Safeguarding public health

MHRA

Public Assessment Report

Mutual Recognition Procedure

BAYER ASPIRIN COMPLEX 500MG/30MG GRANULES FOR ORAL SUSPENSION

UK/H/0509/001/E01
UK MA no: PL 00010/0280

Bayer Plc

BAYER ASPIRIN COMPLEX 500MG/30MG GRANULES FOR ORAL SUSPENSION

LAY SUMMARY

On 6th May 2008, Bulgaria, Czech Republic, Hungary, Poland, Slovakia and Slovenia granted Bayer Plc a Marketing Authorisation (licence) for the medicinal product Bayer Aspirin Complex 500mg/30mg Granules for Oral Suspension. This is available for the treatment of symptoms of nasal congestion, and cold-related pain and fever.

The product contains the active ingredients acetylsalicylic acid (aspirin) and pseudoephedrine hydrochloride, which have pain-relieving, anti-inflammatory, fever-reducing and nasal decongestant properties.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Bayer Aspirin Complex 500mg/30mg Granules for Oral Suspension outweigh the risks, hence Marketing Authorisations have been granted.

The licence was subsequently cancelled in the UK on 13th January 2009.

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Module 1

Product Name	Bayer Aspirin Complex 500mg/30mg Granules for Oral Suspension
Type of Application	Fixed combination, Article 10b
Active Substance	Acetylsalicylic acid (aspirin) Pseudoephedrine hydrochloride
Form	Granules for Oral Suspension 500mg/30mg
Strength	500mg acetylsalicylic acid and 30mg pseudoephedrine hydrochloride
MA Holder	Bayer plc, Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA
RMS	UK
CMS	Bulgaria, Czech Republic, Hungary, Poland, Slovakia and Slovenia
Procedure Number	UK/H/0509/001/E01
Timetable	Day 90: 6th May 2008

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

BAYER ASPIRIN COMPLEX
500 mg / 30 mg Granules for Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 500 mg acetylsalicylic acid and
30 mg pseudoephedrine hydrochloride

For a full list of excipients, see 6.1

3 PHARMACEUTICAL FORM

Granules for oral suspension
White granules

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of nasal congestion with cold-related pain and fever

4.2 Posology and method of administration

ASPIRIN COMPLEX is not recommended for use in children aged under 16 years, unless on the advice of a doctor. Due to limited experience with ASPIRIN COMPLEX in adolescents a specified dose recommendation can not be given.

Where one of the symptoms predominate, treatment with mono therapy is more appropriate.

ASPIRIN COMPLEX must not be taken for more than 3 days without consulting a physician.

Adults: The contents of 1-2 sachets.
If necessary, the single dose may be repeated at intervals of 4-8 hours. A maximum daily dose of 6 sachets must not be exceeded.

ASPIRIN COMPLEX must be suspended in a glass of water before taking.

4.3 Contraindications

Hypersensitivity to pseudoephedrine, to acetylsalicylic acid or other salicylates, or to any of the excipients.

- Gastric or duodenal ulcers;
- Haemorrhagic diathesis;
- Pregnancy;
- Breastfeeding;
- Severe hepatic failure;
- Severe renal failure;
- Severe uncontrolled cardiac failure;
- Combination with methotrexate at doses of 15 mg/week or more;
- Severe hypertension;
- Severe coronary artery disease;
- Concomitant intake of monoamine oxidase inhibitor drugs.

4.4 Special warnings and precautions for use

- Concomitant treatment with anticoagulants;
- History of gastro-intestinal ulcers or history of gastro-intestinal bleedings;
- Impaired renal function;
- Impaired hepatic function;
- Hypersensitivity to anti-inflammatory or antirheumatic drugs or other allergens;
- Hyperthyroidism, mild to moderate hypertension, diabetes mellitus, ischemic heart disease, elevated intraocular pressure, prostatic hypertrophy, or sensitivity to sympathomimetic agents;
- Elderly patients may be particularly sensitive to central nervous system effects of pseudoephedrine.

There is a possible association between acetylsalicylic acid and Reye's Syndrome when administered to children with a fever. For this reason, do not give ASPIRIN Complex to children aged under 16 years, unless on the advice of a doctor.

Acetylsalicylic acid may precipitate bronchospasm and induce asthma attacks or other hypersensitivity reactions. Risk factors are present bronchial asthma, hay fever, nasal polyps, or chronic respiratory disease. This applies also for patients showing allergic reactions (e.g. cutaneous reactions, itching, urticaria) to other substances.

Due to its inhibitory effect on platelet aggregation acetylsalicylic acid may lead to an increased bleeding tendency during and after surgical operations (including minor surgeries, e.g. dental extractions).

At low doses, acetylsalicylic acid reduces the excretion of uric acid. This can trigger gout in patients who already tend to have a low uric acid excretion.

Habitual use of analgesics (particularly combinations of different analgesic drugs) may permanently damage the kidneys (analgesic nephropathy).

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Contains 2 g of sucrose per sachet. This should be taken into account in patients with diabetes mellitus.

4.5 Interaction with other medicinal products and other forms of interaction

Acetylsalicylic acid can enhance/increase:
- the action of anticoagulants,
- the action of platelet aggregation inhibitors (e.g. ticlopidine),
- the risk of gastrointestinal bleeding when taken simultaneously with systemic corticoids or alcohol,
- the plasma concentrations of digoxin,
- the effects and adverse effects of non-steroidal anti-inflammatory drugs,
- the effects of antidiabetics,
- the effects and adverse effects of methotrexate,
- the effect of valproic acid.

Pseudoephedrine can enhance/increase:
- the effects of albuterol tablets (exacerbation of cardiovascular adverse effects); this does not preclude the judicious use of an aerosol bronchodilator of the adrenergic stimulant type,
- the effects of antidepressants including MAO-inhibitors,
- the effects of other sympathomimetic drugs (including local nasal decongestants) .

Acetylsalicylic acid can reduce the effects of:
- aldosterone antagonists and loop diuretics,
- antihypertensives,
- uricosurics.

Pseudoephedrine can reduce the effects of:
- antihypertensive drugs like guanethidine, methyldopa, β-blockers.

4.6 Pregnancy and lactation

Pregnancy

Considering that no data are available on the combination of the two substances, ASPIRIN Complex is contraindicated in pregnancy.

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, acetyl

salicylic acid should not be given unless clearly necessary. If acetylsalicylic acid is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

the mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

The limited data on pseudoephedrine in pregnancy does not show evidence for an increased risk for malformations. Nevertheless, pseudoephedrine should not be taken during pregnancy.

In animal studies both active substances have shown reproductive toxicity (see section 5.3).

Fertility
There is some evidence that drugs which inhibit prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

Lactation
Both salicylates and pseudoephedrine pass into breast milk in small quantities. Since no data is available on the combination of the two substances, ASPIRIN Complex is contraindicated in breastfeeding women.

4.7 Effects on ability to drive and use machines
During treatment with ASPIRIN COMPLEX the ability to react may be impaired. The risk may be further increased due to concomitant intake of alcohol. This should be taken into consideration when increased attention is required, e.g. during car driving.

4.8 Undesirable effects
Possible side-effects of acetylsalicylic acid are:

Immune system disorders

Hypersensitivity reactions (dyspnoea, anaphylaxis, cutaneous reactions), especially in asthmatic patients.

Gastrointestinal disorders

Gastroduodenal complaints (gastralgia, dyspepsia, gastritis);
Nausea, vomiting, diarrhoea;
Gastro-intestinal bleeding (haematemesis, melaena, erosive gastritis), which can lead to iron deficiency anaemia in isolated cases;
Gastro-intestinal ulcers, which can lead to perforation in isolated cases.

Hepatobiliary Disorders

Increase of transaminases.

Blood and lymphatic system disorders

Increase of the risk of bleeding.

Nervous system disorders and ear and labyrinth disorders

Dizziness and tinnitus may be a symptom of overdose.

Possible side-effects of pseudoephedrine are:

Vascular disorders

Increase in blood pressure, although not in controlled hypertension.

Cardiac Disorders

Cardiac effects (e.g. tachycardia).

Nervous system disorders
Central nervous system stimulation (e.g. insomnia, rarely hallucinations).

Renal and urinary disorders
Urinary retention, especially in patients with prostate hyperplasia.

Skin and subcutaneous tissue disorders
Effects on the skin (e.g. rash, urticaria, pruritus).

4.9 Overdose

Acetylsalicylic acid:
There is a difference between chronic overdose with predominantly central nervous disturbances ("salicylism") and acute intoxication, the main feature of which is a severe disturbance of the acid-base equilibrium.

In addition to disturbances of the acid-base equilibrium and the electrolyte balance (e.g. potassium loss), hypoglycaemia, skin eruptions, and gastrointestinal haemorrhage, the symptoms can include hyperventilation, tinnitus, nausea, vomiting, impairment of vision and hearing, headache, dizziness and confusion.

In severe intoxication delirium, tremor, dyspnoea, sweating, dehydration, hyperthermia and coma can occur. In intoxications with lethal outcome, death usually occurs through respiratory failure.

Pseudoephedrine:
Exaggerated sympathomimetic reactions may occur following intoxication e.g. tachycardia, chest pain, agitation, hypertension, wheezing or shortness of breath, convulsions, hallucinations.

The methods used to treat intoxication with ASPIRIN COMPLEX depend on the extent, stage and clinical symptoms of the intoxication. They correspond to the usual measures for reducing absorption of an active ingredient: acceleration of excretion, monitoring of the water and electrolyte balance, disturbed temperature regulation, respiration, and cardiovascular and cerebral function. Prompt medical attention is critical even if there are no signs or symptoms noticeable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nervous system, Other analgesics and antipyretics - Acetylsalicylic acid
ATC-Code: N02B A01

Pharmacotherapeutic group: Respiratory system, Decongestants for systemic use – Sympatomimetics - Pseudoephedrine
ATC-Code: R01B A02

Acetylsalicylic acid belongs to the group of acidic non-steroidal analgesics/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.

Acetylsalicylic acid also inhibits platelet aggregation by blocking thromboxane A2 synthesis in platelets.

Pseudoephedrine is a sympathomimetic agent with alpha-agonistic activity. It is the dextroisomer of ephedrine, both agents are equally effective as nasal decongestants. They stimulate alpha-adrenergic receptors of vascular smooth muscle, thus constricting dilated arterioles within the nasal mucosa and reducing blood flow to the engorged area.

5.2 Pharmacokinetic properties

Acetylsalicylic acid:
Following oral administration, acetylsalicylic acid is absorbed rapidly and completely from the gastrointestinal tract. During and after absorption acetylsalicylic acid is converted into its main metabolite salicylic acid. Maximal plasma levels are reached after 5 - 20 minutes for acetylsalicylic acid and after 0.4 – 1.5 hours for salicylic acid, respectively.

Both acetylsalicylic acid and salicylic acid are extensively bound to plasma proteins and rapidly distributed to all body parts. Salicylic acid appears in breast milk and crosses the placenta.

Salicylic acid is mainly eliminated by hepatic metabolism; metabolites include salicyluric acid, salicyl phenolic glucuronide, salicyl acyl glucuronide, gentisic acid and gentisuric acid.

The elimination kinetics of salicylic acid is dose-dependent, as the metabolism is limited by the capacity of liver enzymes. Thus, the elimination half-life varies between 2 to 3 hours after low doses to about 15 hours at high doses. Salicylic acid and its metabolites are excreted mainly via the kidneys.

Pseudoephedrine:
The drug is absorbed rapidly. Maximum plasma levels are reached after 20 to 120 minutes. The volume of distribution is 2 to 3.3 L. Approximately 70% to 90% of the drug is excreted unchanged in the urine. The liver is the primary site of metabolism, norpseudoephedrine is the primary active metabolite. This compound is excreted in the urine as about 1% of the pseudoephedrine dose in normal subjects but may account for about 6% of the administered dose in patients with chronically alkaline urine. Pseudoephedrine is excreted into human breast milk.

The half-life of the drug is 5 to 6 hours at a urine pH 5 to 6. However, the half-life of the drug is dependent upon the pH of the urine: a value of 50 hours was reported for a patient with persistent alkaline urine and 1.5 hours were reported in a patient with very acidic urine.

Conventional haemodialysis is only minimally effective at removal of pseudoephedrine.

5.3 Preclinical safety data

The preclinical safety profile of acetylsalicylic acid is well documented. In animal tests salicylates caused kidney damage and gastrointestinal ulcers. Acetylsalicylic acid has been adequately tested for mutagenicity and carcinogenicity; no relevant evidence of a mutagenic or carcinogenic potential was found.

Salicylates have been found to have teratogenic effects in a number of animal species. There have been reports of implantation disturbances, embryotoxic and fetotoxic effects, and disturbances of learning capacity in the offspring after prenatal exposure.

Pseudoephedrine is a nasal decongestant with long-term marketing experience in humans. There is no evidence that pseudoephedrine has a mutagenic potential. At a maternally toxic dose, pseudoephedrine induced foetotoxicity (reduced foetal weight and delayed ossification) in rats. Fertility studies or peri-postnatal studies have not been performed for pseudoephedrine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric Acid Anhydrous
Sucrose
Hypromellose
Saccharin
Orange Flavour including benzyl alcohol, alpha tocopherol, modified starch E1450 and maltodextrin

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

5 x 2 and 10 x 2 Sachets (Paper / Aluminium / Polyethylene) packed into cardboard outers.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

Bayer plc
Bayer House
Strawberry Hill
Newbury, Berkshire
RG14 1JA
Trading as Bayer plc, Consumer Care Division

8 MARKETING AUTHORISATION NUMBER(S)

PL 0010/0280

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26.11.2001
Date of last authorisation: 16.11.2006

10 DATE OF REVISION OF THE TEXT

December 2006

Module 3
Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

ASPIRIN COMPLEX

Granules for Oral Suspension

Acetylsalicylic Acid 500 mg, Pseudoephedrine Hydrochloride 30 mg

Read all of this leaflet carefully because it contains important information for you.
This medicine is available without prescription. However, you still need to use ASPIRIN Complex Granules carefully to get the best results from it.

- Keep this leaflet, you may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must contact a doctor if your symptoms worsen or do not improve within 3 days.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Content of this leaflet:

1. What ASPIRIN Complex Granules is and what it is used for
2. Before you take ASPIRIN Complex Granules
3. How to take ASPIRIN Complex Granules
4. Possible side effects
5. How to store ASPIRIN Complex Granules
6. Further information

1. WHAT ASPIRIN COMPLEX GRANULES IS AND WHAT IT IS USED FOR

ASPIRIN Complex Granules has pain-relieving, anti-inflammatory, fever-reducing and nasal decongestant properties. The white granules contain two drug substances, Acetylsalicylic acid (Aspirin) and Pseudoephedrine hydrochloride.
This medicine is used for the treatment of the symptoms of nasal congestion and cold-related pain and fever.
If you have only one of the symptoms above it may be more appropriate to take a medicine that contains only one of the drug substances.

2. BEFORE YOU USE ASPIRIN COMPLEX GRANULES

Do not take ASPIRIN Complex Granules if you:

- are allergic (hypersensitive) to acetylsalicylic acid or any of the other ingredients of the product;
- are allergic to salicylates, the class of substances to which acetylsalicylic acid belongs;
- suffer from stomach ulcers;
- have an increased tendency to bleed;
- are pregnant or breast feeding;
- have liver or kidney failure;
- have severe, unstable heart failure;
- are also taking 15 mg (or more) of methotrexate per week;
- have very high blood pressure or severe coronary artery disease;
- are also taking a antidepressant medicine containing a monoamine oxidase (MAO) inhibitor.

Take special care with ASPIRIN Complex Granules if you:

- are allergic (hypersensitive) to other analgesics, anti-rheumatics or anti-inflammatory medicines;
- suffer from allergies (e.g. with rash, itching, nettle rash), asthma, hay fever, swelling of the mucous membrane of the nose (nasal polyps) or long-standing lung diseases;
- are also taking medicines to thin the blood and to prevent it clotting (anticoagulants);
- have a history of stomach ulcers or gastrointestinal bleeding;
- have impaired kidney and liver function;

- are about to have surgery (including minor operations such as tooth extractions);
- suffer from an overactive thyroid, diabetes mellitus, heart diseases, increased pressure in the eye, an enlarged prostate gland, or sensitivity to some ingredients in cough/cold medicines e.g. phenylephrine and ephedrine (sympathomimetic substances);
- take a number of painkillers together. You are at risk of permanent kidney disease;
- are prone to having gout. At low doses acetylsalicylic acid reduces the excretion of uric acid in urine, which may cause a gout attack.

If you are unsure whether you should take this medicine, consult your doctor or pharmacist.

Use in the elderly
Elderly patients may be particularly sensitive to pseudoephedrine and may experience sleeplessness or sense things that are not real (hallucinations).

Use in children
There is a possible association between acetylsalicylic acid and Reye's syndrome when given to children. Reye's syndrome is a very rare disease, which can be fatal. For this reason acetylsalicylic acid should not be given to children aged under 16 years, unless on the advice of a doctor.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
The action of the following medicines may be affected if taken together with ASPIRIN Complex Granules. Please tell your doctor because he/she may need to adjust the dose of these below medicines.

ASPIRIN Complex Granules may increase the effectiveness of:

- Medicines that thin the blood and help to prevent it clotting so easily, e.g. ticlopidine;
- Medicines such as cortisone or prednisolone, when taken by mouth or by injection;
- Digoxin (to treat heart failure or irregular heart beat) by increasing the amount of digoxin that is in your blood;
- Anti-inflammatory and analgesic medicines (non-steroidal analgesics / anti-inflammatory medicines).
- Medicine to lower blood sugar (antidiabetics);
- Methotrexate (possibly causing more side effects);
- Valproic acid (medicine for treating epilepsy);
- Antidepressants including MAO-inhibitors;
- Salbutamol tablets which may cause your heart to beat irregularly or faster. This should not stop you using an inhaler instead (at the prescribed dose);
- Other medicines containing phenylephrine and ephedrine or other sympathomimetic substances such as those included in nasal decongestants e.g. nose drops.

ASPIRIN Complex Granules may reduce the effectiveness of:

- Medicines that treat water retention (aldosterone antagonists and loop diuretics);
- Medicines that lower blood pressure (antihypertensives such as guanethidine, methyldopa, β-blockers);
- Medicines for the treatment of gout that promote excretion of uric acid in the urine (e.g. probenecid, sulphinpyrazone);

Taking ASPIRIN Complex Granules with food and drink
It does not matter whether the product is taken with or without food. However the granules must be added to a glass of water and stirred well before taking. Drinking alcohol while taking acetylsalicylic acid can increase the risk of gastrointestinal bleeding, and impair your ability to react.

Pregnancy and breast-feeding
Due to lack of experience with the combination of drugs in ASPIRIN Complex Granules, the

product must not be used during pregnancy or if you are breast feeding.

Ask your doctor or pharmacist for advice before taking any medicines.

Fertility
The product belongs to a group of medicines (NSAID) which may impair the fertility in women. This effect is reversible on stopping the medicine.

Driving and using machines
During treatment with this medicine, your ability to react may be impaired. The risk may be further increased if you drink alcohol at the same time. This should be taken into consideration when increased attention is required, e.g. when driving.

Important information about some of the ingredients of ASPIRIN Complex Granules
This product contains 2 g of sucrose (sugar) per sachet (equivalent to 0.17 bread exchange BE). This should be taken into account if you have diabetes mellitus. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE ASPIRIN COMPLEX GRANULES

Always take your medicines exactly as directed in the patient information leaflet. You should ask your doctor or pharmacist if you are unsure how to take the medicine.

Unless otherwise prescribed, the dosage is as shown in the following table:

Age	Single dose	Total daily dose
Adults	**1-2 sachets**	**Up to 6 sachets**

If necessary, single doses can be taken at intervals of 4 to 8 hours. The total daily dose should not exceed 6 sachets.

Pour the contents of one or two sachets of ASPIRIN Complex Granules in a glass of water and stir well. Drink the entire content of the glass immediately. NB: the granules do not dissolve completely.

Do not give to children under 16 years of age, unless on the advice of a doctor. Due to limited experience a dosage recommendation for adolescents can not be given.

Do not take this medicine for more than 3 days without talking to your doctor.

If you take more ASPIRIN Complex Granules than you should
Headaches, dizziness, convulsions, being sick, noises in the ears, a fast heartbeat (tachycardia), chest pain, agitation or shortness of breath may occur in the event of overdosage.
If overdosage with this product is suspected, contact a doctor immediately.

4. POSSIBLE SIDE EFFECTS

Like all medicines, ASPIRIN Complex Granules can cause side effects, although not everybody gets them.

Possible side-effects due to acetylsalicylic acid are:
These are all very serious side effects and you may need urgent medical attention or hospitalisation. Tell your doctor immediately or go to your nearest hospital if you notice any of the folllowing:

- Stomach ulcers that may in isolated cases lead to perforation;

- Gastrointestinal bleeding that may in isolated cases lead to iron deficiency anaemia. Signs of gastrointestinal bleeding are passing of black stools or vomiting blood;
- Allergic reactions (such as difficulty in breathing, rash possibly with a fall in blood pressure), particularly in asthmatics.

These are all serious side effects and you may need urgent medical attention. Tell your doctor if you notice any of the following:

- Increase in the risk of bleeding;
- Gastrointestinal discomfort such as stomach ache, indigestion and inflammation of the lining of the stomach;
- Increase of liver proteins (enzymes).

These are all mild, side effects:

- Nausea, vomiting, diarrhoea

Possible side effects due to pseudoephedrine are:

These are all serious side effects and you may need urgent medical attention. Tell your doctor if you notice any of the below:

- Cardiac effects (e.g. a fast heartbeat);
- Urinary retention, especially in patients with prostate hyperplasia;
- Increase in blood pressure, although not in controlled hypertension;
- Insomnia, rarely hallucinations and other central nervous system stimulation;
- Effects on the skin (e.g. rash, nettle rash, itching).

If you experience any of the above side-effects, **stop taking the product**. Let your doctor know so that he/she can assess the severity of the reaction and decide on any other necessary action. If you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ASPIRIN COMPLEX GRANULES

Keep out of the reach and sight of children.
Do not use the product after the expiry date printed on the carton and sachets. The expiry date refers to the last day of that month.Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What ASPIRIN Complex Granules contains
Each sachet contains the active substances acetylsalicylic acid (500 mg) and pseudoephedrine hydrochloride (30 mg).
The other ingredients are citric acid anhydrous, sucrose, hypromellose, saccharin, orange flavour (including benzyl alcohol, alpha tocopherol, modified starch and maltodextrin).

What ASPIRIN Complex Granules looks like and contents of the pack
White granules for oral suspension.
This product is available in packs containing 10 or 20 sachets.

Marketing Authorisation Holder and Manufacturer
Product licence holder: Bayer: [to be completed nationally]
Manufactured by: [to be completed nationally]

Name of the product in other Member States
Although the product is approved in other Member States it may not always be marketed.

Austria:	ASPIRIN Complex – Granulat zur Herstellung einer Suspension zum Einnehmen
Germany:	ASPIRIN Complex Granulat
Luxembourg:	Rhinoaspirine

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]

Module 4
Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

ASPIRIN® COMPLEX
500 mg / 30 mg Granules for Oral Suspension
Acetylsalicylic acid / pseudoephedrine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains Acetylsalicylic Acid 500 mg and Pseudoephedrine Hydrochloride 30 mg.

3. LIST OF EXCIPIENTS

Contains sucrose.

4. PHARMACEUTICAL FORM AND CONTENTS

10 sachets [20 sachets] Granules for oral suspension

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

8. EXPIRY DATE

EXP: (month/year)

9. SPECIAL STORAGE CONDITIONS

-

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

-

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[Nationl MA-Holder]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch no:

14. GENERAL CLASSIFICATION FOR SUPPLY

[Pharmacy only]

15. INSTRUCTIONS ON USE

For the treatment of nasal congestion and cold-related pain and fever.

Unless otherwise prescribed, adults: 1-2 sachets of granules per dose. The daily dose should not exceed 6 sachets. Dissolve the granules in a glass of water and stir well before taking.

Do not take this medicine for more than 3 days without talking to your doctor.

Read the package leaflet before use.

16. INFORMATION IN BRAILLE

ASPIRIN Complex Granules

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

ASPIRIN®COMPLEX
500 mg / 30 mg Granules for Oral Suspension
Acetylsalicylic acid / pseudoephedrine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains Acetylsalicylic Acid 500 mg and Pseudoephedrine Hydrochloride 30 mg.

3. LIST OF EXCIPIENTS

Contains sucrose.

4. PHARMACEUTICAL FORM AND CONTENTS

Granules for oral suspension

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

8. EXPIRY DATE

EXP: (month/year)

9. SPECIAL STORAGE CONDITIONS

-

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

-

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[Nationl MA-Holder]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch no:

14. GENERAL CLASSIFICATION FOR SUPPLY

[Pharmacy only]

15. INSTRUCTIONS ON USE

For the treatment of nasal congestion and cold-related pain and fever.

Adults: 1-2 sachets of granules per dose. The daily dose should not exceed 6 sachets.
Dissolve the granules in a glass of water and stir well before taking.

Do not take this medicine for more than 3 days without talking to your doctor.

Read the package leaflet before use.

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

On 6th May 2008, Bulgaria, Czech Republic, Hungary, Poland, Slovakia and Slovenia granted Bayer Plc a Marketing Authorisation (licence) for the medicinal product Bayer Aspirin Complex 500mg/30mg Granules for Oral Suspension for the symptomatic treatment of nasal congestion with cold-related pain and fever.

This application was submitted under Article 10b of 2001/83/EC, as a fixed combination product containing 500mg acetylsalicylic acid and 30mg pseudoephedrine hydrochloride by the mutual recognition procedure (MRP) with the UK as reference member state (RMS). A licence had previously been granted in the UK on 26th November 2001, and licences had previously been granted in Austria, Germany and Luxembourg on 24th June 2002 by first-wave MRP (UK/H/0509/001/MR).

The main active ingredients are acetylsalicylic acid and pseudoephedrine hydrochloride. Acetylsalicylic acid has analgesic, antipyretic and anti-inflammatory properties. Pseudoephedrine hydrochloride is a sympathomimetic amine with α-agonist activity that acts as a decongestant.

No new preclinical studies were conducted, which is acceptable given the extensive use of the two drug substances.

A satisfactory programme of clinical studies has been conducted to support this new combination of established drug substances. Satisfactory bioequivalence studies have been conducted to bridge between the development and commercial formulae.

The RMS has also been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation. For manufacturing sites within the community, the RMS 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.

The licence was subsequently cancelled in the UK on 13th January 2009.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Bayer Aspirin Complex 500mg/30mg Granules for Oral Suspension
Name(s) of the active substance(s) (INN)	Acetylsalicylic acid (aspirin) Pseudoephedrine hydrochloride
Pharmacotherapeutic classification (ATC code)	N02 BA01: acetylsalicylic acid R01 BA02: pseudoephedrine
Pharmaceutical form and strength(s)	Granules for oral suspension containing 500mg acetylsalicylic acid and 30mg pseudoephedrine hydrochloride
Reference numbers for the Mutual Recognition Procedure	UK/H/0509/001/E01
Reference Member State	United Kingdom
Member States concerned	Bulgaria, Czech Republic, Hungary, Poland, Slovakia and Slovenia.
Name and address of manufacturer responsible for batch release in the EEA	1. Bayer Bitterfield GmbH., Ortsteil Greppin, Salegaster Chaussee 1, 06803 Bitterfeld-Wolfen, Germany. 2. Kern Pharma SL., Poligon Industrial Colon II, Venus, 72 E-08228 Terrassa, Barcelona, Spain.
Date of first authorisation	26th November 2001
Marketing Authorisation Number(s)	PL 00010/0280
Name and address of the authorisation holder	Bayer Plc, Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

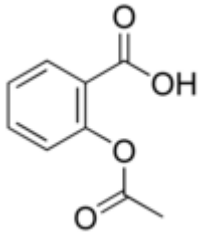
DRUG SUBSTANCE

Aspirin

INN: Acetylsalicylic acid

Chemical name: 2-ethanoylhydroxybenzoic acid
2-(acetyloxy)benzoic acid
Acetylsalicylate
Acetylsalicylic acid
O-acetylsalicylic acid

Structure:



Physical form: A colourless to white crystalline powder, slightly soluble in water, freely soluble in alcohol, soluble in chloroform and in ether.

Molecular formula: $C_9H_8O_4$

Molecular weight: 180.15

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance acetylsalicylic acid. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Any potential impurities have been identified and characterised.

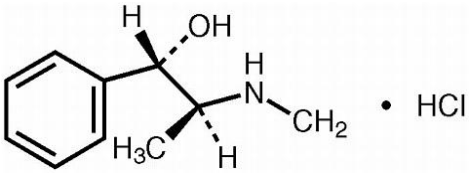
Batch analysis data are provided and comply with the proposed specification.

Specifications have been provided for all packaging used. All primary packaging complies with current European Directives concerning contact with food.

Based on stability studies, a suitable retest period has been proposed for the active substance. Suitable post approval stability commitments have been given to provide additional stability data as and when it becomes available.

Pseudoephedrine hydrochloride

INN: Pseudoephedrine hydrochloride
Chemical name: (1S, 2S)-2-(methylamino)-1-phenylpropan-1-ol hydrochloride
Structure:



Physical form: A colourless to white crystalline powder, freely soluble in water and alcohol, and sparingly soluble in methylene chloride.
Molecular formula: $C_{10}H_{16}ClNO$
Molecular weight: 201.7

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance pseudoephedrine hydrochloride. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Any potential impurities have been identified and characterised.

Batch analysis data are provided and comply with the proposed specification.

Specifications have been provided for all packaging used. All primary packaging complies with current European Directives concerning contact with food.

Based on stability studies, a suitable retest period has been proposed for the active substance. Suitable post approval stability commitments have been given to provide additional stability data as and when it becomes available.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of pharmaceutical excipients citric acid anhydrous, sucrose, hypromellose, saccharin and orange flavour (consisting of benzyl alcohol, alpha tocopherol, modified starch E1450 and maltodextrin). All ingredients comply with their European Pharmacopoeia monograph, with the exception of orange flavour (which is controlled to a suitable in-house specification).

None of the excipients contain materials of animal or human origin.

Pharmaceutical Development

The objective of the pharmaceutical development programme was to develop a dispersible product containing 500 mg acetylsalicylic acid and 30 mg pseudoephedrine hydrochloride as drug substances.

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development has been stated and is satisfactory.

The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

Manufacturing Process
A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of both products. The results are satisfactory.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for any working standards used.

Container-Closure System
The finished product is packaged in sachets composed of paper, low-density polyethylene and aluminium. These are then packed into cartons in pack sizes of 10 or 20 sachets. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the product
Stability studies were performed in accordance with current guidelines, using product manufactured by the proposed finished product manufacturer and in the packaging proposed for marketing. The results support a shelf-life of 3 years, with no specific storage instructions.

Bioequivalence/bioavailability
See clinical assessment.

Summary or Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL text and Label text are pharmaceutically acceptable.

As the product is not currently being marketed in the UK, only text mock-ups of the PIL and labels have been provided. However, the marketing authorisation holder has committed to submitting colour mock-ups of any PIL or labels (along with the results of PIL user testing) before marketing any pack size of the product.

Pharmaceutical Expert Report
The Pharmaceutical Expert Report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

MAA Form
The MAA form is pharmaceutically satisfactory.

CONCLUSION
The document is pharmaceutically satisfactory. It is recommended that a marketing authorisation is granted for this application.

III.2 PRE-CLINICAL ASPECTS

Acetylsalicylic acid has been used for the treatment of pain, fever and inflammation for more than a century. Pseudoephedrine is a sympathomimetic agent with α-agonist activity and is widely used as a nasal decongestant. The efficacy and safety of both ingredients are extensively documented in the medical literature and supported by long clinical experience.

The Pre-clinical Expert Report has been written by an appropriately qualified person and consists largely of a review of published papers, relating to both pre-clinical and clinical data. This is satisfactory.

The Summary of Product Characteristics is satisfactory from a pre-clinical viewpoint.

It is recommended that a marketing authorisation is granted for this licence.

III.3 CLINICAL ASPECTS

PHARMACOKINETICS

Pharmacokinetic interaction studies

The applicant has carried out a pharmacokinetic interaction study with this new fixed combination in order to comply with the Note for Guidance for Fixed Combination Medicinal Products (CPMP/EWP/240/95).

The study compared the fixed combination of acetylsalicylic acid (ASA) 500mg and Pseudephedrine (PE) 30mg to each active ingredient in a single-dose, open-label, randomised, three-treatment, three-period, Latin-square design study.

The study determined the pharmacokinetic characteristics and relative bioavailability of ASA, and its active metabolite salicylic acid (SA), and PE. For SA and PE, no interaction was recognised if the 90% confidence intervals for C_{max} and AUC were between 80 and 125%. For ASA, no interaction was stated if the respective 90% confidence intervals were between 70 and 143%. Results were as follows:

Pharmacokinetic parameter	**Ratio (90% CI)**
AUC_{norm} ASA	101.55 (93.74–110.02)
AUC_{norm} SA	92.98 (85.45–101.17)
AUC_{norm} PE	106.60 (100.30–113.30)
$C_{max\ (norm)}$ ASA	94.39 (80.22–111.07)
$C_{max\ (norm)}$ SA	89.95 (82.28–98.11)
$C_{max\ (norm)}$ PE	96.44 (82.25–113.07)

These data demonstrate that the single-dose kinetics of the fixed combination are equivalent to those of the individual components.

The applicant has also performed a pharmacokinetic study comparing the relative bioequivalence of the final formulation proposed for marketing with the trial formulation used in the clinical development study (see below). This compared the rate and extent of absorption of ASA, SA and PE following a single dose of 500mg ASA/30 mg PE of each formulation. Healthy male volunteers were evaluated in an open, randomised, three-factorial, two-treatment two-period crossover study.

Results are shown below:

Pharmacokinetic parameter	Ratio (90% CI)
AUC_{norm} ASA	108.29(104.59–112.13)
AUC_{norm} SA	102.46 (98.85–106.20)
AUC_{norm} PE	101.20 (94.37–108.53)
$C_{max\ (norm)}$ ASA	109.16 (96.19–123.89)
$C_{max\ (norm)}$ SA	99.94 (95.28–104.83)
$C_{max\ (norm)}$ PE	102.40 (94.32–111.17)

These data demonstrate that the two formulations can be regarded as bioequivalent.

Dose-finding

No dose-finding work has been performed in humans. A number of products combining an NSAID with pseudoephedrine are licensed in the EU. The applicant states that these products provide a rationale for the choice of doses in the finished product and, therefore, that dose-finding work in humans is unnecessary.

Bioequivalence studies

Three bioequivalence studies were performed. The first two studies were pivotal and aimed to demonstrate that the pharmacokinetic profiles of the individual components were the same when administered together as when administered separately (Study IMP48 and Study 0288). The third study was supportive in nature and aimed to show bioequivalence between the formulation proposed for marketing approval and the formulation used in one of the two pivotal trials (0288).

Pivotal studies

The two pivotal studies were of almost identical design and are therefore described together. The main difference between the trials is that one (IMP48) assessed sore throat pain while the other (0288) assessed nasal congestion.

The trials were randomised, double-blind, double-dummy, parallel-group, single-dose, placebo and active-controlled trials, each conducted in two centres. In both trials there were four treatment groups, Aspirin 1000mg + Pseudoephedrine 60mg (A1000+P60), Aspirin 500mg + Pseudoephedrine 30mg (A500+P30), Acetaminophen 1000mg + Pseudoephedrine 60mg (Ace1000+P60) and placebo. A summary of the key trial design features is given in the table below.

Trial	Entry criteria	Randomisation	Efficacy assessments	Primary efficacy endpoint	Primary analysis
IMP48	≥ 6 on the STPS	644 patients stratified by 6-7 and 8-10 on STPS	STPS and STPRS	TOTPAR 0-6 hours	ANOVA comparing A1000+P60 vs Placebo
0288	≥ 6 on the NCS	645 patients stratified by 6-7 and 8-10 on NCS	NCS and TNCRS	AUC of NCS 0-2 hours	ANOVA comparing A1000+P60 vs Placebo adjusting for strata

STPS – Sore Throat Pain Scale (0-10), STPRS - Sore Throat Pain Relief Scale (0-6), NCS – Nasal Congestion Score (0-10), TNCRS – Total Nasal Congestion Relief Score, TOTPAR – sum of pain relief scores (STPRS) weighted by time intervals, AUC – Area under the curve.

An intention-to-treat (ITT) analysis was considered primary in both trials. An evaluable patient population (PP) was also assessed to verify the robustness of the results.

A number of secondary endpoints were assessed in both trials. These comprised comparisons of the remaining active groups versus placebo, assessments across different time periods (e.g. 0-2 hours, 0-4 hours and 0-6 hours) for each endpoint and assessments using other rating

scales. To control for the number of statistical tests performed, each endpoint was assessed via a closed test procedure. This means that individual pairwise comparisons were only performed if an overall test comparing all four treatments was statistically significant.

In IMP48, A1000+P60 and A500+P30 were significantly superior to placebo in relieving pain associated with sore throat:

- For the high-dose group, these differences were also apparent in the subgroup of patients with severe symptoms at baseline, and were borderline significant over 0-2 hours and 0-4 hours in the moderate group. However, these latter p-values were not generated according to the closed-test procedure and should, therefore, be treated with some caution.
- For the low-dose group, there was little evidence of an effect in the moderate group and only borderline evidence of an effect at 0-2 hours in the severe group.

Among the raft of secondary endpoints, significant effects were also observed for both doses on headache, sinus pressure pain, general muscular aches, feverish discomfort and runny nose, and for the high-dose only on cough discomfort, head heaviness, head fullness, earache and stuffy nose. Neither dose showed evidence of an effect on eye pain. Not all patients suffered from each of these symptoms at baseline and so these comparisons are based on limited numbers of patients. However, they provide useful supportive data. The third active treatment group also compared favourably with placebo. An informal ranking of the active treatments would place acetaminophen plus pseudoephedrine between the high and low doses of aspirin plus pseudoephedrine.

In 0288, A1000+P60 and A500+P30 were significantly superior to placebo in relieving nasal congestion, regardless of rating scale used or time-point assessed. For the high-dose group, these differences were also apparent in both subgroups of patients split by severity of symptom at baseline. For the low-dose group, there was no evidence of an effect in those patients with moderate symptoms at baseline and only borderline evidence of effects in more severe patients. The third active treatment group also compared favourably with placebo. Again, an informal ranking of the active treatments would place acetaminophen plus pseudoephedrine between the high and low doses of aspirin plus pseudoephedrine.

Comments on Methodology:
The CPMP guideline on fixed combination medicinal products states that confirmatory clinical trials should preferably compare the fixed combination to its individual components. The applicant recognises that the pivotal trials have not adhered to the guidance on this point. They state that the omission of a test against the individual substances is based on the well-established pharmacodynamic properties of the individual substances in the intended indications, i.e. aspirin does not posses a genuine vasoconstrictive effect relative to pseudoephedrine and pseudoephedrine does not posses a genuine analgesic effect for the relief of pain associated with the common cold. Provided that the efficacy of each component will not be affected by the concomitant administration of the other, these arguments are probably acceptable as the applicant is not claiming an additive or synergistic effect of the combination on any one symptom.

In general the statistical input is of high quality. Endpoints and analysis methods were adequately pre-specified and are considered appropriate. Where the assumptions underlying the ANOVA could not be supported, sensitivity analyses have been performed using a non-parametric procedure (Kruskal-Wallis Test) in IMP48 and using a square-root transformation of the data in 0288. The effect of strata at baseline and interactions of treatment effect with centre were investigated. There were some minor methodological concerns with the statistical analysis including:

- The closed test procedure has not always been followed; i.e. pairwise comparisons have been made where the overall test was non-significant. The resulting p-values should be treated with caution.
- The clinical relevance of the treatment effect is difficult to assess as differences between treatment means and associated confidence intervals have not been presented.
- Some endpoints are calculated in terms of change from baseline score, but baseline score has not been included as a covariate in the statistical analysis. This may lead to a loss of precision. However, it does not introduce a bias in favour of the test treatment.

Furthermore, some features of the trial designs mean that evidence of efficacy sufficient to support the proposed SPC must be extrapolated from the trial results. Clinical judgement is required as to whether this is appropriate.

Each trial concentrates on a different symptom. Efficacy has not been assessed in patients experiencing both symptoms concurrently. The trials assessed only single-dose usage. Efficacy of multiple dosing has not been assessed. Only two centres randomised patients to the trial. A larger number of centres would render the trial results more generalisable.

Overall Conclusions
The pivotal trials can only be accepted as sufficient evidence of efficacy if it is considered that confirmatory evidence of efficacy against the individual components is not required. This requires that the efficacy of each component will not be affected by the concomitant administration of the other.

There are no major methodological concerns with the trial and, therefore, the results are considered reliable. Both A1000+P60 and A500+P30 demonstrated statistically significant reductions in sore throat pain and nasal congestion compared with placebo.

The applicant's proposal to license A500+P30 and use 1-2 doses, as required, seems reasonable. Provided the data from these pivotal trials can be extrapolated as required, then the evidence of efficacy appears to be sufficient. However, given the trial entry criteria and the apparent increase in efficacy in more symptomatic patients, it might be considered that the moderate to severe nature of the symptoms at baseline should be reflected in the indication.

EFFICACY

Two pivotal efficacy studies have been carried out by the applicant. One study evaluated efficacy in sore throat relief and the second study evaluated efficacy in relieving nasal congestion.

The *Notes for Guidance on Fixed Combination Medicinal Products* (CPMP/EWP/240/95) stipulates that studies should demonstrate the efficacy of the active ingredients in the fixed-dose combination compared to the individual actives alone, preferably in a factorial study.

The applicant has not complied with this guidance and has argued that comparison against the individual actives is not necessary because of the well-established pharmacodynamics of the individual substances in the intended indications. This rationale is discussed below.

Study 1: Sore throat relief
This was a randomised, double-blind, parallel-group single-dose placebo-controlled study evaluating the analgesic efficacy of ASA/PE, ASA 500mg/PE 30mg and ASA 1000mg/PE 60mg in adult subjects with sore throat arising from the common cold.

The primary efficacy parameter was the "sum of pain relief scores weighted by time intervals" (TOTPAR) up to 6-hour post dosing time interval for ASA 1000mg/PE 60mg versus placebo.

The secondary efficacy parameters were:
- TOTPAR for the same time intervals ASA 500mg/PE 30mg versus placebo
- TOTPAR for the 6-hour post dose interval for ASA 1000mg/PE 60mg versus paracetamol 1000mg/ PE 60mg
- TOTPAR for the 6-hour post dose interval for ASA 1000mg/PE 60mg versus ASA 500mg/PE 30mg
- TOTPAR for the initial 2-hour post dosing and 4 hour post dosing for ASA 500mg/PE 30mg and ASA 1000mg/PE 60mg.
- Antipyretic effect and other analgesic parameters.

The results were purported to demonstrate a significant treatment effect for sore throat pain relief after administration of ASA 1000mg/PE 60 mg. The relief in sore throat pain was significantly higher in comparison to placebo during the initial 6-hour post dose period.

Regarding TOTPAR, there were statistically significant benefits in all active treatments and in all time periods compared to placebo. Benefit was more evident in the ASA 1000mg/PE 60mg group than in the Paracetamol 1000mg/PE 60 mg group or the ASA 500mg/ PE 30mg group (please also see the statistical comments above).

Study 2: Nasal congestion
This was a randomised, two-centre, double-blind, placebo-controlled, double-dummy, parallel-group, single-dose, efficacy and safety study to evaluate the efficacy and safety of ASA 1000mg/PE 60mg, ASA 500mg/PE 30mg and paracetamol/PE in adult subjects with nasal congestion associated with upper respiratory tract infection.

The primary efficacy parameter was the AUC of summed differences in nasal congestion scores for the initial 2 hours post dosing for ASA 1000mg/PE 60mg versus placebo.

The secondary efficacy parameters included comparisons of the AUC of summed differences in nasal congestion scores for the initial 2 hours post-dosing for ASA 500mg/PE 30mg versus placebo and ASA 500mg/PE 30mg versus paracetamol 1000mg/60mg PE.

The results purported to show that a statistically significant treatment effect was demonstrated in patients after administration of ASA 1000mg/PE 60mg. Nasal congestion was significantly lower than placebo in the initial 2 hours following administration. Please see the statistical assessment above.

SAFETY

Study 1: 65 adverse events, including symptoms of the common cold and gastrointestinal events (nausea, abdominal pain, dyspepsia and diarrhoea). No serious adverse events were reported.

Study 2: 153 adverse events were reported, most were mild in intensity. Relation to study drug causality was attributed as "none" in 19.6%, "remote" in 32.0% and as "possible" in 48.4%. No serious adverse events due to study drug were reported.

EXPERT REPORTS

The Clinical Expert Report has been written by an appropriately qualified person and is a suitable summary of the clinical aspects of the dossier.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC), PATIENT INFORMATION LEAFLET (PIL), LABELLING & APPLICATION FORM (MAA)

These are all clinically satisfactory.

DISCUSSION

The *Notes for Guidance on Fixed Combination Medicinal Products* (CPMP/EWP/240/95) advises that pivotal clinical efficacy studies for such products includes a test against the individual actives in the new fixed combination. These studies carried in support of this application do not conform to this guideline. They do, however, include a placebo arm and recognised active comparator combinations at appropriate dosages.

The applicant reasonably asserts that the omission of comparisons against the individual actives is justified because of the well-established different pharmacodynamic profiles of the actives. ASA does not possess any vasoconstrictor activity and conversely PE does not possess analgesic activity. The clinical programme, therefore, focussed on the two core symptoms of common cold; namely sore throat and nasalcongestion, which occur together. The evaluation of efficacy in the pivotal studies was based on the selection of target symptoms with moderate to severe intensity in validated clinical models.

The applicant has also provided justification for the use of single-dose designs. Symptoms of nasal congestion and sore throat pain have been documented to be clinically most prominent on the first 2 days of a cold and decline thereafter. The acute assessment of target symptoms of defined intensity is, therefore, more powerful than summation results collated in a total symptom score obtained over several days of observation, when the natural course of the disease would become a compounding factor. These considerations favour the single-dose design. The studies do provide convincing evidence of efficacy, and the choice of actives and their respective doses in the proposed fixed combination have been adequately justified.

MEDICAL CONCLUSION

The grant of a marketing authorisation is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Bayer Aspirin Complex 500mg/30mg Granules for Oral Suspension are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

The studies submitted do provide convincing evidence of efficacy, and the choice of actives and their respective doses in the proposed fixed combination have been adequately justified. Satisfactory justifications have been provided for the omission of comparisons against the individual actives and the use of single-dose studies exclusively.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for similar products.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with acetylsalicylic acid and pseudoephedrine hydrochloride is considered to have demonstrated the therapeutic value of the products. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome
15/08/2008	IA	To register the change in address of the batch release site Bayer Bitterfeld GmbH	Granted 18/09/2008
01/10/2008	IA	To register a change in address of the MA holder in Austria only	Granted 16/10/2008
22/08/2008	IB	To register a change in the product name in Germany only	Granted 28/11/2008
13/01/2009	Cancellation	De-registration of Bayer Aspirin Complex 500mg/30 mg Granules for Oral Susp (PL 00010-0280) with the MHRA	Granted 13/01/2009