti-inflammatory drug (NSAID)-induced urticaria/angioedema, and ASA- or NSAID-induced anaphylaxis. While each disease subtype may be distinguished by unique clinical features, the underlying mechanisms that contribute to these phenotypes are not fully understood. However, the inhibition of the cyclooxygenase-1 enzyme is thought to play a significant role. Additionally, eosinophils, mast cells, and their products, prostaglandins and leukotrienes, have been identified in the pathogenesis of AERD (Stevens 2015).

IV.5.5 Safety related to drug-drug interactions and other interactions

A general introduction on ASA and drug interactions is provided by the MAH. Interactions accompanied by literature (references) are discussed in the following order: contraindicated combinations, combinations not recommended, combinations requiring precautions for use and combinations to be taken into account. This is considered sufficient.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, 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 Acetylsalicylic acid Ratiopharm.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

For this well-established use application, reference was made to clinical studies and experience with the active substance acetylsalicylic acid. No new clinical studies were conducted. The MAH presented an adequate literature overview of ASA pharmacokinetics, pharmacodynamics, clinical efficacy and clinical safety. The Clinical overview discussed published studies from 1962 to 2019. The beneficial effect of ASA in the symptomatic treatment of mild-moderate pain and fever is considered established. The bridging to literature data is considered sufficient.

The safety profile of acetylsalicylic acid is well known. The most common adverse events are typical gastrointestinal adverse events. Gastrointestinal adverse events are well documented and warnings regarding potential adverse events are adequately reflected in the proposed SmPC.

V. USER CONSULTATION

The package leaflet (PL) 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 PL was English. The test consisted of: a pilot test with two participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Acetylsalicylzuur Ratiopharm is a well-established use medical product and has a proven chemical-pharmaceutical quality. ASA is an effective drug, which is considered widely established. The benefit/risk balance is considered positive.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that well-established use has been demonstrated for Acetylsalicylzuur Ratiopharm with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 November 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

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