Public Assessment Report

Co-Amilofruse 5/40 Tablets

PL 14894/0414

Ranbaxy (UK) Limited

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Lay Summary

The MHRA granted Ranbaxy (UK) Limited a Marketing Authorisation (Licence) for the medicinal products Co-Amilofruse 5/40 Tablets (PL 14894/0414) on 20th October 2006.

Co-Amilofruse 5/40 Tablets contains two active ingredients, amiloride hydrochloride dihydrate and furosemide and are indicated for the induction of prompt diuresis (increase in urine production).

No new or unexpected safety concerns arose from this simple application and it was judged, therefore that the benefits of Co-Amilofruse 5/40 Tablets outweigh the risks, hence a Marketing Authorisation was granted.

SCIENTIFIC DISCUSSION

1. INTRODUCTION

This Public Assessment Report is based on the National Assessment Report for the recently granted Market Authorisation for Co-Amilofruse 5/40 Tablets held by Ranbaxy UK Limited. This simple application was based on essential similarity, under article 10.1(a)(i), to Co-Amilofruse Tablets 5/40 (PL 13931/0001) held by Chanelle Medical and granted in the UK on 2nd November 2000.

Co-Amilofruse 5/40 Tablets contains two active ingredients, amiloride hydrochloride dihydrate and furosemide and are indicated for the induction of prompt diuresis (increase in urine production). The product's legal status is Prescription Only Medicine.

A signed declaration from the proposed MA holder confirming that they have access to all data pertaining to the application was provided. Satisfactory expert statements from pre-clinical, clinical and pharmaceutical experts confirming that proposed product is of acceptable quality and that there are no toxicological, pharmacological or clinical reasons why a Marketing Authorisation should not be granted. Expert's CVs have been provided and are considered acceptable.

2 DRUG SUBSTANCE

The proposed drug substance specifications for the active ingredients amiloride hydrochloride dihydrate and furosemide are in line with the drug substance specification for the reference product. The active substance manufacturers are the same as previously authorised for the cross-referenced product. Certificates of Suitability were included for the sources of the drug substances.

3. DOSAGE FORM

Pack sizes of 28 and 56 tablets have been proposed which is consistent with details registered for the cross-reference products. The proposed shelf-life (3 years) and storage conditions (Store in the original package, Keep container in outer carton) are acceptable.

The qualitative composition of the dosage form is shown below

Amiloride Hydrochloride Dihydrate
Furosemide
Lactose
Maize Starch
Magnesium Stearate
Sunset Yellow (El10)
Povidone (K30)
Pregelatinised Maize Starch
Sodium Starch Glycolate

The formula, reference to standards and modifiers are in line with reference product. This product contains lactose and satisfactory declarations regarding TSE compliance have been received from the suppliers.

3.1 Manufacture

A brief description of the manufacturing method was provided. A statement from the pharmaceutical expert indicates that an identical manufacturing process to that for the cross-reference product is used. Applicant has provided the details for the manufacturing approvals previously granted. A satisfactory finished product specification was provided.

4. Summary of Product Characteristics/PIL/Label

4.1 Summary of Product Characteristics

The SPC is essentially similar to the cross reference product with minor changes in line with a recent renewal of the reference product.

4.2 Patient Information Leaflet

Patient information leaflet is near identical to that approved for the cross-reference product with minor changes in line with a recent renewal of the reference product.

4.3 Labels

Labelling was satisfactory with one minor amendment.

PRE-CLINICAL ASSESSMENT

No new data were submitted and none are required for an application of this type.

CLINICAL ASSESSMENT

No new data were submitted and none are required for an application of this type.

CONCLUSION

A Marketing Authorisation was granted.

OVERALL CONCLUSION AND RISK/BENEFIT ANALYSIS

Quality

The data for these applications are consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

Preclinical

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

Efficacy

No new efficacy data for were submitted and none are required for this type of application.

Risk Benefit Assessment

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's products are identical to the cross-reference products which, in turn, have been shown to be interchangeable with the innovator products. Extensive clinical experience with ibuprofen is considered to have demonstrated the therapeutic value of the compound. The risk benefit for Co-Amilofruse 5/40 Tablets is therefore considered to be positive.

STEPS TAKEN DURING ASSESSMENT

1	The MHRA received the application on 14th June 2005.
2	Following initial assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 1st November 2005, 31st August 2006.
3	The applicant provided further information in regard to the quality assessment on 3rd March 2006 and 29th September 2006
4	The application was determined on 19th October 2006.

SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

Co-Amilofruse tablets 5/40.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Furosemide 40 mg and Amiloride Hydrochloride equivalent to amiloride hydrochloride anhydrous 5 mg.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Circular orange tablets with a breakline and embossed JJ on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Co-Amilofruse tablets 5/40 are indicated where prompt diuresis is required, particularly in conditions where potassium conservation is important, e.g. congestive cardiac failure, nephrosis, corticosteroid therapy and oestrogen therapy, and for ascites associated with cirrhosis.

4.2. Posology and method of administration

Adults:
The usual daily dosage for adults is one tablet to be taken in the morning - this may be increased to two tablets.

Elderly patients:
The dosage should be adjusted according to diuretic response. Extreme care should be taken with dosage in the elderly as this patient group is more susceptible to serious side effects associated with electrolyte disturbance.

Children:
Not recommended for use in children.

4.3. Contraindications

Hyperkalaemia (serum potassium > 5.3 mmol/litre), Addison's disease, acute renal failure, anuria, severe progressive renal disease, electrolyte imbalance, precomatose states associated with cirrhosis, concomitant potassium supplements, spironolactone or triamterene, known sensitivity to furosemide or amiloride.

Co-Amilofruse tablets 5/40 are contraindicated in children as safety in this age group has not been established.

4.4. Special warnings and special precautions for use

Warnings:
Patients with prostatic hypertrophy or impairment of micturition have an increased risk of developing acute urinary retention during diuretic therapy.
Cephaloridine nephrotoxicity may be increased by concomitant administration of diuretics such as Co-Amilofruse tablets 5/40.

Precautions:
Patients who are being treated with Co-Amilofruse tablets 5/40 require regular supervision with monitoring of fluid and electrolyte states to avoid excessive loss of fluid.
Co-Amilofruse tablets 5/40 should be used with particular caution in elderly patients or those with potential obstruction of the urinary tract or disorders rendering electrolyte imbalance precarious.

Hypochloraemia, hyponatraemia and raised blood urea nitrogen may occur during vigorous diuresis especially in seriously ill patients. Close monitoring of serum electrolytes and urea should therefore be undertaken in these patients.

This product contains the excipient lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This product also contains the excipient sunset yellow FCF (E110) which may cause allergic reactions.

4.5. Interactions with other medicaments and other forms of interaction

Dosage of the following concurrently administered medicines may require adjustment: cardiac glycosides, lithium, non-depolarising muscle relaxants or anti-hypertensive agents.

Co-Amilofruse Tablets 5/40 should be discontinued prior to a glucose tolerance test.

4.6. Pregnancy and lactation

The safety of use of Co-Amilofruse Tablets 5/40 during pregnancy and lactation has not been established. It should only be used during pregnancy if considered essential by the physician and is not recommended during lactation in patients breast feeding infants.

4.7. Effects on ability to drive and use machines

None stated.

4.8. Undesirable effects

Discomfort, gastric upset, nausea, vomiting, diarrhoea and constipation may occur. If a skin rash appears or pruritus occurs, treatment should be withdrawn.
Rare adverse effects may include minor psychiatric disturbances, disturbances in liver function tests, and ototoxicity.
Bone marrow depression occasionally complicates treatment, necessitating withdrawal of the product.
Serum calcium levels may be reduced.
Regular monitoring of the haematopoietic state is necessary during treatment.
Serum cholesterol and triglyceride levels may rise during treatment.
Serum uric acid levels may rise during treatment with Co-Amilofruse tablets 5/40 and acute attacks of gout may be precipitated.
Furosemide may cause latent diabetes to become manifest. It may be necessary to increase the dose of oral hypoglycaemic agents in diabetic patients.
Hyperkalaemia has been observed in patients receiving amiloride hydrochloride. As ACE inhibitors may elevate serum potassium levels, especially in renal impairment combination with Co-Amilofruse Tablets 5/40 should be avoided in elderly patients or other patients with compromised renal function. If use of the combination is deemed essential, clinical condition and serum electrolytes must be carefully monitored.

4.9. Overdose

Treatment of overdosage should be aimed at reversing dehydration and correcting electrolyte imbalance, particularly hyperkalaemia. Emesis should be induced or gastric lavage performed. Treatment is symptomatic and supportive. If hyperkalaemia is noticed, appropriate measures to reduce serum potassium must be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Amiloride is a mild diuretic which appears to act mainly on the distal renal tubules. It is described as potassium-sparing since, like spironolactone, it increases the excretion of sodium and reduces the excretion of potassium. Unlike spironolactone, however, it does not act by specifically antagonising aldosterone. Inhibition occurs by inhibition of sodium ion transport through ion channels in the luminal membrane. Amiloride does not inhibit carbonic anhydrase. It diminishes the kaliuretic effects of other diuretics, and may produce an additional natriuretic effect.

Furosemide is a potent diuretic which inhibits the reabsorption of electrolytes primarily in the ascending limb of the loop of Henle and also in the distal renal tubules. It may also have a direct effect in the proximal tubules. Excretion of sodium, potassium, calcium and chloride ions is increased and water excretion enhanced. It has no clinically significant effect on carbonic anhydrase. Furosemide has a steep dose-response curve which gives it a wide therapeutic range.

5.2. Pharmacokinetic properties

Amiloride is incompletely absorbed (about 50%) from the gastrointestinal tract. Amiloride is not metabolised. After an oral dose peak plasma levels are reached after about 3-4 hours. When taken on an empty stomach amiloride takes effect about 2 hours after oral administration and its diuretic action reaches a peak in 6 to 10 hours. The plasma half-life is 6 - 9 hours. Amiloride is weakly bound to plasma proteins. About 50% is excreted unchanged in the urine and about 40% of the dose is excreted in the faeces.

Furosemide: Food intake reduces the bioavailability by about 30%. There appears to be no pre-systemic metabolism and the mean bioavailability is about 52%. It is extensively bound to plasma proteins, mainly albumin. The volume of distribution ranges from 170 - 270 ml/kg. The plasma half-life is 45 to 60 minutes. There is a correlation between the serum concentration of Furosemide and its diuretic effect and also between the diuretic effect and urine concentration. Elimination is mainly via the kidneys, both filtration and proximal tubular secretion being involved. Furosemide is partly metabolised to and excreted as a glucuronide in serum and bile.

5.3. Preclinical safety data

No information submitted.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose
Maize Starch
Magnesium Stearate
Sunset Yellow FCF (E110)
Povidone (K30)
Pregelatinised Maize Starch
Sodium Starch Glycollate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Three years.

6.4. Special precautions for storage

Store in the original package.
Keep blister in outer carton.

6.5. Nature and contents of container

Blister packs consisting of plastic strips of green PVC (250 micron) and Aluminium foil (20 micron).
Each strip contains 14 tablets.
Pack sizes: 28 and 56 tablets.

6.6. Instructions for use/handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Ranbaxy (UK) Limited,
3rd Floor, CP House,
97/107 Uxbridge Road, Ealing
London W5 5TL
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 14894/0414

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/10/2006

10 DATE OF REVISION OF THE TEXT

20/10/2006

LABELS AND LEAFLETS

PATIENT INFORMATION LEAFLET

Co-Amilofruse Tablets 5/40

This leaflet contains information about your medicine. Please read it carefully before you take your medicine. For further information, ask your doctor or pharmacist.

WHAT IS IN YOUR MEDICINE ?

Co-Amilofruse Tablets 5/40: Circular orange tablets with a breakline and embossed JJ on one side for oral administration only. Each tablet contains furosemide 40 mg and amiloride hydrochloride 5 mg (as dihydrate).

The tablets also contain lactose, povidone, pregelatinised starch, maize starch, magnesium stearate, sodium starch glycollate and sunset yellow FCF (E110).

Pack size: 28 and 56 tablets.

Manufacturer:
Chanelle Medical,
Loughrea, Co. Galway,
Ireland.

MA Holder:
Ranbaxy (UK) Limited,
3rd Floor, CP House, 97/107 Uxbridge Road,
Ealing, London W5 5TL, United Kingdom

WHAT IS CO-AMILOFRUSE ?

The name of your medicine is Co-Amilofruse tablets 5/40. Each tablet contains 5 mg of the active ingredient amiloride hydrochloride and 40 mg of the active ingredient furosemide. Amiloride hydrochloride and furosemide both belong to a group of medicines called diuretics.

WHAT IS YOUR MEDICINE FOR ?

Co-Amilofruse tablets 5/40 are used in conditions where increased excretion of the urine is required, for example in conditions such as heart failure, kidney problems, treatment with corticosteroids or oestrogen, or problems associated with liver disease.

ARE YOU TAKING ANY OTHER MEDICINES ?

If you are taking any of the following medicines, tell your doctor:

- Heart medication (cardiac glycosides)
- Lithium (used to treat depression)
- Muscle relaxants
- Medicines used to treat high blood pressure (e.g. captopril)*
- Hypoglycaemic agents (used to regulate blood sugar levels in diabetes)**
- Cephaloridine (an antibiotic)***

*A group of medicines known as ACE inhibitors (used to treat high blood pressure) may raise the potassium levels in the blood. If you are taking ACE inhibitors, take special care when taking Co-Amilofruse tablets 5/40, especially in elderly patients or if you have kidney problems. Always follow your doctor's advice.
**If you are diabetic, your doctor may increase your dose of hypoglycaemic agents (used to regulate blood sugar levels) while you are taking Co-Amilofruse tablets 5/40.
***If you are taking Cephaloridine, the potential risk of damage to the kidneys may be increased while taking Co-Amilofruse tablets 5/40.

If you are taking any other medicines, tell your doctor or pharmacist.

WHAT DO YOU NEED TO KNOW BEFORE TAKING THIS MEDICINE ?

If the answer to any of the following questions is **YES, DO NOT** take this medicine before consulting your doctor:

- Are you allergic to amiloride hydrochloride, furosemide or any diuretics ?
- Are you allergic to any of the other ingredients in this medicine ? (See "What is in your medicine ?" above).
- Do you suffer from any blood disorders such as hyperkalaemia (high levels of potassium in the blood) ?
- Do you suffer from Addison's disease ?
- Do you suffer from diabetes?
- Do you suffer from an enlarged prostate?
- Do you have difficulties urinating?
- Have you any liver or kidney problems ?
- Are you pregnant or breast-feeding ?

Co-Amilofruse should be discontinued before a glucose tolerance test.

Important:
Your medicine contains a small amount of an inactive ingredient called lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Your medicine also contains a small amount of an inactive ingredient called Sunset yellow FCF (E110) that may cause allergic reactions.

While taking Co-Amilofruse tablets 5/40, you should be under the regular supervision of your doctor. Regular blood and/or urine tests may be carried out. This is very important in order to maintain your normal blood constitution. Certain changes in your blood may occur during treatment with Co-Amilofruse tablets 5/40. Regular blood checks will ensure that your blood remains normal during treatment. This is particularly important in elderly patients or if you suffer from any kidney problems or urinary tract disorders.
The following may occur during treatment with Co-Amilofruse tablets 5/40, especially in seriously ill patients:

- Low levels of chloride in the blood.
- Low levels of sodium in the blood.
- Higher levels of urea nitrogen in the blood.

Close supervision by your doctor and regular blood tests should be taken in seriously ill patients.

Take special care if you have an enlarged prostate or have trouble urinating, as further problems with urination may develop while taking Co-Amilofruse tablets 5/40.

HOW SHOULD YOU TAKE YOUR MEDICINE ?

Your doctor will advise on the dosage suitable for your condition. Take your medicine according to your doctor's instructions. **DO NOT** stop taking the tablets until your doctor tells you to.

Usual dosage:
The tablet should be taken in the morning.

Adults: The normal dosage is one tablet daily, although this may be increased to two tablets.

Children: Co-Amilofruse tablets 5/40 are not recommended for use in children.

Elderly: As for adults. Co-Amilofruse tablets 5/40 should be used with caution in elderly patients.

WHAT SIDE EFFECTS CAN OCCUR USING THIS MEDICINE ?

Most medicines can result in some side effects. The following side effects may occur:

Stomach upset, nausea, vomiting, diarrhoea and constipation may occur.

If a skin rash or itching occurs, tell your doctor immediately.

Rarely mood changes and disturbances of hearing and balance may occur.

Abnormalities in liver function tests may occur.

Blood monitoring should be regularly carried out during treatment.

Blood levels of calcium may be reduced during treatment.

Blood levels of cholesterol and triglyceride may rise during treatment.

Sometimes bone marrow depression may occur (The bone marrow produces blood cells – bone marrow depression is when this production of blood cells is affected). If this happens, your doctor may advise you to stop taking Co-Amilofruse tablets 5/40.

Undiagnosed diabetes may become apparent during treatment with Co-Amilofruse tablets 5/40.

If you suffer from gout, take special care while taking Co-Amilofruse tablets 5/40, as attacks of gout may be brought on. This is due to higher levels of uric acid present in the blood.

If you notice any of the above side effects or any other side effects not listed above, tell your doctor.

WHAT IF YOU TAKE TOO MUCH OF YOUR MEDICINE ?

If you accidentally take too many tablets you should contact your nearest doctor or hospital casualty department **IMMEDIATELY**.

HOW SHOULD YOU STORE YOUR MEDICINE ?

The expiry date is stated on the label. "Exp" is short for expiry. **DO NOT** take your medicine after this date. Store in the original package. Keep blister in outer carton. **DO NOT** transfer it to another container. Return any unused tablets to your pharmacist for disposal.

REMEMBER: This medicine has been prescribed for you. **DO NOT** give it to anyone else, even if they appear to have the same symptoms as you, as it may be harmful to them.

Ranbaxy (UK) Ltd.

Date of leaflet preparation: March 2006.

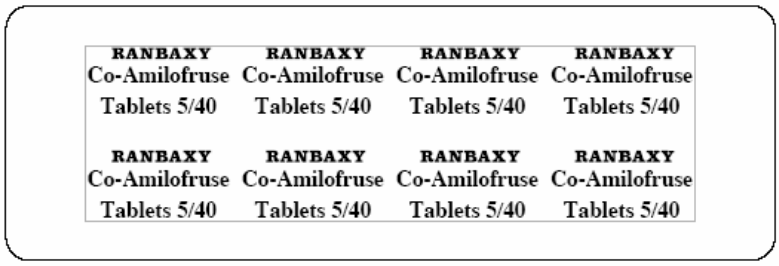
LA3213

Braille Translation:

co-amilofruse
tablets 5/40

denotes unique number sign


KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
56 TABLETS
5/40mg
POM
PL 14894/0414
5 01525 050628
After dispensing label here
BN.
EXP.
The tablets also contain lactose and sunset yellow FCF E110.
Maximum sodium content per tablet: 0.13 mg
For oral use.
Use only as directed by a physician.
Store in the original package.
Keep blister in outer carton.
MA Holder:
Ranbaxy (UK) Limited,
3rd Floor, CP House,
97/107 Uxbridge Road,
Ealing, London W5 5TL,
United Kingdom
LA3213
RANBAXY
Co-Amilofruse Tablets 5/40
(Furosemide 40 mg,
Amiloride Hydrochloride 5 mg)
56
TABLETS
RANBAXY
Co-Amilofruse Tablets 5/40
(Furosemide 40 mg,
Amiloride Hydrochloride 5 mg)
5/40mg
Each tablet contains Furosemide 40 mg and amiloride hydrochloride 5 mg (as dihydrate).
Please read enclosed leaflet carefully
RANBAXY
Co-Amilofruse Tablets 5/40
(Furosemide 40 mg, Amiloride Hydrochloride 5 mg)
5/40mg
PACK CONTAINS
56 TABLETS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