HYPERSENSITIVITY REACTIONS (HSR) TO ABACAVIR / LAMIVUDINE

Important risk minimisation material for Healthcare Professionals

Objectives of this Important risk minimisation material

- The aim of this educational programme is:

To increase understanding and awareness of abacavir hypersensitivity reactions by Healthcare professionals and expand on the information already included in the product information.

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Section - 1
Key Risk Minimization Activities Abacavir Hypersensitivity Reactions (HSR)

Key Risk Minimisation Activities: Abacavir HSR (1 of 2)

- Abacavir HSR is characterised by fever and/or rash with other symptoms indicating multi-organ involvement.
- Symptoms usually appear within the first 6 weeks (median time to onset 11 days) although HSR may occur at any time during therapy.
- The risk of abacavir HSR is higher for patients who test positive for the HLA-B*5701 allele. However, abacavir HSR have been also reported at a lower frequency in patients who do not carry this allele.
- Patient's HLA-B*5701 status must always be documented prior to initiating treatment with abacavir.
- Abacavir should never be initiated in following patients:
  - All patients with a positive HLA-B*5701 status
  - Patients with a negative HLA-B*5701 status who had a suspected abacavir HSR on a previous abacavir-containing regimen

Key Risk Minimisation Activities: Abacavir HSR (2 of 2)

- If HSR is suspected; abacavir must be stopped immediately, even in the absence of the HLA-B*5701 allele. This is because, delay in stopping treatment with abacavir after the onset of hypersensitivity, may result in an immediate and life-threatening reaction.
- Never re-initiate abacavir or any other product containing abacavir, after stopping the treatment for a suspected Abacavir HSR.
- Restarting abacavir following a HSR can result in the return of symptoms within hours. These symptoms are usually more severe than initial presentation and may include life-threatening hypotension or can be fatal in rare instances.
- Patients experiencing a suspected HSR should be instructed to dispose off or return their remaining abacavir-containing tablets in order to avoid taking abacavir accidentally or restarting abacavir on their own.

Section – 2
Pharmacogenetic Testing

Recommendations for screening patients for Hypersensitivity Reactions (HSR)

Pharmacogenetic Risk Factors for Abacavir HSR

- Patients who are positive for the HLA-B*5701 allele are at risk for abacavir HSR.[1-2]
- A prospective pharmacogenetic screening for HLA-B*5701 is used to identify patients at high risk for abacavir HSR before initiating abacavir therapy.
- No other pharmacogenetic markers have been detected in any ethnic groups that increase the susceptibility of patients to abacavir HSR.[3]

1. Mallal et al. *Lancet*. 2002;359:727-732.
2. Hetherington et al. *Lancet*. 2002;359:1121-1122.
3. Martin et al. *Proc Natl Acad Sci USA 2004:101;4180-4185.*

Importance of Clinical diagnosis in early detection of patients with Abacavir Hypersensitivity Reactions (HSR)

- HLA-B*5701 allele is not always present in patients with suspected abacavir HSR.
- Therefore, screening patients for the presence of HLA-B*5701 may not predict who will experience HSR to abacavir.
- Clinical diagnosis of suspected abacavir HSR is of utmost importance for clinical decision making regarding stopping treatment with abacavir.
- HLA-B*5701 screening for risk of abacavir hypersensitivity should never be substituted for appropriate clinical vigilance and patient management in individuals receiving abacavir

Recommendations for HLA-B*5701 Screening

- Before initiating treatment with abacavir, screening for HLA-B*5701 needs to be performed in ALL patients.
- Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir.
- HLA-B*5701 status must always be documented prior to initiating abacavir therapy.
- Abacavir should not be used in patients with:
  - HLA- B*5701 allele
  - Negative HLA-B*5701 status who had a suspected abacavir HSR on a previous abacavir-containing regimen

HLA-B*5701 Screening: Relevance of clinical vigilance and appropriate use of HLA-B*5701 screening test

- In HLA-B*5701–negative patients, clinical vigilance is the key for detecting abacavir HSR.
- If HSR cannot be ruled out on clinical grounds, it is important to permanently discontinue abacavir and not rechallenge with abacavir even in the absence of the HLA-B*5701 allele.
- This is because of the potential for a severe or even fatal reaction in such patients.
- After a suspected HSR, results of pharmacogenetic tests for risk of abacavir hypersensitivity should never be used to support a drug rechallenge decision.
- HLA-B*5701 testing must not be used as a diagnostic test after a patient has started treatment with abacavir.

What is HLA-B*5701 Test?

HLA-B*5701 is a specific human genetic variation, which is associated with susceptibility to Abacavir hypersensitivity

HLA-B*5701 test is a prospective screening method to predict hypersensitivity to abacavir

- The HLA-B*5701 allele occurs at approximately 5% frequency in European populations, 1% in Asian populations, and less than 1% in African populations.[1]
- HLA-B*5701 test identifies people at high risk for this serious allergic reaction; however, HLA-B*5701 negative people can also experience HSR.

[1] Torkamani, A. Abacavir and HLA-B*5701. Accessed at http://emedicine.medscape.com/article/ 1969668-overview. Accessed on 31 March 2016.

HLA-B*5701: Who Should be Tested?

- Only patients without the HLA-B*5701 allele should commence treatment with Abacavir

Those who should be tested include:

- All patients who have not yet started HIV treatment and who are going to start an abacavir regimen.
- All patients who have started HIV treatment but who have never taken an abacavir regimen but who are going to start an abacavir regimen.
- All patients of unknown HLA-B*5701 status who have stopped an abacavir-containing regimen and who are going to restart an abacavir regimen

People who have been previously diagnosed with an abacavir HSR should not receive abacavir. HLA-B*5701 testing is not necessary for these people.

What do the HLA-B*5701 Test Results Mean?

Result	Meaning	Note
Negative	• Patient has lower risk of experiencing an allergic reaction to abacavir than a carrier of HLA-B*5701. • Patient can be considered for treatment that includes abacavir.	Patient may nevertheless still experience an HSR and should consult their doctor if this is suspected.
Positive	• Patient is at greater risk of experiencing an allergic reaction to abacavir than a person who has tested negative for HLA-B*5701. • Treatment with abacavir is not recommended.	

The rate of discontinuation due to hypersensitivity to Abacavir has been cut from 8% to 3% owing to genetic screening (P=0.01)[1]

[1] Rauch et al. *Clin Infect Dis*. 2006;43:99-102.

Section - 3
Diagnosis and Management of Abacavir HSR

The objectives of this section are to:

- Understand the symptoms of abacavir HSR

- Understand how to diagnose HSR based on:
  - Physical examination
  - Laboratory investigations

- Management of abacavir HSR

Symptoms of Abacavir Hypersensitivity Reactions (HSR)

- Occurs in approximately 5 to 8% of patients[1]
- Symptoms can occur at any time during treatment with abacavir, however, higher frequency is seen during the first 6 weeks of therapy [1].
- Symptoms worsen in intensity with continued abacavir therapy.
- Abacavir HSR displays multi-organ involvement with symptoms like fever, skin rash, gastrointestinal disorders (nausea, vomiting, diarrhea), malaise, myalgia, arthralgia, and respiratory symptoms (cough, sore throat)[2], though there is no rule that individual symptom will always be present.
- Symptoms usually reduce in intensity after stopping (de-challenging) abacavir.[2]

[1] Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, et al; PREDICT-1 Study Team. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med. 2008 Feb 7;358(6):568-79.

[2] SmPC Kivexa film-coated tablets. ViiV Healthcare UK Ltd. Last updated on 09Feb2016 https://www.medicines.org.uk/emc/medicine/15707

Signs and Symptoms of HSR (1 of 2)

- Almost all patients developing hypersensitivity reactions will have fever and/or rash (usually maculopapular or urticarial) as part of the syndrome, however reactions have occurred without rash or fever.
- Other key symptoms include gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise.
- The signs and symptoms of this HSR are listed below. These have been identified either from clinical studies or post marketing surveillance.

Body involvement	Signs and Symptoms
Skin	**Rash** (usually maculopapular or urticarial)
Gastrointestinal tract	**Nausea, vomiting, diarrhoea, abdominal pain**, mouth ulceration
Respiratory tract	**Dyspnoea, cough**, sore throat, adult respiratory distress syndrome, respiratory failure
Miscellaneous	**Fever, lethargy, malaise**, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis

Signs and Symptoms of HSR (2 of 2)

Body involvement	Signs and Symptoms
Neurological/Psychiatry	**Headache**, paraesthesia
Haematological	Lymphopenia
Liver/pancreas	**Elevated liver function tests,** hepatitis, hepatic failure
Musculoskeletal	**Myalgia**, rarely myolysis, arthralgia, elevated creatine phosphokinase
Urology	Elevated creatinine, renal failure

- Those reported **in at least 10%** of patients with a hypersensitivity reaction are in bold text.
- Almost all HSR to abacavir include fever and/or rash. It is important to remember abacavir HSR can present as other signs and symptoms including respiratory and gastrointestinal symptoms.

SmPC Kivexa film-coated tablets. ViiV Healthcare UK Ltd. Last updated on 09Feb2016
https://www.medicines.org.uk/emc/medicine/15707

Additional Abnormalities on Physical Examination and in Laboratory Tests in Abacavir HSR

- HSE can be diagnosed based on abnormalities in physical examination
- The true incidence of laboratory abnormalities in abacavir HSR is unknown however it is likely that laboratory tests values were probably conducted in more severe cases
- Abnormalities detected on physical examination and in laboratory tests are outlined below:

Physical examination abnormalities	Laboratory test abnormalities
Rash (usually maculopapular or urticarial)	Haematology: Lymphopenia and thrombocytopenia
Abdominal tenderness, mouth ulceration, pharyngitis	Elevated liver enzymes (Aspartate aminotransferase / alanine aminotransferase)
Dyspnea, respiratory distress	Increased serum creatinine and creatinine phosphokinase
Fever, edema, lymphadenopathy, hypotension, conjunctivitis	Chest x-ray normal or diffuse bilateral or lobular infiltrates
Headache, paraesthesia	

Hetherington et al. *Clin Ther*. 2001;23:1603-1614.

Clinical Management of Abacavir Hypersensitivity Reactions (HSR) (1 of 2)

- Regardless of HLA-B*5701 status, abacavir MUST be discontinued immediately in patients experiencing HSR.[1]
- Delay in stopping treatment with abacavir after the onset of hypersensitivity may result in worsening of symptoms and may lead to immediate and life-threatening condition.[1]
- Abacavir HSR should be clinically managed as per the symptoms and their severity.
- Abacavir or any medicinal product containing abacavir, MUST NEVER be restarted in patients who have stopped therapy due to HSR.[1]

If acute illness cannot be differentiated from HSR, STOP abacavir

[1] SmPC Kivexa film-coated tablets. ViiV Healthcare UK Ltd. Last updated on 09Feb2016 https://www.medicines.org.uk/emc/medicine/15707

Clinical Management of Abacavir Hypersensitivity Reactions (HSR) (2 of 2)

- Restarting abacavir following HSR results in return of symptoms promptly (within hours). This recurrence is usually more severe than initial presentation and may include life-threatening hypotension and death.
- Abacavir MUST BE PERMANENTLY discontinued even if hypersensitivity cannot be ruled out.
- Patients who have experienced an HSR should be asked to return the remaining medicinal product to avoid taking it accidentally or restarting.

Rechallenge can result in more rapid and severe reaction, which can be fatal.

Rechallenge is contraindicated

SmPC Kivexa film-coated tablets. ViiV Healthcare UK Ltd. Last updated on 09Feb2016
https://www.medicines.org.uk/emc/medicine/15707

Section – 4
Counselling the Patients

Objectives of this section are:

To highlight the importance of counselling the patients to reduce the incidence of HSR and facilitate early detection of HSR for proper management.

Counselling the Patients
Abacavir / Lamivudine 'Alert Card'

- Inform patients that a "Patient Alert Card" is available in the pack of abacavir / lamivudine which they should carry with them at all times.
- All patients must be made aware of the possibility of HSR due to abacavir that may be a life-threatening reaction and that the risk of HSR is increased if they are HLA-B*5701 positive.
- Patients should be advised to contact their physician immediately for advice on whether they should stop taking abacavir if:
- They develop skin rash; OR
- They develop one or more symptoms from at least two of the following groups:
  - Fever
  - Shortness of breath, sore throat or cough
  - Nausea or vomiting or diarrhea or abdominal pain
  - Extreme tiredness or achiness or generally ill feeling
- Patients must be advised to seek medical advice from emergency unit of nearest hospital urgently if the doctor is unavailable.

Counselling the Patients
Abacavir / Lamivudine Alert Card (with blister and bottle pack)

- In order to avoid consuming abacavir accidentally or restarting abacavir, patients who have experienced an HSR should be asked to return the remaining abacavir tablets or oral solution to the pharmacy.
- Patients must be advised to contact their doctor before restarting abacavir if they have stopped it for any reason, particularly due to possible adverse reactions or illness.
- Patients must also be informed that a HLA-B*5701 negative patient can also experience an abacavir hypersensitivity reaction. Therefore, ANY patient who develops signs or symptoms consistent with a possible hypersensitivity reaction to abacavir MUST CONTACT THEIR DOCTOR IMMEDIATELY
- If patients have discontinued abacavir due to HSR in past, they MUST NEVER TAKE abacavir or any other medicine containing abacavir again as within hours they may experience a life-threatening lowering of blood pressure or death.

Section – 5
Clinical Studies for Abacavir Hypersensitivity

Clinical Studies for Abacavir Hypersensitivity

- HLA-B*5701 screening is an effective and feasible way to reduce the incidence of abacavir HSR as depicted by the data from the Western Australian Cohort.[1]
- After the data from Western Australia cohort study[1] were observed, some treatment centers introduced HLA-B*5701 screening for abacavir hypersensitivity
- To validate the association of screening with HLA-B*5701, the following clinical studies were conducted :
  - **PREDICT-1 study**: A prospective study established the role of the HLA-B*5701 allele as a predictive marker for abacavir hypersensitivity
  - **SHAPE study**: A retrospective study conducted in United States provides supporting data
  - **ARIES study**: A prospective study using HLA-B*5701 screening that demonstrated lower abacavir HSR after implementation of HLA-B*5701 screening compared with historical studies that did not use genetic screening methods.

[1] Rauch et al. *Clin Infect Dis*. 2006;43:99-102.

PREDICT-1 Study

A pivotal, double blinded, randomised clinical trial to establish the effectiveness of the HLA-B*5701 allele as a predictive marker for abacavir (ABC) hypersensitivity reaction (HSR)

1,956 ABC naive subjects randomised 1:1 in a double blinded fashion to:

–Arm A) Retrospective HLA B*5701 testing after starting ABC therapy (Controls)

–Arm B) Prospective HLA-B*5701 screening; positive patients excluded pre- ABC therapy

Retrospective epicutaneous patch testing (EPT) in all cases of clinically suspected ABC HSR

Table 1: incidence of hypersensitivity reaction to abacavir

ABC HSR[1]	Arm A	Arm B	p value	OR (95% CI)[2]
Clinically Suspected	7.8% (66/847)	3.4% (27/803)	<0.0001	0.40 (0.25–0.62)
Immunologically (EPT) Confirmed	2.7% (23/842)	0.0% (0/802)	<0.0001	0.03 (0.00–0.18)

1 Intention to treat evaluable population 2 Odds ratio (OR), Confidence interval (CI)

Conclusion: Prospective HLA-B*5701 screening and avoidance of abacavir therapy in subjects with a positive test result:

- Significantly reduced incidence of a clinically suspected abacavir HSR
- Completely eliminated the incidence of skin patch test–confirmed abacavir HSR.

These data emphasize that skin patch testing should not be used as a clinical tool for diagnosis or to justify abacavir rechallenge

SHAPE Study
(Study of Hypersensitivity to Abacavir and Pharmacogenetic Evaluation)

- SHAPE was a retrospective case-control study to estimate the sensitivity and specificity of HLA-B*5701 as a marker for abacavir hypersensitivity reactions in both white and black populations, using skin patch testing to supplement clinical diagnosis of abacavir hypersensitivity[2]

Conclusions

- Sensitivity of HLA-B*5701 in white and black subjects with skin patch test–confirmed abacavir hypersensitivity was 100%.
- Lower sensitivity of HLA-B*5701 screening was observed when abacavir hypersensitivity was defined by clinical diagnosis alone.
- The presence of the HLA-B*5701 allele is associated with increased risk of abacavir hypersensitivity, regardless of race.
- Not all HLA-B*5701–positive subjects had a positive skin patch test result

[1]Hughes et al. *Pharmacogenomics*. 2004;5:203-211.
[2]Saag et al. *Clin Infect Dis*. 2008;46:1111-1118.

Limitations of Skin Patch Testing

- Skin patch testing cannot be used as a screen for patients who have not previously received abacavir.
- Regardless of the outcome of a skin patch test, patients must stop treatment with abacavir if hypersensitivity is suspected clinically.
- Skin patch test results must **NEVER** be used to support rechallenging abacavir in the routine clinical setting.
- Skin patch testing should **NEVER** change clinical diagnosis of abacavir hypersensitivity.

A SKIN PATCH TEST IS NOT A SUBSTITUTE FOR HLA-B*5701 SCREENING!

ARIES Study

A Large, Open-label Prospective Study Using HLA-B*5701 Screening

- This study of subjects starting abacavir therapy excluded HLA- B*5701–positive individuals from enrollment.
- The rate of abacavir HSR among HLA-B*5701–negative subjects (N=517) was assessed.
- At 30 weeks, 4 individuals (0.8%) were diagnosed with clinically suspected abacavir HSR.
- **In this study, abacavir HSR rates were dramatically lower after implementation of *HLA-B*5701* screening compared with historical studies without prospective screening in this diverse patient population.**

Young et al. *AIDS*. 2008;22:1673-1675.

Summary of Clinical Studies

- Increased risk of abacavir hypersensitivity is associated with the presence of HLA-B*5701 allele, regardless of race.
- Prior to the start of treatment, a prospective screening for HLA-B*5701 helps identify patients who are at higher risk (HLA-B*5701-positive cases) of developing abacavir HSR.
- If the status of HLA-B*5701 is unknown, the patient should be screened.
- Avoiding treatment with abacavir in subjects with the HLA-B*5701 allele significantly reduces the incidence of clinically diagnosed cases of hypersensitivity
- If HLA-B*5701 screening for risk of abacavir HSR should never be substituted for appropriate clinical vigilance and patient management in individuals receiving abacavir. Clinical diagnosis of suspected abacavir HSR remains the basis for clinical decision making.
- Data from clinical studies do not support the use of skin patch testing in routine clinical practice.

Section – 6
Hypersensitivity Case Studies

Hypersensitivity case studies

Three case scenarios are presented to illustrate Abacavir HSR:

- Case 1 illustrates typical features of abacavir HSR
- Case 2 illustrates NEVER to rechallenge with abacavir in patients experiencing HSR with abacavir
- Case 3 illustrates that HSR can be experienced in patients tested negative for HLA-B*5701

Case Study 1 (1 of 2)

- A 33 year old male patient on didanoside 400 mg/day, lamivudine 150 mg twice a day, abacavir 300 mg twice a day, indinavir 800 mg twice a day, ritonavir 100 mg twice a day and nevirapine 200 mg twice a day (after a 2 week lead-in period of 200 mg / day) developed slight rash on his arms after one and half week
- This was attributed to nevirapine which was continued and rash disappeared after a few days. During following weeks, patient complained about slight nausea.
- After 7.5 weeks, he suddenly developed the following symptoms:
  - Temperature (40^0C)
  - Sore throat
  - Ulcers on upper and lower lips
  - Diarrhea
  - Abdominal pain

Sankatsing, Sanjay UC, Prins, Jan M. Agranulocytosis and fever seven weeks after starting abacavir. AIDS Dec 2011; 15(18): 2464-65

Case Study 1 (2 of 2)

- Physical examination revealed:
  - Enlarged lymph nodes in the neck
  - Oral cavity and throat were normal
  - No skin rash
  - Two ulcers on lips
  - Spleen was enlarged and painful
- Investigations revealed white blood cell (WBC) count 1.1 X 10^9/L with < 10% granulocytes

Course of action:

- An allergic reaction was suspected and abacavir was stopped.
- After 2 days, temperature was normalized, abdominal pain and other symptoms resolved but he developed generalized erythema which also subsided in 2 days without specific therapy.
- Neutrophil count started increasing after 2 days of stopping abacavir and normalized after 9 days.
- Conclusion: this case illustrates the importance of clinical vigilance in the diagnosis of Abacavir HSR. In this case patient presented without rash (which occurs in 3% of patients treated with abacavir) and symptoms appeared after 7.5 weeks of treatment; typically symptoms appear within 6 weeks of starting treatment with abacavir.

Sankatsing, Sanjay UC, Prins, Jan M. Agranulocytosis and fever seven weeks after starting abacavir. AIDS Dec 2011; 15(18): 2464-65

Case Study 2 (1 of 2)

- After one week of initiation of therapy with abacavir 300 mg twice a day with nelfinavir, 46 year old male patient developed:
  - Sudden fever
  - Chills
  - Myalgia
  - Nausea
  - Gastrointestinal discomfort
  - Shortness of breath
- After 24 hours of onset of symptoms, he was admitted to hospital.
- Physical examination and laboratory tests were normal with the following observations:
  - Temperature 40^0C
  - Blood pressure 100/60 mm of Hg
  - No skin rash
  - Oxygen saturation – 90%
  - CT Chest - Normal
  - Blood, urine, sputum - Normal
- Abacavir was stopped at admission and his temperature dropped 24 hrs later
- Patient was told not to re-introduce abacavir

Leila E, Lioter, Yves J et al. Abacavir rechallenge has to be avoided in case of hypersensitivity reaction. AIDS Jul 1999; 13(11): 1419

Case Study 2 (2 of 2)

- After 12 days of discontinuing abacavir, patient restarted on his own.
- He was found unconscious at home few hours later.
- On admission, he was in shock with:
  - Respiratory distress
  - Fever 40^0C
  - Generalized rash
  - Central venous pressure 10 cm
  - Confusion
  - Myalgia
- All investigations were normal with no evidence of infection.
- Diagnosis of anaphylactic shock was made and patient was managed with i.v. saline, dobutamine, adrenaline, furosemide and steroids.
- BP returned to normal, rash disappeared with desquamation of extremities
- Acute respiratory distress syndrome and renal insufficiency later worsened leading to death 22 days later.
- **Conclusion: this case illustrates the importance of NEVER challenging with abacavir after experiencing HSR**

Leila E, Lioter, Yves J et al. Abacavir rechallenge has to be avoided in case of hypersensitivity reaction. AIDS Jul 1999; 13(11): 1419

Case Study 3

- A 31 year old Taiwanese male patient was started on HAART with a regimen of efavirenz, lopinavir / ritonavir, stavudine and abacavir.
- After 1 week of this treatment, he suddenly developed:
  - Fever 38^0C
  - Generalized maculopapular skin rash
  - Chills
  - Headache
- Blood tests showed WBC count of 0.7 X 10^9/L and Absolute neutrophil count (ANC) of 0.2 X 10^9/L.
- All investigations for causes of fever were negative.
- Abacavir HSR was suspected and it was discontinued.
- All symptoms resolved in 2 days and ANC increased over the following days.
- Genotyping showed that patient was HLA-B*5701 negative.
- **Conclusion: this case illustrates that patients who test negative for HLA-B*5701 can also experience HSR**

Truchis P, Mathez D, Abe E, et al. Abacavir induced agranulocytosis in two Taiwanese patients tested HLA-B*5701 negative. AIDS 2011; 24(8)